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Veterinary Herbal Medicine: A Systems-Based Approach

Susan G. Wynn and Barbara J. Fougère

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CHAPTER

This chapter reviews traditional and scientific approaches to the use of herbal medicine in treating an array of conditions by system. Clinically, it is common to find more than one system affected, so it is important to consider the whole patient and not just the diagnosis or system. In this section formulas are offered as starting points; however, it is intended that they should be modified to match the needs of the individual patient wherever possible (see Chapter 19).

Frequently treatment with orthodox medicine has already been implemented. In the authors' experience herbal medicines can frequently be used alongside the conventional approach but can also be used instead in many instances, particularly for complicated or chronic conditions. Care should always be taken to consider possible drug-herb interactions and herb-herb interactions, dosing, and the vitality of the patient. Inexperienced veterinary herbalists are advised to cross reference with the monographs and chapters pertaining to prescribing and pharmacology. In many cases below, studies are described that involve experimental animal models and herb extracts (as opposed to whole herbs). It is important to maintain proper perspective on if and how these studies relate to clinical patients, whether they are safe in the species of interest, and how dosing of an herb might differ from doses described in the studies.

HERBS FOR BLOOD AND IMMUNOLOGIC DISORDERS

Of all the systems discussed in this section, the immune system is at once the most difficult and the most self-evident to treat. Practitioners are frequently asked how to "stimulate the immune system," yet herbalists and scientists alike realize that the complexity of immune function makes this effort at least naïve and at best inadvisable. Immune function represents an ecologic balance within the body that is attained with contributions from endocrine and neurologic activities. It has even been recognized that the "invaders" fought by the immune system are not all bad—we may even need our viruses to help us fend off the development of tumors and our bacteria to maintain normal immune function.

So any attempt to modify immune function must take into account the relationship between the patient and all functions of the immune system, as well as the environment and its microbial influences that interface with the forward defenses of the immune system. In this sense, traditional concepts of clinical disease and empirically determined treatments may be even more useful than evidence-based guidance, simply because our knowledge of the complexities of immune function is so limited. We truly must treat an entire patient, instead of bone marrow and secondary immune organs.

Similarly, disorders of the blood are about more than just the bone marrow. For instance, hyperlipidemia in people is surely not just a problem with the blood—it is a lifestyle problem in many cases. Although this section is all about blood and immune disorders, every condition that is listed requires a global approach to treatment. Herbs inherently provide complex actions that address more than one deranged process in the body.

Mechanisms of Interest

Adaptogens

These plants have been noted both traditionally and in human clinical trials and animal studies to increase resistance to stress, which predisposes animals to disease, including infection. Adaptogens generally work by modulating the hypothalamic-pituitary-adrenal axis, but many have other effects as well, such as modulation of immune function.

ASIAN GINSENG *(PANAX GINSENG):* Hundreds of scientific papers have established that *Panax ginseng* has numerous clinical effects. In laboratory animals, these include central nervous system (CNS) stimulation; protection against exogenous damage from radiation, toxins, and infection; protection from physical and psychological stress; and an influence on carbohydrate and lipid metabolism and immune stimulation. All of these may

bear on an animal's response to stress. Recently, investigators have developed rat models of stress that have resulted in measurable physical and chemical changes. In these studies, pretreatment with ginseng attenuated the stress-induced rise in corticosterone, hyperglycemia, immune suppression, increased adrenal gland weight, gastric ulceration, and other signs of chronic stress (Rai, 2003b; Kim, 2003). The dose in rats used in one study was 100 mg/kg of ginseng root powder (Rai, 2003b). The saponin-rich fraction of ginseng also reduced the secretion of catecholamines from bovine adrenal medullary chromaffin cells (Tachikawa, 2004).

AMERICAN GINSENG *(PANAX QUINQUEFOLIUS):* This herb is biochemically similar to *Panax ginseng;* however, the plant has not been studied as extensively as *P. ginseng*.

BACOPA *(BACOPA MONNIERI):* Rai and colleagues (2003a) showed that a dose of 40 mg/kg of a standardized extract reversed stress-induced ulcer development, and higher doses (80 mg/kg) additionally prevented increases in adrenal gland weight in rats.

ELEUTHERO *(ELEUTHEROCOCCUS SENTICOSIS):* Water extracts high in isofraxidin and eleutherosides B and E (especially E) reduced corticosterone levels in stressed mice (Kimura, 2004). On the contrary, in human athletes, Eleuthero slightly worsened a hormonal indicator of stress after 6 weeks of training. The athletes were administered 8 mL daily of a 33% hydroethanolic extract (Gaffney, 2001).

CORDYCEPS *(CORDYCEPS SINENSIS):* This herb is not a well known adaptogen; nonetheless, one laboratory animal study suggests that it may have antistress properties. A hot water extract was administered to stressed rats (150 mg/kg daily), and investigators found that stress-induced changes in adrenal and thyroid gland weights, as well as changes in cholesterol and alkaline phosphatase, were suppressed (Koh, 2003).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* A standardized extract given to rats at 25 mg/kg and 50 mg/kg suppressed stress-induced changes in blood glucose levels, glucose intolerance, corticosterone levels, gastric ulceration, immunosuppression, and mental depression (Bhattacharya, 2003). A single withanolide, as well as a withanolide-free fraction, has shown adaptogenic activity in stress models (Kaur, 2003; Singh, 2003a).

RHODIOLA *(RHODIOLA ROSEA):* Russian studies have long suggested that the root of this plant has adaptogenic activity. Two double-blind, placebo-controlled human clinical trials used an extract of *Rhodiola* and found significant improvements in cognitive functions, fatigue, and "neuromotoric tests" (Spasov, 2000; Darbinyan, 2000).

OTHER HERBS: Other adaptogens include *Andrographis paniculata,* gotu kola, *Codonopsis pilosa,* licorice, and *Schisandra*.

Anticoagulant Herbs

Anticoagulation is a less common therapeutic strategy in veterinary medicine than in human medicine. Herbs with anticoagulant activity may be considered for animals at risk for thrombosis, such as cats with cardiomyopathy or dogs undergoing heartworm treatment or possibly for animals that are immobilized for long periods.

DAN SHEN *(SALVIA MILTIORRHIZA):* According to in vitro and animal studies, this herb may have multiple effects, including interference with extrinsic blood coagulation, antithrombin III-like activity, inhibition of platelet aggregation, and promotion of fibrinolytic activity.

OTHER HERBS: Herbs with antiplatelet activity include garlic *(Allium sativum),* turmeric *(Curcuma longa),* ginger *(Zingiber officinale), Plectranthus forskholi,* and *Salvia miltiorrhiza*.

Anti-inflammatory Herbs

Herbs with anti-inflammatory properties probably work through a large variety of mechanisms. Some are recognized cyclooxygenase (COX)-2 inhibitors, and others are not as well defined. The mechanisms of inflammation are reviewed more completely in the section on musculoskeletal herbs. In autoimmune conditions, anti-inflammatory herbs should be directed toward the organ involved; this is explored further in relevant sections of this text.

Blood Tonics

These herbs are used both for frank anemia and for the traditional Chinese medicine signs of "Blood Deficiency," which include dry and itchy skin, dream-disturbed sleep, dry coat, and dry eyes.

DANG GUI, DONG QUAI *(ANGELICA SINENSIS):* This is a traditional Chinese herb that is used to tonify as well as "invigorate" the blood. A case report in a human kidney patient with anemia who was resistant to erythropoietin treatment indicated that treatment with this herb improved hematologic measures (Bradley, 1999). Wang (2001) found that dang gui improved measures of erythrocyte deformability and fragility.

REHMANNIA *(REHMANNIA GLUTINOSA):* In traditional Chinese medicine, this herb is used to "cool" the Blood and is an important herb in treating Yin deficiency, which is seen, for example, in patients with diabetes. However, one Chinese study suggested that in people with chronic aplastic anemia, Rehmannia root could improve symptoms and recovery (Yuan, 1998). In anemic mice, the root appeared to enhance replication of certain bone marrow progenitor cells (Yuan, 1992).

RHODIOLA *(RHODIOLA ROSACEA):* This is a European and Asian plant that has been used traditionally to treat anemia. In vitro studies have suggested that it protects human erythrocytes from damage caused by glutathione depletion and hemolysis that occurs via oxidation (De Sanctis, 2004). An extract appeared to stimulate replication of mouse bone marrow cells in vitro as well (Udintsev, 1991).

OTHER HERBS: Other herbs suggested by traditional herbalists include Codonopsis, Nettle, and Ashwagandha. Herbs especially used for iron deficiency anemia include yellow dock, nettle, and parsley.

Immune Modulators

A Medline search on "immune" and "herbal" would suggest that a legion of plants may stimulate some aspect

of immune function. The problem here is that most studies have been conducted in vitro or at best in experimental animals and most of these plants have not been used traditionally for immune support. The herbs described below give researchers plenty to explore and are those that are deemed most useful by herbalists. Immune stimulant herbs have been implicated in reactivation or worsening of autoimmune disease, and they should be used with caution in these patients (Lee, 2004c).

Medicinal Fungi: These are very likely to work in similar ways. Individual fungi are listed here:

- Reishi *(Ganoderma lucidum)*
- Maitake *(Grifola frondosa)*
- Shitake *(Lentinula edodes)*
- Turkey tail *(Trametes versicolor)*
- Cordyceps *(Cordyceps sinensis)*
- Hime-matsutake *(Agaricus blazei)*
- Chaga *(Inonotus obliquus)*

All these fungi contain polysaccharide complexes and sterols that appear to enhance cell-mediated immune function and that may have antitumor activity as well (Ooi, 2000; Wasser, 1999; Zhu, 1998b). Still, structural differences have been noted in some of the primary constituents, and it is possible that their activities in vivo are somewhat different. As a rule, polysaccharide complexes such as those found in medicinal fungi are more likely to be completely extracted in aqueous or dried preparations than in alcohol extracts.

ECHINACEA *(ECHINACEA* SPP*):* Extracts have been shown to increase phagocytic activity in human peripheral monocytic cells, to promote production of various cytokines, and to enhance natural killer cell function, all of which involve the innate immune system as opposed to specific, adaptive processes. Most clinical studies in humans have involved upper respiratory infection and, in fact, Echinacea may shorten the duration of the common cold (Percival, 2000), depending on the form administered. Echinacea is often recommended for chronic recurrent viral upper respiratory infection in cats, and some practitioners use Echinacea to treat patients with retroviral infection. Although some practitioners caution against the long-term use of Echinacea because toxicity or autoimmune conditions may result, this concern has not been well documented. However, immunostimulants are probably best used as pulsed treatments if they are administered on a long-term basis, because full response to treatment is probably reached in a few weeks and does not continue to increase. In a 4-day observational study conducted at the Ohio Eclectic College in 1935, students were administered Echinacea before meals and at bedtime. Leukocyte counts increased 24 to 48 hours after initiation of treatment. Short-term (2- to 4-week), on-off administration is most sensible. The Echinacea monograph (see Chapter 24) describes studies in swine and horses that suggest immune modulating effects in these species.

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* This traditional Chinese herb has been shown to increase T cell–mediated immune function in vitro in mice, as well as in uncontrolled trials in humans (Zhao, 1990; Sun, 1983; Yoshida, 1997).

GINSENG POLYSACCHARIDES AND SAPONINS: These have shown immunostimulating capacity in vitro and in animal models (Kitts, 2000). In one study, rats with chronic *Pseudomonas aeruginosa* lung infection were administered extracts of *Panax ginseng;* the treated group exhibited higher bacterial clearance and lower serum immunoglobulin levels than did the untreated group, which suggests enhancement of cell-mediated immunity (Song, 1998).

THUNDER GOD VINE *(TRIPTERYGIUM WILFORDII):* This herb appears to be a true immune suppressant. Extracts of this plant have been investigated in human clinical trials for the treatment of rheumatoid arthritis, myasthenia gravis, lupus erythematosus, graft rejection, asthma, and other immune-mediated problems, generally with positive results (Tao, 2000; Tao, 2002). Various trials have shown reductions in interleukin (IL)-6, IL-5, IL-2, NF-kappaB, and CD 4+ levels, caused by an extract or by single constituents such as triptolide. In one trial, it was effective for rheumatoid arthritis when applied topically (Cibere, 2003). The plant has some toxicity, most notably causing infertility in both males and females.

OTHER HERBS: Other herbs used traditionally as immune stimulants include Eleuthero *(Eleutherococcus senticosis),* Schisandra *(Schisandra chinensis),* Privet *(Ligustrum lucidum),* Usnea *(Usnea barbath),* Thuja *(Thuja occidentalis),* Lomatium *(Lomatium dissectum),* and Baptisia. However, many others, including *Andrographis paniculata, Codonopsis pilosa, Ligusticum wallichii, Paeonia lactiflora, Phytolacca decandra, Picrorrhiza kurroa, Poria cocos,* Propolis, and *Uncaria tomentosa,* are employed as immune enhancers. Other plants that have been used as immune stimulants tend to be high in vitamins such as vitamin C (rosehips) and flavonoids (beet root, black currant).

Hemidesmus indicus and *Tylophora indica* may also have immune suppressant activity. The effect of an ethanolic extract of each herb was studied on delayed-type hypersensitivity, humoral response to sheep red blood cells, skin allograft rejection, and phagocytic activity of the reticuloendothelial system in mice. *Tylophora indica* appeared to stimulate phagocytic function while inhibiting the humoral component of the immune system. *Hemidesmus indicus* suppressed both cell-mediated and humoral components of the immune system (Atal, 1986).

Antihyperlipidemics

GARLIC *(ALLIUM SATIVUM):* This herb has shown modest efficacy in lowering cholesterol and triglyceride levels in laboratory animals and people (Ackermann, 2001). Garlic has the potential for causing Heinz body anemia in dogs and especially in cats. Many veterinarians, however, use garlic for their patients and monitor blood parameters.

RED YEAST RICE *(MONASCUS PURPUREUS):* This is a natural statin that has been shown to reduce cholesterol and triacylglycerol concentrations in controlled trials in humans (Heber, 1999). Similar to other statins, it may cause rhabdomyolysis. This author (SW) has

observed a case of rhabdomyolysis in a dog who was being treated with both red yeast rice and gemfibrozil.

GUGULIPID *(COMMIPHORA MUKUL):* This herb contains resins that have been shown to have cholesterol- and triglyceride-lowering activity in humans (Singh, 1994) and laboratory animals. However, the overall effect is mild to moderate compared with cholesterol-lowering drugs used in people (Caron, 2001).

GLOBE ARTICHOKE *(CYNARA SCOLYMUS):* This herb has been shown in human clinical trials to lower cholesterol and triglycerides, at doses ranging from 900 to 1920 mg per day. Globe artichoke leaf extract not only increases choleresis and, therefore, cholesterol elimination, but it also has been shown to inhibit cholesterol biosynthesis (Kraft, 1997b). It is suggested that a possible mechanism of action might be the indirect inhibition of hydroxymethylglutaryl–CoA reductase (HMG-CoA) (Gebhardt, 1998). In vitro studies have documented a concentration-dependent inhibition of de novo cholesterol biosynthesis in cultured rat and human hepatocytes for globe artichoke leaf extract given at 0.03 to 0.1 mg/mL (Petrowicz, 1997).

Hemostatics

Many hemostatics in Western herbal medicine are astringent and exert their effects through direct contact with skin or mucous membranes to stop bleeding via a styptic action. The concept is different in Chinese medicine, where bleeding may be due to Excess Heat in the blood (so it should be cooled) or Blood Stasis (which causes bleeding by allowing blood to back up and subsequently "overflow," or extravasate, around the area of stasis). A bruise is an example of Blood Stasis, and hematochezia and epistaxis are often due to Blood Heat.

YUNNAN PAI YAO *(WHITE MEDICINE FROM YUNNAN PROVINCE):* This is the most popular Chinese herbal formula in veterinary medicine for the control of hemorrhage. The formula contains San qi *(Panax notoginseng),* an herb that has a reputation for being able to stop bleeding anywhere in the body. Other herbs in the formula (according to the label on a box purchased in 2005) are *Ajuga patantha, Dioscorea opposita, Dioscorea nipponica, Erodium stephanianum, Alpinia officinarum,* and *Dryobalanops aromatica* (or *Blumea balsamifera*). The formula is often guarded, and labels don't always provide an ingredient list, but it always contains pseudoginseng (San Qi or Tienchi) *Panax pseudoginseng,* and variously Chinese yam *(Dioscorea opposita),* yam rhizome *(Dioscorea hypolglauca),* sweet geranium *(Erodium stephanianum)* and galangal rhizome *(Alpinia officinarum)* (Polesuk, 1973). Yunnan bai yao has been shown to decrease both clotting times and prothrombin times (Ogle, 1977) and to initiate platelet release (Chew, 1977).

OTHER HERBS: Other herbs used as hemostatics include Horsetail *(Equisetum arvense),* Witch hazel *(Hamamelis virginiana),* Oak bark *(Quercus robur),* Nettle leaf *(Urtica dioica),* Lesser periwinkle *(Vinca minor),* Grape *(Vitis vinifera),* Rehmannia, and Trillium. Astringent herbs include agrimony *(Agrimonia eupatoria),* cranesbill *(Geranium maculatum),* and yarrow *(Achillea millefolium).*

A Chinese herbal formula, Wen-She decoction (WSD), resolved acute upper digestive tract hemorrhage in an open sequential controlled trial. It was concluded that WSD was an excellent treatment for hemorrhage of the upper digestive tract. WSD consists of *Codonopsis pilosa, Atractylodes macrocephala, Poria cocos, Glycyrrhiza uralensis, Zingiber officinale, Os sepia, Halloysitum rubrum,* and *Astragalus membranaceus* (Gong, 1989).

REVIEW OF SPECIFIC HEMATOLOGIC AND IMMUNOLOGIC CONDITIONS

Anemia, General

Therapeutic rationale

Anemia must be addressed by determining the cause, such as immune-mediated destruction, blood loss, or bone marrow suppression. Blood tonics may offer temporary support while the cause is addressed, and may even stimulate hematopoiesis.

A formula to build on might consist of a combination of blood tonics (Rehmannia and Dang gui), adaptogens (such as Rhodiola or Ashwagandha), and herbs that address the conventional diagnosis as well. Red root *(Ceanothus americanus)* has an indication for use with an enlarged spleen, which may be seen in autoimmune hemolytic anemia.

A prescription for anemia might include the following:

Dang gui	33% (circulatory stimulant, anti-inflammatory, vasodilator, antiallergic, warming)
Rhodiola	33% (immune modulating, adaptogen)
System- or organ-specific herb	33% (such as an astringent for gastrointestinal tract bleeding)

Autoimmune Disorders, General

Therapeutic rationale

- Reduce inflammation and tissue destruction at target organs.
- Modulate the inappropriate immune response.

Aside from Thunder God Vine, which has significant toxicity and is not widely available, few herbs address autoimmune disorders as a general class of medicine. *Hemidesmus indicus, Tylophora indica,* and *Stephania tetrandra* are immune suppressants that must be used very carefully by experienced herbalists. Ideally, the prescription addresses the underlying or perpetuating factors that contribute to the pathophysiology. Autoimmune disease may be precipitated by viral infection, so antiviral herbs may need to be used. Prescriptions generally include anti-inflammatory herbs, as well as those that address specific organ involvement and "leaky gut" (see later section on dermatologic herbs for more information). Herbs that enhance elimination should also be included. Immune-modulating herbs described earlier as immune stimulant are not always inappropriate but should be chosen with special attention to all of their purported effects. Focusing on maintaining systemic health rather than on suppressing the immune system is a worthwhile

strategy, and herbal medicine is particularly useful when combined with the conventional treatment of autoimmune disease.

A prescription for autoimmune disease support follows:

Rehmannia	40%
Bupleurum	20%
Milk thistle	20%
Bilberry	20%

Coagulopathy and Bleeding

Therapeutic rationale

- Identify specific clotting defect and treat accordingly.

When coagulation defects cause signs of bleeding, possibly the most important herb to choose is yunnan pai yao. Hemostatic and astringent herbs may also address bleeding from gastrointestinal tract mucous membranes; in traditional herbal medicine, they may have systemic effects. These include yarrow, agrimony, and shepherd's purse. Red root *(Ceanothus americanus)* is also astringent and is indicated when the spleen is enlarged, as is often seen in some immune-mediated coagulopathies. Cinnamon was valued by the Eclectics, primarily for postpartum hemorrhage, but also for hemoptysis and bleeding that occurs elsewhere.

Hyperlipidemia

Therapeutic rationale

- Identify predisposing factors such as endocrinologic disorders, liver disease, and pancreatitis.
- Reduce dietary fat.
- Clear excess serum lipids.

Formulas that contain garlic, globe artichoke, guggul, and red yeast rice may be effective but should be combined with herbs that address any predisposing cause. In addition, herbalists may prescribe aids to digestion and biliary function, such as globe artichoke, dandelion root, prickly ash *(Zanthoxylum americanum),* and calamus *(Acorus calamus)*. Some medicinal fungi, including Reishi, have also been shown to have antihyperlipidemic properties.

A prescription for hyperlipidemia (1) follows:

Garlic	5%
Guggul	30%
Reishi	25%
Dandelion	15%
Calamus	15%
Prickly ash	10%

A prescription for hyperlipidemia (2) is presented here:

Globe artichoke	60%
Dandelion root	30%
Garlic	10%

Herbal Treatment of Bleeding

Nonspecific Sign	Herb
Bleeding gums	Bilberry, Witch hazel
Hematemesis	Cranesbill, Yunnan pai yao
Hematuria	Yunnan pai yao, Rehmannia, Trillium
Hemoptysis	Bugleweed, Yunnan pai yao, Cinnamon
Gastric hemorrhage	Yarrow, Atractylodes, Agrimony, Plantain, Shepherd's purse, Cranesbill

Immune Deficiency or Suppression

Therapeutic rationale

- Identify causative factors (e.g., retroviral or other chronic disorders).

Patients with poor immunity should be prescribed herbs from three main groups:

1. **Immune-enhancing herbs.** Selection can be based on traditional notions of organ or system affinity, or may be combined according to their other effects on the body. Herbs to consider include Echinacea *(Echinacea purpurea, E. angustifolia, E. pallida),* Astragalus *(Astragalus membranaceus), Ligusticum walchii,* Pau d'arco *(Tabebuia avellanedae),* Usnea *(Usnea barbata), Picrorrhiza kurroa,* Ginseng (*Panax* spp), and medicinal fungi such as Reishi mushroom *(Ganoderma lucidum),* Maitake mushroom *(Grifola frondosa),* Shitake mushroom *(Lentinus edodes),* Turkey tail *(Trametes versicolor),* and Cordyceps *(Cordyceps sinensis).*
2. **Tonic and adaptogenic herbs.** These include Panax, Eleutherococcus, and Ashwagandha. As a general guide, stimulating herbs should be avoided during the acute phase of an infection. This is perhaps derived from traditional Chinese medicine, wherein stimulating and tonic herbs are contraindicated in Deficient Yin patterns with Heat signs—typically, fever and inflammation or infection. One study on Eleutherococcus showed that administration before induced listeriosis infection in rabbits and mice increased resistance to infection. However, when administration occurred simultaneously with an induced infection, the severity of disease was exacerbated (Farnsworth, 1966). Despite this, Eleutherococcus is frequently found in low doses in formulations for acute infection such as cold and flu.
3. **Bitter herbs.** Gentiana or any of the bitters described under the gastrointestinal system should be considered; these are generally cooling herbs. If the patient is cool or cold, the cooling effect should be countered with warming herbs. One of the proposed theories for the benefit of bitters is the general improvement that occurs in digestive function, hence enhanced gut-associated lymphoid tissue function. Better immunity at the gut level (T helper 3 cell mediated) helps to moderate and regulate T helper 1 and T helper 2 cells, thereby improving immune balance systemically.

Echinacea and Astragalus are two of the most popular "immune" herbs in human herbal medicine. Echinacea improves phagocytosis and generally enhances immune

surveillance. It must be used in high doses during acute infections, such as infected wounds or viral infections. In humans, doses of 20 to 30 mL per day can be taken; it takes about 3 days for phagocytic activity to peak. Many studies that detract from the benefits of Echinacea are flawed by incorrect dosing and improper extract type. Echinacea can be used for chronic bacterial and viral infections, postviral syndromes, acquired immunodeficiency syndrome resulting from feline leukemia virus (FAIDS), in the appropriate formulas, autoimmune disease and long-term allergies and intolerances. It can be used during chemotherapy or pneumonia, and for chronic purulent or pyodermic skin infection—at relatively high doses in all cases (in humans, 15 mL per day for serious chronic states of immune deficiency). Doses as high as 40 mL on the first day followed by 16 mL daily were used in one positive clinical trial (Goel, 2004). Astragalus, on the other hand, is more appropriately used as a preventive measure during disease outbreaks or for chronic immune incompetence and autoimmune disease (especially nephritis). The dose in humans is between 20 and 40 mL per week. High dosing in the case of Echinacea is an important consideration because it does influence efficacy.

A prescription for general immune support follows:

Echinacea	40%
Oregon grape root	20%
Astragalus	20%
Licorice	20%

Infection

Infections are addressed in this text within the sections on specific systems or organs in which they occur. Herbalists generally develop formulas that combine antimicrobial activity, organ support, and immune stimulation (where appropriate). For instance, a formula for pneumonia might include antimicrobials such as thyme and sage, immune support from Astragalus and Echinacea, and expectorants such as elecampane and horehound. It should be noted that some of these herbs have multiple indications that magnify their effects on the respiratory tract (Thyme is both antimicrobial and expectorant, Echinacea is an immune stimulant and an antimicrobial, and Astragalus is an immune stimulant that is specifically associated with the lung in traditional Chinese medicine).

Herbal management of infections should include the following:

- Immune-enhancing herbs, whether acute or chronic.
- Organ support herbs (Milk thistle for the liver, Saw palmetto for the prostate, etc.).
- Herbs that act against specific microbes (fungal, bacterial, protozoal), if known. The activity of most antiseptic herbs is mild and most effective for dermatologic (topically) or gastrointestinal tract infection. Hydrastis is particularly indicated for gastrointestinal tract infection.
- Viral infection can be treated with Saint John's Wort (for enveloped viruses such as herpes, hepatitis, poxvirus, paramyxovirus, retrovirus, coronavirus). Thuja may be helpful against a range of viruses such as papovaviridae, poxviridae, picornaviridae, and bunyaviridae viruses.

Thrombocytopenia

Therapeutic rationale

- Identify platelet pathology.
- Suppress immune-mediated damage, if autoimmune in origin.
- Give blood or platelet transfusions.
- Administer anabolics to enhance regeneration.

No herbs specifically address thrombocytopenia; however, anecdotally, yunnan pai yao is effective in controlling resultant hemorrhage. (See also the section on coagulation disorders, earlier.)

Sheng xue ling

One formula that may be useful in treating idiopathic thrombocytopenic purpura is Sheng xue ling (SXL). In an open study in China, 86 human cases of ITP were divided randomly into two groups. A total of 56 patients were treated with SXL, and 30 patients were administered prednisone, each for 3 months. In the SXL group, the "total effective rate" at 3 months was 85.71%, similar to prednisone (83.33%), but at 6 months, efficacy for SXL was greater (91.07%) than that of the prednisone group (53.33%), without adverse reactions. Bleeding was alleviated; blood platelet count was increased; platelet-associated immunoglobulin and IL-4 dropped; natural killer cell activity increased; and T lymphocyte subsets gradually returned to normal level. All differences described here were statistically significant. The mechanism by which the formula might work was not identified (Zhou 2005).

HERBS FOR CANCER

General Considerations

Cancer biology is yet to be fully understood. Cellular mutation may occur as a result of free radical damage (with activation of oncogenes or suppression of tumor suppressor genes) and genetic susceptibility and toxicity (e.g., hepatopathogenic toxins). In traditional herbal medicine, cancer is nearly always viewed as a sign of systemic toxicity. However, immune dysregulation has to be considered, and can occur with stress, toxin, heavy metal and pesticide exposure, dysbiosis, hormonal imbalance, nutrient imbalance, infection, inflammation, and radiation. Chemotherapy is also a major cause of immune dysregulation; for example, vincristine is weakly myelosuppressive, and cyclophosphamide and glucocorticoids are strongly myelopsuppressive.

Many chemotherapeutic drugs currently in use in medicine were first identified in plants, including taxol, vinblastine and vincristine, and etoposide and teniposide (Boik, 1996). Herbs offer a rational potential in the treatment of cancer in animals; however, it is important to note that herbs may be used for purposes other than direct antitumor activity. On the other hand, just about any selection of herbs prescribed to treat a patient will more than likely have some anticancer activity because of the presence of widely occurring anticancer constituents like flavonoids.

Although little research has been conducted in cats and dogs specifically, a plethora of research pertains to rats,

mice, hamsters, and guinea pigs. At least pocket pets are amply catered to if they are diagnosed with cancer! Herbs can be used to help manage the effects of chemotherapy; to assist in recuperation after chemotherapy, radiation, or surgery; to complement conventional cancer treatment; to provide an alternative to conventional treatment in some cases; to assist in cancer prevention; and to support various systems that are affected by cancer. One of the approaches used by veterinary herbalists is to treat cancer as a chronic disease, with emphasis on improving the health of the whole body, regardless of the presence of cancer. Anecdotal evidence from veterinary herbalists indicates that herbs offer improved quality of life and may support remission in some cases.

The rational use of herbal medicine for the treatment of patients with cancer depends on a growing understanding of the biological mechanisms by which cancer cells proliferate, maintain life, and die. These include differentiation (the maturation process of cells), angiogenesis (the growth of new blood vessels into tumors), apoptosis (programmed cell death), invasion (the spread of the tumor mass into adjacent tissue), metastasis (the spread of tumor cells to distant locations), mitosis (the proliferation of cells), and evasion of the immune system. As these mechanisms have become elucidated, their weak points have been identified and have become the targets of research that is both conventional and complementary (Boik, 1996). The selection of several herbs that have different mechanisms of action provides a broad spectrum of anticancer activity. A holistic strategy that incorporates all elements discussed here is proposed under "Review of Strategies for Cancer Prescriptions" at the end of this section.

Targets Unique to Neoplastic Cells for Cancer Therapy

- Genetic instability
- Abnormal transcription factor activity
- Abnormal signal transduction
- Abnormal cell-to-cell communication
- Abnormal angiogenesis
- Invasion and metastasis
- Abnormal immune function

Mechanisms of Interest

Antineoplastic/cytotoxic actions

It is logical to select herbs is on the basis of cancer biology. An extremely comprehensive review of anticancer plants and natural compounds is provided in John Boik's book, *Natural Compounds in Cancer Therapy* (2001). This book explains in great detail the mechanisms of action of many plants and their constituents. It is important to note that most herbs have many actions, and this list is merely indicative of the wide range of such mechanisms that have been documented. (Search Medline for more information; use the herb name and cancer or activity as search terms.)

Boik highlights the importance of synergism as a strategy by which lower doses can be used without reduced efficacy; he also discusses the use of herbs with different antineoplastic mechanisms for targeting events that take place in the progression of cancer. Choosing compounds that have direct-acting, indirect-acting, and immune-stimulating activities is likely to inhibit procancer events. Constituents like flavonoids can target multiple aspects of tumor biology.

Adaptogens

This strategy recognizes that a patient can live with cancer as opposed to having to die of cancer. Many of our elderly animal patients, in particular, have never been in better health than when they are on herbal and nutritional treatment, even though they have cancer, because the prescriptions that they are given promote overall health. Herbs should be used to strengthen body resistance, and vitality is enhanced through the use of adaptogens. Most adaptogens also have anticancer activity.

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* Astragalus induces cell differentiation and cell death in vitro (Cheng, 2004) and exerts anticarcinogenic effects through activation of cytotoxic activity and the production of cytokines in mice (Kurashige, 1999).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* The antitumor and radiosensitizing effects of *Withania* have been studied. Growth of carcinoma in mice was inhibited and survival increased with *Withania* treatment, especially when it was combined with radiation (Sharada, 1996). When given before irradiation, it synergistically increased survival, even in mice with advanced tumors (Devi, 1995). Complete regression of sarcoma in mice caused by *Withania* root extract was observed (Devi, 1992).

ELEUTHERO *(ELEUTHEROCOCCUS SENTICOSIS):* This herb was able to inhibit tumor growth and prolong survival time in tumor-bearing mice; these effects were significantly related to enhanced immune response (Xie, 1989). Siberian ginseng appeared to reduce the quantity of conventional antimetabolites that were needed to attain antiproliferative effects on tumor cells in vitro (Hacker, 1984).

ASIAN GINSENG *(PANAX GINSENG):* This herb induces cell differentiation, reduces the effects of chemical carcinogens, mitigates inflammatory carcinogenesis, induces apoptosis, inhibits proliferation, and has proved beneficial in the treatment of a number of cancers in humans (Helms, 2004).

Immune Modulators

Most conventional chemotherapeutic agents are immunosuppressant and cytotoxic in nature, and they exert a variety of adverse effects that are particularly evident in cancer chemotherapy. Botanically based immunomodulators and immune stimulators are employed as supportive or adjuvant therapy to overcome the adverse effects of these agents and to restore normal health. Many of these herbs also have anticancer activity.

Anticancer Mechanism of Selected Herbs and Constituents

Apoptosis Inducers
- Greater celandine *(Chelidonium majus)* (Note: This is a very strong herb that is usually administered topically.)
- Baical skullcap *(Scutellaria baicalensis)*
- Bupleurum *(Bupleurum falcatum)*
- Boswellia *(Boswellia serrata)*
- Turmeric *(Curcuma longa)*
- Saint John's Wort *(Hypericum perforatum)*
- Garlic *(Allium sativum)*
- Flavonoids (apigenin, luteolin, genistein, quercetin, reversatrol)

Differentiation Inducers
- Burdock *(Articum lappa)*
- Boswellia *(Boswellia serrata)*
- Berberine
- Flavonoids (reversatrol, apigenin, luteolin, genistein, quercetin)
- Emodin

Cytotoxic Agents
- Mistletoe *(Viscum album)*
- Limonene
- Emodium

Inhibitors of Angiogenesis

These include herbs and constituents that inhibit increased vascular permeability, or that beneficially affect prostanoid and leukotriene systhesis, or that inhibit mast cell degranulation.
- Butcher's broom *(Ruscus aculeatus)*
- Gotu kola *(Centella asiatica)*
- Horse chestnut *(Aesculus hippocastanum)*
- Garlic *(Allium sativum)*
- Turmeric *(Curcuma longa)*
- Siberian ginseng *(Eleutherococcus senticosis)*
- Ginkgo *(Ginkgo biloba)*
- Picrorrhiza *(Picrorrhiza kurroa)*
- Flavonoids (including proanthocyanidins, anthocyanidins, reversatrol, genistein, apigenin, luteolin, quercetin)
- Emodium

Inhibitors of Local Invasion

These are herbs or constituents that inhibit hyaluronidase and its assistant enzymes or elastase, or that affect collagen or cell migration.
- Gotu kola *(Centella asiatica)*
- Horse chestnut *(Aesculus hippocastanum)*
- Butcher's broom *(Ruscus aculeatus)*
- Turmeric *(Curcuma longa)*
- Panax *(Panax ginseng)*
- Hawthorn (*Crataegus* spp)
- Bilberry *(Vaccinium myrtillus)*
- Dong quai *(Angelica sinensis)*
- Flavonoids (proanthocyanidins, anthocyanidins, apigenin, reversatrol, genistein, luteolin, quercetin)
- Mushroom polysaccharides
- Emodin
- Boswellic acids

Inhibitors of Metastasis

These are herbs or constituents that have anticoagulant activity.
- Aloe succus *(Aloe vera)*
- Green tea *(Camellia sinensis)*
- Cordyceps *(Cordyceps sinensis)*
- Reishi mushrooms *(Ganoderma lucidum)*
- Garlic *(Allium sativum)*
- Panax *(Panax ginseng)*
- Astragalus *(Astragalus membranaceus)*
- Dong quai *(Angelica sinensis)*
- Feverfew *(Tanacetum parthenium)*
- Dan shen *(Salvia miltiorrhiza)*
- Turmeric *(Curcuma longa)*
- Flavonoids (including reversatrol, anthocyanidins, genistein, apigenin, luteolin, quercetin)
- Emodium

Immune-modulating herbs can also be employed when chemotherapy is not used. (See "Immune System Herbs" earlier in this chapter or refer to individual monographs in this book for additional details.)

CORDYCEPS *(CORDYCEPS SINENSIS):* Controlled, open-label clinical studies have found that Cordyceps appeared to restore immune cell function in patients with advanced cancer who were given conventional cancer therapies (Zhou, 1995; Zhu, 1998b). Of 59 patients with advanced lung cancer, 95% were able to complete chemotherapy and radiotherapy with the use of Cordyceps compared with 64% of controls. More than 85% of Cordyceps-treated patients showed more normal blood cell counts versus 59% of controls (Zhu, 1998b). A study in patients with various types of tumors found that a cultured mycelium extract of Cordyceps (6 g/d for over 2 months) improved subjective symptoms in most patients. White blood cell counts were maintained at <3000/mm^3, and tumor size was significantly reduced in approximately half of patients (Zhu, 1998b).

ECHINACEA *(ECHINACEA PURPUREA):* Mice who received dietary Echinacea daily throughout life, from youth until late middle age, demonstrated significant longevity/survival differences, as well as differences in various populations of immune/hematopoietic cells. Key immune cells, acting as the first line of defense against developing neoplasms and natural killer (NK) cells, were significantly elevated in absolute number in their bone marrow production site, as well as in the spleen. Cells of the myeloid/granulocyte lineages remained at control

levels in the bone marrow and the spleen in Echinacea-consuming mice. Thus, it appears that regular intake of Echinacea may indeed be beneficial or prophylactic because it maintains elevated levels of NK cells, which are elements in immunosurveillance against spontaneously developing tumors (Brousseau, 2005).

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* The efficacy of this herb in enhancing quality of life and reducing the toxicity of chemotherapy in human patients with malignant tumors was investigated. Astragalus (by injection) supplemented by chemotherapy was noted to inhibit the development of tumors, decrease the toxic or adverse effects of chemotherapy, elevate immune function, and improve quality of life in treated patients (Duan, 2002).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* This herb demonstrates antitumor properties in mice and protects against induced carcinogenic effects. It also reverses the adverse effects of a carcinogen (urethane) on total leukocyte count, lymphocyte count, body weight, and mortality (Singh, 1986). Significant increases in hemoglobin; red blood cell, white blood cell, and platelet count; and body weight were observed in cyclophosphamide-, azathioprine-, and prednisolone-treated mice that were given *Withania* versus controls (Ziauddin, 1996).

OTHER HERBS

- Siberian ginseng *(Eleutherococcus senticosis)*
- Cat's claw *(Uncaria tomentosa)*
- Pau d'arco *(Tabebuia avellanedae)*
- Shitake and Reishi mushrooms

Alteratives

In traditional herbal medicine, alteratives represent a key strategy for the treatment of cancer. Alteratives act through the lymphatic, blood, and eliminatory systems to facilitate and enhance the breakdown and removal of metabolic wastes. They are also used to improve the absorption and assimilation of nutrients. Alteratives are thus considered to be "blood purifiers" or "detoxifiers", believed to circulate and improve blood flow, while removing waste from blood and lymph. The function of these herbs is to optimize the body's eliminative functions performed via the liver, kidneys, lungs, and gastrointestinal system.

Ideally, these herbs are chosen according to their other actions and affinities for particular organs or systems, so as to maximize their benefit. For example, poke root and cleavers are specific for the lymphatic system. Many of these herbs contain alkaloids and flavonoids and have documented anticancer activity; many others have not been studied. Modifying prescriptions every 2 to 3 months reduces the risk of potential toxicity associated with some of these herbs.

Alteratives include the herbs listed here:

BURDOCK *(ARTICUM LAPPA):* Differentiation-inducing activities have been demonstrated against mouse myeloid leukemia cells. The most active derivative induced more than half of leukemia cells to become phagocytic cells (Umehara, 1996).

DANDELION ROOT *(TARAXACUM OFFICINALE):* In vitro antitumor activity has been documented for an aqueous extract of dandelion. The mechanism of action was thought to be similar to that of tumor polysaccharides such as lentinan (Baba, 1981).

SHEEP SORREL *(RUMEX ACETOSELLA):* One study found that *Rumex acetosella* polysaccharide displayed antitumor activity in mice that were implanted with sarcoma (180 solid tumors) (Ito, 1986).

OREGON GRAPE *(MAHONIA AQUIFOLIUM):* Berberine has anticancer activity and exhibits the ability to induce apoptosis in leukemia cells (Kuo, 1995; Yang, 1996). In addition, some protoberberines are highly effective as cytotoxic agents against several carcinoma lines; berberine consistently showed the highest cytotoxicity among the alkaloids tested (Cernakova, 2002).

OTHER HERBS

- Barberry *(Berberis vulgaris)*
- Echinacea *(Echinacea pupurea)*
- Stillingia *(Stillingia sylvatica)*
- Yellow dock *(Rumex crispus)*
- Poke root *(Phytolacca decandra)*
- Cleavers *(Gallium aparine)*
- Red clover *(Trifolium pratense)*

Antioxidants

Herbs with potent antioxidant activity generally have anticancer activity as well. Whether to use antioxidants concurrently with chemotherapy or radiotherapy has been questioned. Chemotherapy and radiotherapy cause DNA damage to both normal cells and cancer cells by causing free radical damage; one concern is that antioxidants will reduce the efficacy of treatment. On the other hand, antioxidants protect healthy tissue from damage, and after and between conventional treatment, antioxidants continue to offer benefit as anticancer agents themselves. Anecdotal evidence provided by veterinary herbalists indicates that herbal antioxidants can continue to be used alongside conventional treatment without adversely affecting the outcome.

GREEN TEA *(CAMELLIA SINENSIS):* Green tea polyphenols in mice increased antioxidant levels and glutathione peroxidase, catalase, and quinine reductase in skin, small bowel, liver, and lungs. These combined activities make green tea an effective chemopreventive agent against the initiation, promotion, and progression of multistage carcinogenesis (Katiyar, 1997). Human clinical trials suggest that the concentrated extract EGCG (epigallocatechin gallate), dosed at approximately 200 mg daily, is most efficient at improving blood antioxidant levels.

REDGRAPE *(VITIS VINIFERA):* Resveratrol, a phytoalexin found in red wine, inhibits the metabolic activation of carcinogens, has antioxidant and anti-inflammatory properties, decreases cell proliferation, and induces apoptosis (Bianchini, 2003; Granados-Soto, 2003). Oligomeric proanthocyanidins (OPCs) increased NK cell cytotoxicity, modulated levels of interleukins from immune compromised mice (including those

infected with retrovirus) (Cheshier, 1996), and demonstrated antimutagenic activity in vitro (Seo, 2001).

HAWTHORN *(CRATAEGUS SPP):* Crataegus contains OPCs, and much of what is known about grape seed extract applies to Crataegus.

MILK THISTLE *(SILYBUM MARIANUM):* Silymarin and silibinin (silybin) are antioxidants that react with free radicals, transforming them into more stable, less reactive compounds (Morazzoni, 1995). The cancer chemoprevention and anticarcinogenic effects of silymarin have been shown to be caused by its major constituent, silibinin (Bhatia, 1999). Its antitumor effect occurs primarily at stage I tumor promotion; silymarin may act by inhibiting COX-2 and IL-1α (Zhao, 1999). Such effects may involve inhibition of promoter-induced edema, hyperplasia, the proliferation index, and the oxidant state (Lahiri-Chatterjee, 1999). Silibinin may also have antiangiogenic effects (Yang, 2005; Singh, 2005).

TURMERIC *(CURCUMA LONGA):* The abilities of turmeric to scavenge radicals, reduce iron complex, and inhibit peroxidation may explain the possible mechanisms by which turmeric exhibits its beneficial effects in medicine (Tilak, 2004). The anticancer properties of curcumin have been demonstrated in cultured cells and animal studies. Curcumin inhibits lipoxygenase activity and is a specific inhibitor of COX-2 expression. It halts carcinogenesis by inhibiting cytochrome P450 enzyme activity and increasing levels of glutathione-S-transferase (Chauhan, 2002).

DAN SHEN *(SALVIA MILTIORRHIZA):* Dan shen is a potent antioxidant that demonstrates free radical scavenging activity (Xia, 2003). Recent studies showed that one of its tanshinone constituents possesses cytotoxic activity against many kinds of human carcinoma cell lines, induces differentiation and apoptosis, and inhibits invasion and metastasis of cancer cells. Its mechanisms are believed to be inhibition of DNA synthesis and proliferation of cancer cells; regulation of the expression of genes related to proliferation, differentiation, and apoptosis; inhibition of the telomerase activity of cancer cells; and change in the expression of cellular surface antigen (Yuan, 2003).

BILBERRY *(VACCINIUM MYRTILLUS):* The anthocyanosides in bilberry inhibit protein and lipid oxidation (Morazzoni, 1995). Components of bilberry have been reported to exhibit potential anticarcinogenic activity in vitro, as demonstrated by inhibition of the induction of ornithine decarboxylase (ODC) by the tumor promoter phorbol 12-myristate 13–acetate (TPA) (Bomser, 1996).

SCHISANDRA *(SCHISANDRA CHINENSIS):* Schisandra lignans act as free radical scavengers and inhibit iron-induced lipid peroxidation and superoxide anion production (Lu, 1992). Geranylgeranoic acid, a constituent of Schisandra, has been shown to induce apoptosis in a human hepatoma–derived cell line (Shidoji, 2004).

GINKGO *(GINKGO BILOBA):* This leaf extract has significant antioxidant activity because of its flavonoid and terpenoid components. Recent studies with various models show that the anticancer properties of Ginkgo are related to antioxidant, antiangiogenic, and gene-regulatory actions. Antiangiogenic activity may involve antioxidant activity and the ability to inhibit both inducible and endothelial forms of nitric oxide synthase. Exposure of human breast cancer cells to a Ginkgo extract altered expression of the genes involved in the regulation of cell proliferation, cell differentiation, or apoptosis. Exposure of human bladder cancer cells to a Ginkgo extract produces an adaptive transcriptional response that augments antioxidant status and inhibits DNA damage. Flavonoid and terpenoid constituents of Ginkgo extracts may act in a complementary manner to inhibit several carcinogenesis-related processes; therefore, the total extracts may be required for optimal effects (DeFeudis, 2003).

GINGER *(ZINGIBER OFFICINALE):* Some pungent constituents in ginger and other zingiberaceous plants such as gingerol have potent antioxidant and anti-inflammatory effects, and some of them exhibit antitumor promotional activity in experimental carcinogenesis (Surh, 1998). The chemopreventive effects are probably associated with antioxidative and anti-inflammatory activities (Surh, 1998).

ROSEMARY *(ROSMARINUS OFFICINALIS):* Several extracts and constituents of rosemary have exhibited antioxidant activity (ESCP, 1999). The volatile oil was reported to be toxic to leukemia cells (Ilarionova, 1992). Topical administration of a methanol extract 5 minutes before application of carcinogens to the dorsal surface of mice reduced the irritation and promotion of tumors. Application of rosemary extract before carcinogen application reduced the formation of metabolite–DNA adducts by 30% and 54%, respectively (Huang, 1994). In rats, dietary supplementation with 1% rosemary extract for 21 weeks reduced the development of induced mammary carcinoma in the treated group, compared with the control group (40% vs 75%, respectively) (Singletary, 1991).

Analgesics

Cancer patients suffering pain may be administered anti-inflammatory, antispasmodic, and analgesic herbs as necessary. A review of these herbs can be found in the section on neurology, pain, and behavior.

Platelet-Activating Factor Inhibitors

Platelet-activating factor (PAF) is an ether-linked phospholipid that has been postulated to be a stimulator of malignant tumor growth; it may be significant in the early stages of tumor development.

GINKGO *(GINKGO BILOBA):* Ginkgolides have been reported to competitively inhibit the binding of PAF to its membrane receptor (Braquet, 1987).

Anticachectic Activity

COPTIS *(COPTIS CHINENSIS):* This herb was investigated in mice bearing colon carcinoma cells that cause IL-6–related cachexia after cell injection. Coptis significantly attenuated weight loss in tumor-bearing mice compared with controls, without changing food intake or tumor growth. It was therefore shown to exert an anticachectic

effect associated with tumor IL-6 production, and it was suggested that this effect might be due to berberine (Iizuka, 2002).

Anticancer Action by Organ/System

Following is a brief review of just some of the herbs that may be beneficial for the treatment of particular organ/system cancers. It is intended as a starting point rather than a comprehensive review. In vivo studies are discussed; herbs that are supported by in vitro studies are only listed.

Respiratory system: small cell lung carcinoma

CHASTE TREE *(VITEX AGNUS-CASTUS):* Metastasis (Ohyama, 2003).

GRAPE SEED *(VITIS VINIFERA):* Oral administration of grapeseed extract reduced the number of metastatic nodules induced in mice by 26.07% compared with a control group treated with ethanol (Martinez 2005).

GREEN TEA AND BLACK TEA *(CAMELLIA SINENSIS):* Consumption of tea (Camellia sinensis) has been suggested to prevent cancer, heart disease and other diseases. Animal studies have shown that tea and tea constituents inhibit carcinogenesis of the skin, lung, oral cavity, esophagus, stomach, liver, prostate and other organs (Lambert 2003). For example, mice were given decaffeinated green or decaffeinated black tea in their drinking water before, during, and after treatment with a carcinogen. Mice that received 0.63% or 1.25% green tea, or 1.25% black tea, exhibited a reduction in liver tumor numbers of 54%, 50%, and 63%, and a decrease in the mean number of lung tumors of 40%, 46%, and 34%, respectively, compared with controls (Cao 1996). In some experiments, reduction in tumor number and size has been observed in the tea-treated groups; in other experiments, decreased tumor incidence has also been observed (Yang 2005). Black tea preparations have been shown to reduce the incidence and number of spontaneously generated lung adenocarcinomas and rhabdomyosarcomas in mice; they also were noted to inhibit the progression of lung adenoma to adenocarcinoma. In many of these experiments, tea consumption resulted in reduced body fat and body weight; these factors may also contribute to the inhibition of tumorigenesis (Yang, 2005).

CRUCIFEROUS VEGETABLES: Feeding mice diets enriched in dried cruciferous vegetables (cabbage and collards) resulted in a significant decrease in the number of pulmonary metastases after the animals had been injected intravenously with mammary tumor cells. Cruciferous vegetables may be beneficial in cancer prevention (Scholar, 1989).

FLAXSEED *(LINUM USITATISSIMUM):* Mice were fed a basal diet, or the basal diet supplemented with 2.5%, 5%, or 10% flaxseed, for 2 weeks before and after an intravenous injection of 0.75×10^5 melanoma cells. The median number of tumors in mice fed the 2.5%, 5%, and 10% flaxseed-supplemented diets was 32%, 54%, and 63% lower, respectively, than that in controls. The addition of flaxseed to the diet also caused a dose-dependent decrease in tumor cross-sectional area and tumor volume. Flaxseed reduces metastasis and inhibits the growth of metastatic secondary tumors in animals (Yan, 1998).

Reproductive system: mammary carcinoma

CALENDULA *(CALENDULA OFFICINALIS):* In a study of mice fed for 3 weeks a diet containing a calendula extract (high in the carotenoid lutein), mammary tumor cells were infused into the mammary glands. Tumor latency increased and tumor growth was inhibited in a dose-dependent manner by dietary lutein. In addition, dietary lutein was reported to enhance lymphocyte proliferation (Chew, 1996).

CHASTE TREE *(VITEX AGNUS-CASTUS):* (Ohyama, 2003).

GARLIC *(ALLIUM SATIVUM):* Organosulphur compounds markedly inhibited growth of canine mammary cells in culture (Sundaram, 1993).

GRAPESEED: Procyanidins in grapeseed could be used as chemopreventive agents against breast cancer through suppression of in situ estrogen biosynthesis (Eng, 2003).

MILK THISTLE *(SILYBUM MARIANUM):* (Bhatia, 1999).

FLAXSEED *(LINUM USITATISSIMUM):* This herb is the richest source of lignans and α-linolenic acid; it was investigated regarding its effects on the growth and metastasis of established human breast cancer in a mice model. Compared with controls, those supplemented with 10% flaxseed showed a significant reduction in tumor growth rate and a 45% reduction in total incidence of metastasis. Lung metastasis incidence was 55.6% in the control group and 22.2% in the flaxseed group; the incidence of lymph node metastasis was 88.9% in controls and 33.3% in the flaxseed group. Metastatic lung tumor number was reduced by 82% in the flaxseed group. It was concluded that flaxseed inhibits human breast cancer growth and metastasis in a mouse model, and that this effect is due in part to the downregulation of insulin-like growth factor I and epidermal growth factor receptor expression (Chen, 2002).

Urogenital system

Kidney Cancer

BLACK CUMIN *(NIGELLA SATIVA):* This herb provides a chemopreventive effect against induced renal carcinogenesis. Treatment of rats orally with black cumin (50 and 100 mg/kg body weight) resulted in significant decreases in blood urea nitrogen and serum creatinine, as well as in the incidence of tumors (Khan, 2005).

MISTLETOE *(VISCUM ALBUM):* Extracts of mistletoe plant have been used for decades in cancer therapy for nonspecific stimulation of the immune system. Mistletoe lectin has been identified as the active principle with cytotoxic and immunomodulatory potencies. An aqueous mistletoe extract was investigated in renal cell carcinoma, colon carcinoma, and testicular carcinoma. After induction of these tumors, mice were treated with the extract at dose levels corresponding to 0, 0.3, 3, 30, or 300 ng mL/kg/d by the intraperitoneal or subcutaneous route for 4 consecutive weeks. Significant tumor growth

inhibition was observed with these carcinomas at 30 and 300 ng mL/kg/d (Burger, 2001).

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS)* AND CNIDIUM *(LIGUSTRUM LUCIDUM):* Renal cell carcinomas were planted in mice. One group was treated intraperitoneally daily for 10 days with 100 microliters of phytochemicals that contained 500 micrograms each of *Astragalus membranaceus* and *Ligustrum lucidum;* the other group (controls) received saline. A "cure rate" of 57% was obtained with these phytochemicals, which may have exerted their antitumor effects via augmentation of phagocyte and lymphokine-activated killer (LAK) cell activities (Lau, 1994).

Bladder Cancer

KAVA *(PIPER METHYSTICUM):* Flavokawains identified in kava cause strong antiproliferative and apoptotic effects in human bladder cancer cells. The anticarcinogenic effects of flavokawain A were evident in the inhibitory growth (57% inhibition) of bladder tumor cells in a nude mouse model (Zi, 2005).

GARLIC *(ALLIUM SATIVUM):* *Allium sativum* was investigated in induced transitional cell carcinoma in mice. Orally administered *Allium sativum* was tested at doses of 5 mg, 50 mg, and 500 mg per 100 mL of drinking water. Mice that received 50 mg/dl oral *Allium sativum* demonstrated significant reductions in tumor volume when compared with controls, and mice that received 500 mg/dl oral *Allium sativum* exhibited significant reductions in both tumor volume and mortality (Riggs, 1997).

Prostate Cancer

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* The antiproliferative effects of serotonin reuptake inhibitors and serotonin antagonists have been demonstrated in prostate tumors. Because Saint John's Wort components act as serotonin reuptake inhibitors and exert cytotoxic effects on several human cancer cell lines, the effects of treatment with Saint John's Wort extract on the growth of human prostate cancer cells in vitro and in vivo were examined. This study highlighted a significant reduction in tumor growth and in the number of metastases, suggesting that Saint John's Wort may be useful in the treatment of patients with prostate cancer (Martarelli, 2004).

MILK THISTLE *(SILYBUM MARIANUM):* (Bhatia, 1999).

RED CLOVER *(TRIFOLIUM PRATENSE):* (Jarred, 2002).

Neurologic system

BOSWELLIA *(BOSWELLIA SERRATA):* Two observational reports of patients undergoing treatment for brain tumor suggest that boswellia extract may assist in reducing cerebral edema (Streffer, 2001; Janssen, 2000). Experimental and in vitro studies showed that boswellia extract may slow growth and increase apoptosis of tumor cells implanted in the brains of experimental animals (Winking, 2000).

CANNABIS *(Cannabis sativa):* Gliomas are brain tumors that are common in humans. Several studies have shown that cannabinoids—active components of the plant *Cannabis sativa* and their derivatives—slow the growth of different types of tumors, including gliomas, in laboratory animals. Cannabinoids induce apoptosis of glioma cells in culture and inhibit angiogenesis in vivo. It is remarkable that cannabinoids kill glioma cells selectively and can protect nontransformed glial cells from death (Velasco, 2004).

ALOE VERA AND MELATONIN: A clinical study evaluated whether the concomitant administration of aloe may enhance the therapeutic results of melatonin in patients with advanced solid tumor for whom no effective standard anticancer therapies are available. This study included 50 patients with lung cancer, gastrointestinal tract tumor, breast cancer, or brain glioblastoma, who were treated with melatonin alone (20 mg/d orally in the dark period) or melatonin plus A*loe vera* tincture (1 mL twice/d). The percentage of nonprogressing patients was significantly higher in the group treated with melatonin plus aloe than in the melatonin group (14/24 vs 7/26). The 1-year survival percentage was significantly higher in patients treated with melatonin plus aloe (9/24 vs 4/26). Both treatments were well tolerated. The combination may produce some therapeutic benefits, at least in terms of stabilization of disease and survival, in patients with advanced solid tumor, for whom no other standard effective therapy is available (Lissoni, 1998).

MISTLETOE *(VISCUM ALBUM):* Patients with malignant glioma were prospectively enrolled in a clinical trial. The treatment group received a galactoside-specific lectin from mistletoe, called ML-1. Analyses of all patients revealed prolongation of relapse-free intervals/overall survival time for the treatment group as compared with the control group (Lenartz, 2000).

Musculoskeletal system

Osteosarcoma

RED CLOVER *(TRIFOLIUM PRATENSE L.):* Extracts were tested for their ability to stimulate the activity and maturation of osteoblastic osteosarcoma cells. Alkaline phosphatase was chosen as a marker of osteoblasticity. In vitro data clearly suggest a role for red clover isoflavonoids (Chloroform extract) in the stimulation of osteoblastic cell activity and cell differentiation (Wende, 2004).

DIOSGENIN (FOUND IN TRILLIUM, FENUGREEK, AND WILD YAM): This phytochemical was investigated in vitro to determine its effects on proliferation rate, cell cycle distribution, and apoptosis in the human osteosarcoma cell line. Diosgenin treatment resulted in inhibition of cell growth, with a cycle arrest in G1 phase, apoptosis induction, and induced cyclooxygenase activity (Moalic, 2001).

POKEWEED *(PHYTOLACCA AMERICANA):* The plant hemitoxin, pokeweed antiviral protein (PAP), was conjugated to pokeweed extract (TP-3) to produce an immunotoxin that was highly active against osteosarcoma. In vitro studies suggest that it may be useful in the treatment of patients with osteosarcoma and some soft tissue sarcomas (Anderson, 1995). In vivo, TP-3 elicits potent antitumor activity in a hamster cheek pouch model of human osteosarcoma. At nontoxic dose levels, it significantly delays the emergence and progression of leg

tumors and markedly improves tumor-free survival in severe combined immunodeficient mice challenged with human osteosarcoma cells. Thus, it may be useful in the treatment of patients with osteosarcoma (Ek, 1998).

Fibrosarcoma

WORMWOOD *(ARTEMISIA ANNUA):* This herb contains artemisinin, which has been shown to selectively kill cancer cells in vitro and retard the growth of implanted fibrosarcoma tumors in rats. In vitro, it rapidly induces apoptosis in cancer cells (Singh, 2004).

ALOE *(ALOE VERA):* Acemannan is the name given to the major carbohydrate fraction obtained from the gel of the *Aloe vera* leaf. Injection of acemannan has been shown to offer increased immune protection against implanted malignant tumor cells (Merriam, 1995). Acemannan in the presence of interferon-gamma (IFN-γ) induces apoptosis in cancer cells (Ramamoorthy, 1998). It is conditionally licensed by the US Department of Agriculture (USDA) for the treatment of dogs and cats with fibrosarcoma (King, 1995). A total of eight dogs and five cats with histopathologically confirmed fibrosarcoma were treated with acemannan in combination with surgery and radiation therapy. Following four to seven weekly treatments, tumor shrinkage occurred in 4 of 12 animals. Complete surgical excision was performed on all animals between 4 and 7 weeks after initiation of acemannan therapy. Radiation therapy was instituted immediately after surgery. Acemannan treatments were continued monthly for 1 year. In all, 7 of 13 animals were alive and tumor free (range, 440+ to 603+ days), with a median survival time of 372 days. Acemannan may be an effective adjunct to surgery and radiation therapy in the treatment of canine and feline fibrosarcomas (King, 1995). A total of 43 dogs and cats with spontaneous tumor were treated with acemannan by intraperitoneal and intralesional routes of administration. Tumors from 26 of these animals showed marked necrosis or lymphocytic infiltration. Moderate to marked tumor necrosis or liquefaction was noted in 13 animals. In all, 21 demonstrated lymphoid infiltration, and 7 demonstrated encapsulation. A total of 12 animals showed obvious clinical improvement, as assessed by tumor shrinkage, tumor necrosis, or prolonged survival; these included five of the seven animals with fibrosarcoma. It is believed that acemannan exerts its antitumor activity through macrophage activation and the release of tumor necrosis factor, IL-1, and interferon (Harris, 1991).

Rhabdomyosarcoma

GREEN TEA AND BLACK TEA *(CAMELLIA SINENSIS):* Black tea preparations have been shown to reduce the incidence and number of spontaneously generated lung adenocarcinomas and rhabdomyosarcomas in mice (Yang, 2005).

Gastrointestinal tract

ASIAN GINSENG *(PANAX GINSENG):* In case control studies, cancers of lip, oral cavity and pharynx, larynx, lung, esophagus, stomach, liver, pancreas, ovary, and colorectum were significantly reduced through Panax consumption. As to the type of ginseng, cancer was reduced in users of fresh ginseng extract, white ginseng extract, white ginseng powder, and red ginseng. *Panax ginseng* has non–organ specific cancer preventive effects against various cancers primarily because of its ginsenosides (Yun, 2003).

Oral Tumors

BLACK TEA *(CAMELLIA SINENSIS):* An open study in people with oral leukoplakia treated with black tea showed a treatment benefit. Several in vitro and animal studies have suggested the efficacy of tea in the chemoprevention of cancer (Halder, 2005).

GREEN TEA *(CAMELLIA SINENSIS):* In induced squamous cell carcinoma (SCC) in vivo in hamsters, 0.6% green tea powder as drinking fluid or 10 μmol curcumin or combination or nothing (control) was applied topically 3 times weekly for 18 weeks. The combination decreased the incidence, number, and size of SCC and precursor tumors. This activity may be related to suppression of cell proliferation, induction of apoptosis, and inhibition of angiogenesis (Li, 2002).

TURMERIC *(CURCUMA LONGA):* This herb and its active principle, curcumin, have been extensively investigated for their antimutagenic and antioxidant effects in bacterial and animal systems. Turmeric or curcumin or a combination of the two was administered to hamsters in the diet or applied locally for 14 weeks, along with a carcinogen. Tumor number and tumor burden were significantly lower in the animals that received turmeric in the diet and had it applied locally. Histopathologic neoplastic grading was least in the animals fed or painted with curcumin. Turmeric or curcumin in the diet or applied as paint may have a chemopreventive effect on oral precancerous lesions (Krishnaswamy, 1998).

BLACK RASPBERRY *(RUBUS OCCIDENTALIS):* Black raspberries were shown to inhibit oral cavity tumors in hamsters fed 5% and 10% lyophilized black raspberries (LBRs) in the diet for 2 weeks before treatment with a known carcinogen and for 10 weeks thereafter. A significant difference was observed in the number of tumors between the 5% LBR and control groups (27 tumors/14 animals and 48 tumors/15 animals, respectively); an intermediate number of tumors in the 10% berry-treated animals (39 tumors/15 animals) showed that dietary black raspberries inhibit tumor formation in the oral cavity (Casto, 2002).

GARLIC *(ALLIUM SATIVUM):* Administration of garlic (250 mg/kg orally, three times a week) effectively suppressed induced tongue carcinogenesis in rats, as revealed by the absence of carcinomas in the initiation phase and their reduced incidence in the postinitiation phase. Garlic may exert its chemopreventive effects by modulating lipid peroxidation and enhancing the levels of glutathione (GSH), GSH peroxidase, and GSH S-transferase (Balasenthil, 2001).

GINKGO *(GINKGO BILOBA):* This extract induces apoptosis in oral cavity cancer cells (Kim, 2005).

POKEWEED *(PHYTOLACCA AMERICANA):* A pilot study of pokeweed mitogen immunotherapy in pets was conducted. One case reports 3-year remission and apparent cure of gum melanoma metastatic to regional and hilar lymph nodes and to the lungs in an aged dog following pokeweed mitogen therapy. A small total dose of

300 µg induced the remission. However, melanoma may be a uniquely responsive tumor (Wimer, 2000).

NEEM *(AZADIRACHTA INDICA)*: This aqueous extract of neem leaf extract effectively suppressed induced oral carcinogenesis (squamous cell carcinomas in hamsters), as revealed by a reduced incidence of neoplasms. Neem may exert its chemopreventive effects in the oral mucosa through modulation of lipid peroxidation, antioxidants, and detoxification systems (Balasenthil, 1999).

TOMATO *(LYCOPERSICON ESCULENTUM)*: Tomato paste containing lycopene at concentrations of 2.5, 5, or 10 mg/kg body weight was given to hamsters three times per week on days alternate to carcinogen application. Tomato paste containing 5 mg lycopene per kg of body weight exhibited chemopreventive effects that were caused by modulation of lipid peroxidation and enhancement of antioxidants in the target organ, as well as in the liver and erythrocytes (Bhuvaneswari, 2004a). Combined administration of tomato and garlic during induced SCC in hamsters significantly inhibited the development of carcinomas and induced apoptosis (Bhuvaneswari, 2004b).

Gastric Cancer

GINGER *(ZINGIBER OFFICINALIS)*: This herb inhibits the growth of *Helicobacter pylori,* which is a causative agent associated with the development of gastric and colon cancers and may contribute chemopreventive effects (Mahady, 2003).

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS)*: Root specifically inhibits gastric cancer cells growth in vitro and the mechanism is mainly cytostatic but not cytotoxic or inducing apoptosis (Lin 2003).

Colon Cancer

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM)*: These seeds in the diet inhibit colon carcinogenesis in rats by modulating the activities of β-glucuronidase and mucinase. Beneficial effects may be attributed to the presence of fiber, flavonoids, or saponins (Devasena, 2003).

GINSENG: The powder was investigated in an induced rat colon cancer model. Diets containing quercetin, curcumin, silymarin, ginseng, and rutin decreased the number of aberrant cells by 4-, 2-, 1.8-, 1.5-, and 1.2-fold, respectively, compared with controls. All herbal supplements, except silymarin, induced apoptosis, with quercetin being the most potent (3× increase compared with control). Furthermore, ginseng and curcumin were region specific in inducing apoptosis. Taken together, these results suggest that these herbs may exert beneficial effects on decreasing the number of precancerous lesions and inducing apoptosis in the large intestine (Volate, 2005).

Liver Cancer

WHITE PEONY *(PAEONIA LACTIFLORA)*: This herb induced apoptosis in vitro in hepatoma cell lines (Lee, 2002).

CURCUMIN (EXTRACT OF *CURCUMA LONGA*): Curcumin has been studied for its ability to suppress hepatic tumor growth and metastasis in laboratory animals. In a mouse model of hepatocellular carcinoma, daily oral curcumin administration (3000 mg/kg) significantly attenuated tumor capillary growth (Yoysungnoen, 2005). Rats bearing an ascites hepatoma were given curcumin (20 mcg/kg) and tumor growth appeared inhibited (Busquets, 2001). In animals implanted with hepatocellular carcinoma cells and administered curcumin, metastasis was suppressed dose dependently (Ohashi, 2003).

GREEN TEA AND BLACK TEA *(CAMELLIA SINENSIS)*: (Yang, 2005).

PANAX *(PANAX GINSENG)*: (Yun, 2003).

Haematopoietic system

Leukemia

ECHINACEA *(ECHINACEA PURPUREA)*: Leukemia was induced in 4-week-old female mice predisposed to developing leukemia, and the animals were given powdered *Echinacea purpurea* leaves orally three times weekly for 8 weeks (7.5 mg/mouse/wk). Survival was significantly prolonged and enlargement of thymic lymphoma was significantly suppressed compared with controls. Proliferation of leukemia (MuLV) viruses in the thymus was markedly inhibited as compared with untreated controls after the first oral administration of the *E. purpurea* preparation. Endogenous IFN-γ was also effectively augmented with Echinacea; however, the production of other cytokines such as tumor necrosis factor (TNF)-α and IL-12 was minimal. Thus, suppressive effects on MuLV may depend on enhancement of nonspecific immune or cellular immune systems (or both) by Echinacea (Hayashi, 2001). Daily dietary administration of *E. purpurea* root extract to normal mice for as little as 1 week also resulted in significant elevations in NK cells (immune cells that are cytolytic to virus-containing cells and many tumor cells). Such boosting of this fundamental immune cell population suggests a prophylactic role for this herb in normal animals (Currier, 2001). *E. purpurea*–treated mice exhibited a 2.5-fold increase in the absolute numbers of NK cells in their spleens. By 3 months after leukemia induction, *E. purpurea*–treated mice still had 2 to 3 times the normal numbers of NK cells in their spleens compared with controls. No leukemic, untreated (control) mice remained alive at 3 months; however, at 3 months after tumor onset, all major hematopoietic and immune cell lineages in the bone marrow birth site were recorded at normal numbers in *E. purpurea*–consuming, leukemic mice. The survival advantage provided by administration of *E. purpurea* to these leukemic mice versus untreated mice was highly significant (Currier, 2001).

ACEMANNAN (EXTRACT OF *ALOE VERA*): Administration of acemannan for 6 weeks intraperitoneally to clinically symptomatic cats significantly improved both quality of life and survival rate. It was noted that 12 weeks after initiation of treatment, 71% of treated cats were alive and in good health (Sheets, 1991).

Myeloma

BAICAL SKULLCAP *(SCUTELLARIA BAICALENSIS)*: (Ma 2005).

Lymphoma/Lymphosarcoma

MISTLETOE *(VISCUM ALBUM)*: This extract given as subcutaneous applications (3 times per week for 14 consecutive days; 2, 20, 100, and 500 µg/injection per mouse) upregulated thymocyte and peripheral blood leukocyte

counts in tumor-bearing mice. Tumor weight and tumor volume were reduced with doses greater than 20 µg. Injections protected against metastasis of introduced lymphosarcoma and sarcoma cells (Braun, 2002). In another study, non-Hodgkin's lymphoma was induced in mice. One group was fed mistletoe-containing diets (10 mg lectin daily); the other group, a control diet. Diet produced several identifiable changes in morphology and size of non-Hodgkin's lymphoma tumors. In 4 of 15 mice fed the mistletoe-containing diet for 11 days, no evidence of viable tumor was apparent. Results show that this lectin exerts powerful antitumor effects when provided by the oral route (Pryme, 2004).

CAT'S CLAW *(UNCARIA TOMENTOSA):* (Sheng 1998).

GOTU KOLA *(CENTELLA ASIATICA, L.):* Oral administration of crude extract retarded the development of solid and lymphoma ascites tumor and increased the life span of tumor-bearing mice (Babu, 1995).

CORDYCEPS *(CORDYCEPS SINENSIS):* This extract was given orally to mice implanted with lymphoma cells; it reduced tumor size and prolonged mouse survival time. Mice treated with cyclophosphamide (100 mg/kg) 3 and 5 days after tumor transplantation had their immune suppression restored through treatment (Yamaguchi, 1990).

TURKEY TAIL MUSHROOM *(CORIOLUS VERSICOLOR):* (Lau 2004).

BITTER MELON *(MOMORDICA CHARANTIA):* Studies have shown activity in various diseases, including numerous cancers (lymphoid leukemia, lymphoma, choriocarcinoma, melanoma, breast cancer, skin tumor, prostatic cancer, squamous carcinoma of tongue and larynx, human bladder carcinoma, and Hodgkin's disease). Few reports on clinical use in patients with cancer show promising results (Grover, 2004).

INDIAN LONG PEPPER *(PIPER LONGUM):* Alcoholic extract of *Piper longum* (10 mg/animal) inhibited solid tumor development in mice induced with lymphoma and increased the life span of mice bearing carcinoma to 37.3% and 58.8%, respectively (Sunila, 2004).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* Ethanolic root extract provided a significant increase in life span and a decrease in cancer cell number and tumor weight in lymphoma tumor–induced mice. Hematologic parameters were also corrected by *Withania* in tumor-bearing mice (Christina, 2004). *Withania somnifera* possesses cell cycle disruption and anti-angiogenic activity, confirmed *in vitro* and *in vivo,* which may be a mediator for its anticancer action (Mathur 2006).

CURCUMIN *(FROM CURCUMA LONGA):* This herb inhibits cell proliferation and induces apoptosis in a dose-dependent manner in vitro in several primary effusion lymohoma cell lines (Uddin, 2005).

Popular "Anticancer" Herbal Remedies

Iscador, helixor, and eurixor *(Viscum album)*

The primary use of mistletoe is as a palliative cancer therapy. Iscador is a fermented aqueous extract of *Viscum album* that is marketed as IscadorM (from apple trees), IscadorP (from pine trees), IscadorQ (from oak trees), and IscadorU (from elm trees). Helixor is an unfermented aqueous extract of *V. album* L. that is standardized through its biological effects on human leukemia cells in vitro; it is marketed as HelixorA (from spruce trees), HelixorM (from apple trees), and HelixorP (from pine trees). Eurixor is an unfermented aqueous extract of *V. album* L. that is harvested from poplar trees *(V. album).* These extracts are administered parenterally and may cause inflammation at injection sites. The antineoplastic activity of *V. album,* Helixor, and Iscador is documented in vitro and in vivo, and mistletoe preparations have proved effective in fighting solid tumors in eight of ten animal studies (seven in mice, three in rats); in two studies, they significantly inhibited metastasis and reduced tumor volume. In two negative studies, ML did not inhibit chemically induced bladder cancer (Loeper, 1999).

Iscador is an injectable extract of mistletoe (SC 0.045 mg/kg equivalent to lectin concentration of 3.5 ng/kg) (Schramm, 2001). Although Iscador is regarded as a complementary cancer therapy, it is the most commonly used oncologic drug in Germany (Grossarth-Maticek, 2001). A prospective, nonrandomized and randomized, matched-pair study nested within a cohort study was conducted in Germany. A total of 10,226 human patients with cancer were involved in a prospective, long-term, epidemiologic cohort study that included 1668 patients treated with Iscador and 8475 who had taken neither Iscador nor any other mistletoe product (control patients). In the nonrandomized, matched-pair study, the survival times of patients treated with Iscador were longer for all types of cancer studied. In the pool of 396 matched pairs, mean survival times in the Iscador groups (4.23 years) were roughly 40% longer than in control groups. Iscador treatment can achieve a clinically relevant prolongation of survival time for patients with cancer and appears to stimulate self-regulation (Grossarth-Maticek, 2001).

Helixor has been in use since 1968. A number of components with different possible effects have been isolated, including lectins, viscotoxins, and alkaloids. Contraindications include pregnancy, hyperthyroidism, and intolerance. Depending on the type and stage of the tumor, treatment in humans is based on a specific schedule that can be lifelong. Local inflammatory reactions may occur. Fever is desirable (Kast, 1990).

A multicentric, randomized, open, prospective clinical trial was conducted in China. A total of 224 patients with breast, ovarian, and non–small cell lung cancer fulfilled the requirements for final analysis (n = 115 treated with Helixor A; n = 109 control group treated with Lentinan). All patients were provided with standard tumor destructive treatment schedules and were treated with standardized mistletoe extract or Lentinan during chemotherapy. The study showed that complementary treatment with Helixor can reduce the adverse effects of chemotherapy in patients with cancer, thereby improving quality of life (Piao, 2004).

An off-label veterinary protocol has been proposed by Dr. Chris Piper (New Zealand), who prefers to use HelixorP because it produces fever and local swelling at a

level somewhere between the stronger HelixorM and the weaker HelixorA. Clinical effects include pyrexia, leukocytosis, and inhibition of tumor growth. It can be combined with chemotherapy with anecdotal evidence of enhanced well-being, reduced adverse effects of chemotherapy, and increased survival times (personal correspondence, 2005).

Hoxsey formula

The cancer treatment first popularized by Harry M. Hoxsey (1901-1974) is controversial, popular, and one of the longest-lived unconventional herbal therapies for cancer (Spain, 1988). Depending on the type and stage of cancer, and the individual patient's condition, Hoxsey would add to a basic solution of cascara *(Rhamnus purshiana)* and potassium iodide one or more of the following plant substances: poke root *(Phytolacca americana),* burdock root *(Arctium lappa),* barberry or berberis root *(Berberis vulgaris),* buckthorn bark *(Rhamnus frangula),* Stillingia root *(Stillingia sylvatica),* or prickly ash bark *(Zanthoxylum americanum)* (Spain, 1988).

Studies on individual herbs leave no doubt that Hoxsey's formula contains many plant constituents with potential therapeutic activity. Research has identified antitumor activity of one sort or another in all but three of Hoxsey's plants, and two of these three are purgatives; one of them *(Rhamnus purshiana)* contains the anthraquinone glycoside structure now recognized as predictive of antitumor properties (Kupchan, 1976). Whether Hoxsey's particular formula has therapeutic merit is still unsubstantiated by clinical data, despite provocative findings of antitumor properties in many of the individual herbs that he used. However, anecdotal evidence from veterinarians who have used various versions of the formula indicates that it improves quality of life and may inhibit growth of tumors in animals. It is difficult to evaluate the benefits of the traditional approach of detoxification through laxative effects, liver support, improved nutrition, and so forth, all of which may strengthen the immune system and favorably affect the cancer status of a human patient (Spain, 1988); Hoxsey proposed that this was how the formula worked.

A prospective study with no controls evaluated survival for 39 patients with a variety of histologically verified cancers treated at a Mexican clinic. Cancer types for six long-term survivors were lung, melanoma, recurrent bladder cancer and one labial vulva cancer. Twenty three patients were lost to follow-up, and 10 died after an average of 15.4 months. Six remained disease-free with an average follow-up of 48 months (Austin, 1994). A retrospective cohort study followed new cancer patients (n = 149) registered at the same clinic during the first quarter of 1992. At the end of 5 years, 17 (11.4%) were alive, 68 (45.6%) deceased and the status of 64 (43%) unknown. The large proportion lost to follow-up (45.6%) made comparison of the survival of this cohort to the survival of other cohorts of cancer patients reported in the literature impossible (Richardson, 2001).

Various versions of Hoxsey-like formulas are available commercially (Bergner, 1995). The original formula contained an herb identified as *Cascara amarga* (Honduran bark), which is apparently not available in commerce. Most companies substitute *Cascara sagrada* or another alterative in its place.

A Hoxsey-like formula for constitutional cleansing and cancer support is made up of the following (Bergner, 1995):

Licorice root *(Glycyrrhiza glabra)*	6 oz
Red clover *(Trifolium pratense)*	6 oz
Burdock root *(Arctium lappa)*	3 oz
Queen's root *(Stillingia sylvatica)*	2 oz
Oregon grape root *(Berberis aquifolium)*	3 oz
Poke root *(Phytolacca decandra)* (toxic)	2 oz
Cascara sagrada bark *(Rhamnus purshiana)*	2 oz
Buckthorn bark *(Rhamnus frangula)* (toxic)	2 oz
Prickly ash bark *(Zanthoxylum americanum)*	1 oz
Baptisia *(Baptisia tinctoria)*	2 oz
Potassium iodide	$^3/_4$ oz

Human dose: From 30 drops 2× per day to 1 tsp 3× per day

Caution on Phytolacca: This herb, used alone, can raise the white blood cell count, mimicking leukemia.

Another recipe (source unknown), per 5 mL:

Potassium iodide	150 mg
Licorice *(Glycyrrhiza glabra)*	20 mg
Red clover *(Trifolium pratense)*	20 mg
Burdock root *(Arctium lappa)*	10 mg
Stillingia root *(Stillingia sylvatica)*	10 mg
Barberry *(Berberis vulgaris)*	10 mg
Cascara *(Cascara sagrada)*	5 mg
Prickly ash bark *(Zanthoxylum americanum)*	5 mg
Buckthorn bark *(Rhamnus catharticus)*	20 mg
Pokeroot *(Phytolacca americana)*	10 mg

Author's note (BF): We do not include potassium iodide in our practice formula.

Essiac

Another controversial "unproven" herbal remedy is Essiac. Various formulas have been prepared on the basis of four herbs:

1. Burdock root *(Arctium lappa)*
2. Sheep sorrel *(Rumex acetosa)*
3. Turkey rhubarb *(Rheum palmatum)*
4. Slippery elm *(Ulmus fulva)*

Many commercial products consist of varying proportions of these herbs. The powdered formula is decocted over minutes to hours, depending on the supplier.

As with the Hoxsey formula, no controlled trials have substantiated the efficacy of Essiac; however, studies on the herb constituents support antineoplastic activity. In the early 1980s, the Canadian Bureau of Human Prescription Drugs conducted a retrospective review physician summaries about Caisse's patients. Eighty six patient histories were submitted. All had previously received conventional therapy. Of the 86 patients, 1 showed subjective improvement, 5 required fewer analgesics, and 3 remained stable (Office of Technology Assessment, 1990). In a survey of North American consumers of one brand of essiac, 50.6% of respondents reported improvement in their symptoms. 6.6 percent reported adverse events of nausea, vomiting and diarrhea, but 11.8% had exceeded the daily recommended dose (Richardson, 2000).

Antitumor activity has been demonstrated in vivo with burdock, with various fractions inhibiting induced sarcoma by as much as 61% in mice (Dombradi, 1966). Burdock seed contains a number of ligands, including arctigenin, which has been shown to induce differentiation in mouse myeloid leukemia cells. Arctigenin has also demonstrated potent cytoxic effects against a human leukemia cell line, while showing no toxicity toward normal lymphocytes (Hirano, 1994). Sheep sorrel contains emodin, which has antitumor activity; its polysaccharides have displayed antitumor activity in mice implanted with sarcoma (Ito, 1986). Some constituents of rhubarb (aloe, emodin, catechin, and rhein) have shown antitumor activity. Rhein has antitumor activity in vivo, increasing survival time in leukemia-bearing mice in one study, and inhibiting melanoma in mice by 76% in another (Konopa, 1957).

Other formulas

Other traditional cancer formulas include Scudder's alterative (equal parts of corydalis tubers *[Corydalis yanhusuo],* black tag alder *[Alnus serrulata],* figwort *[Scrophularia nodosa],* and yellow dock *[Rumex crispus]*) and Compound Syrup of Scrophulara (figwort leaves and roots, Phytolacca root, *Rumex crispus* root, *Celastrus scandens* bark and root, *Corydalis formosa* root, Podophyllum root, juniper berries, prickly ash berries, and guaiacum wood). The recipes for these formulas are found in Eli Jones' classic, *Cancer: Its Causes, Symptoms and Treatment,* first published in 1911 and recently reprinted (Jones, 1911).

Review of Strategies for Cancer Prescriptions

One of the primary concerns of veterinarians is how to control cancer without weakening the host; herbal therapy offers a very practical and effective solution to this dilemma. In the authors' opinion, when conventional therapy offers a very good chance of curing or sending a cancer into remission, then conventional therapy is warranted, with herbal adjunctive therapy of paramount importance. However, when the outcomes are likely to be palliative, or when they are unknown, then herbal "chemotherapy" is a viable alternative to conventional chemotherapy after risks and benefits of treatment have been weighed. Even with grave prognoses, many cases have demonstrated that improvement in health and longevity is possible, despite the presence of cancer.

The known mechanisms of herbal actions can be integrated in a holistic approach to cancer care through a strategy that incorporates tradition and science. By using a variety of herbs with different anticancer activities, veterinarians are using, in effect, a form of "polyvalent herbal chemotherapy." At the same time, traditional herbal medicine treatment is aimed at treating the patient, rather than the disease. As has been discussed, the number of herbs that have demonstrated some form of anticancer activity is immense and may at first seem overwhelming, but this fact can be used to take advantage of both approaches.

The individual animal's diagnosis, stage of disease, history, presentation, vitality or debility, and system functioning will affect treatment strategy and herb selection. Traditional Chinese herbalists and Western herbalists have always used several herbs in combination and will change formulas over time as the needs of the patient change.

The author proposes that several herbs that treat the individual patient should be combined to obtain the following outcomes:

- Alleviation of signs and symptoms of the patient.
- Relief of possible pain, anemia, poor appetite, cachexia, depression, diarrhea, adverse effects of chemotherapy, bleeding, edema, leukopenia and so forth.
- Appropriate herbs that treat specific areas of the body should be selected, for example, renal herbs or liver herbs for renal or liver cancer.

Alteratives

Cancer is a very diverse disease that is considered by herbalists to be an expression of physiologic imbalance. Treatment seeks to improve physiologic functioning and waste removal through "detoxifying" with the use of gentle aperatives and laxatives, lymphatics, and "blood-cleansing" herbs (i.e., alteratives). Particular attention should be paid to herbs of the gastrointestinal system with concurrent actions, such as cholagogues, liver tonics, bitters, diuretics, and carminatives.

Immune support

Herbs that support the patient should be selected in the first instance, particularly if infection is present (previous high-dose prednisolone therapy is common with occult infections that have often been untreated). Antimicrobials and antiseptics should be considered, if necessary. Herbs that modify or stimulate immunity help the patient's own body to resist the effects of cancer.

Adaptogens

The practitioner seeks to reduce the physical effects of stress and assist "adaptive energy," particularly when the patient is debilitated, but also in an attempt to prevent debilitation. Most adaptogens have multiple actions, and selection must be made according to which is the best one for the patient. For example, a hyperactive young dog with lymphosarcoma would be better treated with *Withania* rather than *Panax;* however, an old, debilitated, sleepy dog might be better suited to *Panax*.

Tumor biology and tumor type

When possible, the practitioner should incorporate herbs that have known antineoplastic activity; often, these are the same herbs that fall into the other categories discussed earlier. When possible, and when the information is available, one should select herbs that have known activity against particular tumor types.

Antioxidants

Patients with cancer or that are on chemotherapy or radiation therapy will benefit from antioxidants. Reviews of the many in vitro, animal, and human studies have demonstrated the beneficial effects of antioxidants on oxidative damage reduction (Conklin, 2000; Labriola,

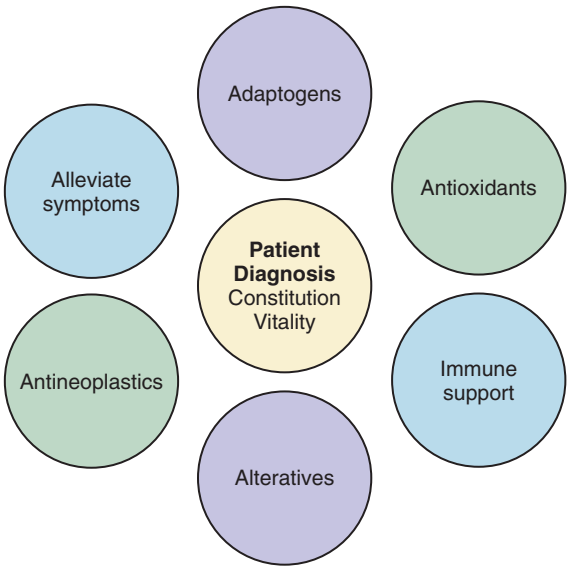

Figure 20-1 Schemata of herbal selection for cancer treatment. Choose herbs that cross provide more than one of these actions, tailored to the patient's needs.

1999; Lamson, 1999). Many herbs with antioxidant activities have antineoplastic activity, and similarly, many antineoplastic herbs have antioxidant activity. (See "Herbs and Chemotherapy" at the end of this section.)

In summary, a simple approach involves considering the effects or potential effects of the cancer on an individual patient with goals toward strengthening bodily resistance and overall health by improving immunity and physiology, alleviating symptoms, and using antioxidant and adaptogen herbs. If this is done, anticancer activity is usually inherent in the prescription. As well, specific herbs can be used for known activity against particular types of cancers. Many herbs exhibit overlapping actions that fulfill more than one action category (Figure 20-1).

Strategy for prescribing using key mechanisms of action focused on the patient

Example: An old dog with hepatic adenocarcinoma that is cold, arthritic, and overweight. Chemotherapy has been declined. (*Note:* This formula could be used concurrently with chemotherapy.)

- Burdock 25% (cold): Differentiation inducer, depurative (alterative), diuretic, mild laxative, mild antiseptic. Traditional use in arthritis, cancer.
- Turmeric 25% (warm): Inhibits metastasis, angiogenesis, local invasion. Is anti-inflammatory, antioxidant, antiplatelet, hepatoprotective, cholagogue. Traditional use in arthritis, cancer, and improved digestion and hepatic function.
- *Panax ginseng* 25% (neutral to warm, dry): Inhibits local invasion, adaptogenic, stimulant, tonic, hypoglycemic, immune stimulant, hepatoprotective, cardioprotective. Traditional use for cancer, chronic inflammation, improved resistance to infection, and minimization of adverse effects of chemotherapy.
- Astragalus 25% (sweet and slightly warm): Inhibits metastasis. An adaptogen, tonic, cardiotonic, immune enhancer, diuretic. Used for cancer, chronic debility, chronic hepatitis.

This formula provides antineoplastic activity; adaptogen, antioxidant, alterative, and immune-supporting herbs; and alleviates symptoms of chronic inflammation (arthritis). In addition, some hepatoprotective and tonic effects are given for this old dog. This formula could be altered with milk thistle, Schisandra, or Bupleurum over time. In addition, this diet should be supplemented with turmeric or green tea for further antioxidant and antineoplastic actions. Generally, the formula is also warming.

Herbs and Conventional Tumor Therapies: Many oncology drugs induce cellular toxicity and death through free radical generation; some concern exists that antioxidants may negate these cytotoxic properties. In a review of all English articles listed in Index Medicus between the years 1990 and 2000 that were related to antioxidants and interactions with anticancer drugs or radiation, the authors concluded, "There is a rational basis for the continued use of antioxidant agents as a therapeutic adjunct in cancer therapy, with such use also offering potential to abrogate the carcinogenic process and mutation-driven drug resistance, but convincing data and widespread acceptance of such a role [are] dependent on additional, appropriately relevant trials" (Block, 2001). Chemotherapeutic drugs that are best known for creating cellular damage by initiating free radical and reactive oxygen species (ROS) damage include the alkylating agents, such as cyclophosphamide, ifosfamide, and melphalan; the tumor antibiotics, such as doxorubicin, bleomycin, and epirubicin; and the platinum compounds, such as cisplatin (Conklin, 2000; Labriola, 1999; Lamson, 1999; Lamson, 2000). Radiation therapy uses ionizing radiation to produce cell kill through free radical generation (Lamson, 1999; Lamson, 2000). Unfortunately, a number of physiologic adverse effects of these therapies (e.g., doxorubicin-induced cardiotoxicity, cisplatin-induced nephrotoxity, bleomycin-induced pulmonary fibrosis) are related to oxidative damage (Conklin, 2000). Evidence is accumulating that antioxidants are helpful in attenuating these side effects (Ferreira, 2004), (Weijl, 2004). Careful selection of herbs that help reduce these adverse effects and protect these organs and systems (see relevant system herbs) can be used. Because antioxidant activity is inherent in many herbs, two options with chemotherapy and radiation therapy are available, if the theoretical concern exists. Herbal treatment should be stopped just before conventional treatment is begun (24-48 hours) and recommenced in approximately 5-7 days depending on the half life of the chemotherapeutic drug (or longer for radiation therapy); or herbal treatment should be continued concurrently. In the authors' experience, concurrent treatment helps to reduce the adverse effects of treatment and to maintain "wellness."

Much has been made in the medical literature of drug-herb interactions, and specifically the CYP450 hepatic microsomal system which is responsible for metabolizing

many commonly prescribed drugs. While the list of *potential* interactions is very long, the evidence for real interference, by herbs, in the metabolism of most drugs is lacking. In many cases, medical experts warn that potentially useful herbs should not be administered on the basis of a single *in vitro* study of a single chemical contained within that plant. Food itself can alter the activities of CYP450 enzymes. Herbs taken orally must pass through the GI tract, be acted upon by digestive enzymes and gut bacteria, pass through portal circulation and get to the liver for whatever processes occur there.

As an example, isolated gingkolic acids from gingko and hyperforin from Saint John's Wort *inhibit* CYP2C19 activity in vitro (Zou, 2002). However, using more complete extracts of the herb of each in humans appears to *induce* CYP2C19 (Wang, 2004). To date, a small number of herbs have been examined in humans and animals for their influences on metabolism of a small number of drugs. Chapter 12 provides a listing of potential herb-drug interactions, and should be used by the practitioner as a starting point for an evidence-based approach to the subject.

HERBS FOR CARDIOVASCULAR DISEASE

General Considerations

Digoxin is the legacy of an herbal success story. Dr. William Withering was widely acclaimed for his discovery of foxglove for the treatment of patients with heart disease. However, Withering did not discover it at all, of course—he observed the treatment successes of a local "herb woman" (or witch, depending on the account one reads) who used foxglove in her formulas. Withering was able to divine which of her herbs was the most promising, and he commenced to chronicle *10 years* of his own experience of treating patients with this plant (published in 1785). This is the proper course of clinical herbal research—investigators should (1) note that a plant in long use may actually have clinical effects, (2) document these effects well, and (3) publish findings for others to put them to the test. Many of the plants discussed in this section have been used as traditional treatments for heart failure, and some have undergone scientific investigation. We know that some of these have interesting effects in vitro, yet they have not been tested clinically. It will be noted when no traditional database is available to guide practitioners in their prescription.

Congestive Heart Failure

Heart failure or congestive heart failure is a clinical syndrome—not a disease. It results from interaction among the heart and neuroendocrine and vascular systems. The heart may increasingly lose capacity to pump blood at a rate that can maintain tissue metabolism requirements, or it may do so at elevated filling pressures, resulting in impaired organ function. Therapy must address inciting causes (if known), improve myocardial function, reduce volume overload, or reduce pressure overload. Drug therapies for myocardial failure are "Band-Aid therapies" that palliate the effects of heart disease for a short duration but do little to address the primary disease process. Some goals of drug therapy are to reduce pulmonary venous pressure and augment systolic performance. In addition, therapy is increasingly targeting neurohormonal changes that hasten the progression of heart failure, including activation of the sympathetic nervous system and the renin-angiotensin system. It is worth noting that some herbs traditionally used for heart failure (such as hawthorn and linden) have mild anxiolytic activity, which may reduce sympathetic nervous system activity.

Mechanisms of Interest

Cardiotonic and cardioprotective herbs

Cardiotonic and cardioprotective herbs are generally rich in flavonoids, which may reduce oxidative stress and reduce capillary fragility. They may also exhibit vasorelaxant activity.

HAWTHORN *(CRATAEGUS* SPP*):* (Upton, 1999, Rigelsky, 2002). This herb may increase myocardial contractility and reduce peripheral vascular resistance. The mechanism is attributed to a slight inhibition of sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase), which might be responsible for the positive inotropic action. Evidence also reveals inhibition of angiotensin-converting enzymes (ACEs) and of interactions with the cyclic adenosine monophosphate (cAMP)-mediated β-adrenergic system, which may explain the vascular effects of the extract. Most trials indicate greatest effect after 6 to 8 weeks of use, and clinical trials in humans suggest that higher doses are more effective in severe cases. In patients with New York Heart Association (NYHA) Class II heart failure (see Table 20-1). 160 to 900 mg divided daily of a particular leaf and flower extract (WS 1442) was effective, but a dose of 1800 mg produced better results in people with Class III failure.

GINKGO *(GINKGO BILOBA):* Ginkgo appears to have vasodilatory effects on peripheral circulation and antioxidant capacity by virtue of the flavonoids it contains. Ginkgo extract and the terpenoid, bilobalide, have potent concentration-dependent vascular smooth muscle relaxant activity; other constituents of Ginkgo have variable effects on cardiomyocyte action potential duration, nitric oxide release in the endothelium and aorta, and Ca^{2+} channel flux (Satoh, 2004; Zhou, 2004a). Ginkgolides inhibit PAF; this may have additive effects for human

TABLE 20-1

New York Heart Association Functional Classification of Heart Failure for Humans

Class I	Heart disease without exercise intolerance or signs of heart failure
Class II	Signs of cardiac-related exercise intolerance exhibited.
Class III	Signs of heart failure during normal activity.
Class IV	Clinical signs at rest or with minimal activity.

TABLE 20-2

International Small Animal Cardiac Health Council Heart Disease Classification Scheme

Class I	Asymptomatic Ia: Signs of heart disease but no cardiomegaly Ib: Signs of heart disease and evidence of compensation (cardiomegaly)
Class II	Mild to moderate heart failure—clinical signs of heart failure are evident at rest or with mild exercise and adversely affect quality of life
Class III	Symptoms at rest—clinical signs of congestive heart failure are immediately obvious IIIa: Home care is possible IIIb: Hospitalization is recommended (cardiogenic shock, life-threatening edema, large pleural effusion, refractory ascites)

patients or cats taking anticoagulants to prevent thrombosis.

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* This Chinese herb is often used as a Qi tonic and has been studied for its therapeutic benefit in the treatment of patients with ischemic heart disease, myocardial infarction, and heart failure, and those who seek relief from anginal pain. Clinical studies have indicated that its in vitro antioxidant activity is the mechanism by which it affords cardioprotective benefit (Miller, 1998).

MOTHERWORT *(LEONURUS CARDIACA):* This herb is traditionally used for palpitations, arrhythmias, and the stress and anxiety that accompany those symptoms. One component, lavandulifolioside, causes significant negative chronotropism, prolongation of the P-Q and Q-T intervals and the QRS complex, and decreased blood pressure (Milkowska-Leyck, 2002). This herb has not been well investigated.

CACTUS *(SELENICEREUS GRANDIFLORUS):* Both the stem and flowers of this herb were very important as a heart remedy to the Eclectics, and yet it is almost never used by veterinary herbalists and has not been scientifically investigated. Ellingwood described the indications for it as "irregular pulse; feebleness of the heart's action; dyspnea; weight; oppression in the chest; violence of the heart's action depending upon atonicity or enervation." This plant has developed a reputation as a strong or toxic herb, but those who have used it most often and have written about it have declared it a safe tonic. A detailed monograph on this plant can be found at the Southwest School of Botanical Medicine Web site at: http://www.swsbm.com/ManualsOther/Selenicereus-Lloyd.PDF. The veterinary dose recommended by Milks (1949) is $^{1}/_{12}$ gr for a horse (0.005 g) and 1/60 gr for a dog (0.001 g), but he was clearly unconvinced of its efficacy at these doses. The previously mentioned monograph describes human doses as low as a fraction of a drop to 0.3 mL, and as high as 1.8 mL three times daily. It has commonly been combined with *Avena sativa* and should be used for several months before its effects are assessed.

COLLINSONIA *(COLLINSONIA CANADENSIS):* This herb has been recommended as a cardiac tonic that acts primarily to improve vascular tone.

OTHER HERBS: Other herbs include the following:

- Corydalis *(Corydalis ambigua)*
- *Panax ginseng*
- *Panax notoginseng*
- *Salvia miltiorrhiza*
- *Terminalia arjuna*

Cardioactive herbs

CACTUS *(SELENICEREUS GRANDIFLORUS):* As previously discussed, this herb is said to be a positive inotrope.

HAWTHORN *(CRATAEGUS OXYANCANTHA):* As was previously discussed, this is a positive inotrope.

LILY OF THE VALLEY *(CONVALLARIA MAJALIS):* Aerial parts contains 40 cardenolides (cardiac glycosides), which, like digoxin, inhibit N^{+}/K^{+}-ATPase pumps. King describes Convallaria thus: "Compared with digitalis, convallaria is generally as efficient, both as a heart tonic and as a diuretic, and in many cases, is said to act better. It is safer than digitalis, which may destroy life by paralyzing the heart—an effect never produced by convallaria. Moreover, it is freer from cumulative effects." The dose that kills 50% of a sample population (LD_{50}) in cats for a single constituent, convallatoxol, was 0.14 mg/kg given intraperitoneally. A human dose for this herb is 0.6 g of powdered herb or 5 to 10 drops of tincture, divided daily. A case report described a dog that had eaten lily of the valley in its fenced yard and died suddenly (Moxley, 1989).

BROOM *(CYTISUS SCOPARIUS* OR *SAROTHAMNUS SCOPARIUS):* This is a rarely used plant that is generally considered a poison and a noxious weed. Its traditional naturopathic uses are as a cardiac stimulant, peripheral vasoconstrictor, and diuretic. King claims that it is useful in "dropsy of the thorax" (pulmonary edema). Combining the herb with dandelion and juniper may reduce toxicity and lend synergistic effects. This author (SW) has no experience with the herb, but it is used by respected naturopaths and herbalists and appears to have potential as an acute or emergency medicine.

BUGLEWEED *(LYCOPUS EUROPAEUS):* This herb is usually recommended for people with thyrotoxic agitation and palpitations. It is considered a diuretic, a nervine, and a peripheral vasodilator. King's (Felter, 1898) describes the action of Lycopus on the heart thus: "Cardiac disease, both organic and functional, has been markedly impressed by lycopus. Administered to patients suffering from endocarditis and pericarditis, it quickly subdues the inflammation. It is a good remedy for cardiac palpitation . . . It is best adapted to those forms of heart disease characterized by irritability and irregularity, with dyspnea and precordial oppression. Lycopus powerfully increases the contraction of the unstriped muscular fibers, particularly those of the heart and arteries, hence its value in cardiac dilatation and hypertrophy, which have been known to undergo marked improvement under its administration. It quickly relieves the suffering and anxiety nearly always experienced in heart disease. It has

favorably influenced exophthalmic goiter." Despite its previous popularity as a treatment for arrhythmia and cardiomyopathy, this herb has not been investigated in clinical trials.

TERMINALIA *(TERMINALIA ARJUNA):* This traditional Indian herb is used for heart problems. A double-blind crossover trial in people with NYHA Class IV congestive heart failure showed that people who received 500 mg three times daily of Terminalia had improved NYHA Class evaluation, end-systolic volume, left ventricular end-diastolic volume, left ventricular stroke volume index, and left ventricular ejection fractions, compared with those given placebo (Bharani, 1995).

FORSKOHLII *(PLECTRANTHUS BARBATUS):* Laboratory animal studies show that the forskolin extract increases myocardial contractile strength and peripheral vasodilation and may also reduce cardiac preload and afterload, possibly by activating adenylate cyclase (Baumann, 1990).

TRIBULUS *(TRIBULUS TERRESTRIS):* This Ayurvedic herb has many traditional uses, including its administration as a diuretic. In vitro studies on isolated heart muscle suggest that it has a positive inotropic effect (Seth, 1976).

BLOOD ROOT *(SANGUINARIA CANADENSIS):* This is considered a cardiotonic herb. In vitro studies confirm that sanguinarine, a benzophenanthridine alkaloid derived from blood root, produced a concentration-dependent positive inotropic effect and increased contractility (108%) that was comparable with the maximal inotropic effect of ouabain. Sanguinarine caused inhibition of Na^+/K^+-ATPase isolated from guinea pig myocardium (Seifen, 1979). Blood root is another strong herb that should be used carefully by trained herbalists.

Circulatory stimulants

CAYENNE *(CAPSICUM ANNUUM):* Capsaicin, a single extract of Capsicum, caused hypertension in dogs and cats when given intravenously. Peripheral vasoconstriction in anesthetized dogs (followed by hypotension) and isolated arterial strips appeared mediated through cholinergic mechanisms (Toda, 1972). The effect of oral ingestion of the whole herb in the treatment of cardiovascular disease is unknown.

PRICKLY ASH *(ZANTHOXYLUM AMERICANUM):* This herb has not been investigated, but the Eclectics valued its use for "sluggish circulation." King describes its effect as "Cardiac action is increased, the pulse becomes slightly accelerated, and the integumentary glands give out an abundant secretion."

GINKGO *(GINKGO BILOBA):* The effects of ginkgo leaf extract have been studied in normal rats and those with ischemic brain damage caused by middle cerebral artery occlusion. Oral administration of ginkgo extract at 100 mg/kg was reported to increase cerebral blood flow in normal rats, but the increase was less marked in rats with cerebral artery occlusion (Zhang, 2000).

OTHER HERBS: Other circulatory stimulants include the following:

- Dong quai *(Angelica sinensis)*
- Horseradish *(Armoracia rusticana)*
- Chuan xiong *(Ligusticum wallichii)*
- Bayberry *(Myrica cerifera)*

Agents that decrease peripheral resistance, hypotensives, and peripheral vasodilators

TERMINALIA: Laboratory animal studies suggest that it has antioxidant activity (Gupta 2001, Karthikeyan, 2003), reduces blood pressure, and demonstrates positive inotropic activity. An uncontrolled study in dogs suggests that it may also have β_2-adrenergic activity (Nammi, 2003).

HAWTHORN *(CRATAEGUS OXYACANTHA):* This herb may increase myocardial contractility and reduce peripheral vascular resistance. Most trials demonstrate greatest effect after 6 to 8 weeks of use. It may enhance the effects of cardiac glycosides (Jellin, 1999) and may have mild antihypertensive effects. In mildly hypertensive humans, 500 mg daily of hawthorn extract led to a reduction in diastolic blood pressure (Walker, 2002).

GARLIC *(ALLIUM SATIVUM):* This herb is popular in the management of human cardiovascular disease; evidence suggests that the primary focus of action involves modulating blood lipids and controlling atherosclerotic disease, although one study in dogs indicated the capacity to reduce diastolic blood pressure and heart rate (Martin, 1992; Nagourney, 1998). Multiple in vitro and ex vivo studies in rats suggest that garlic relaxes vascular smooth muscle through nitric oxide (NO)-mediated mechanisms (Kim-Park, 2000; Baluchnejadmojarad, 2003). Garlic has mild antihypertensive properties in humans, rats, and dogs (Wilburn, 2004; Sharifi, 2003a; Pantoja, 1991; Malik, 1981). Its mechanisms are unknown, but endothelium-derived relaxing and constricting factors, as well as prostaglandin-mediated and NO-mediated mechanisms, are suspected (Banerjee, 2002).

GINKGO *(GINKGO BILOBA):* In vitro studies show that ginkgo causes vasodilation in endothelium and aortic vascular muscles, possibly via Ca^{2+} influx through the Ca^{2+} channel and the activation of NO release (Satoh, 2004).

FORSKOHLII *(PLECTRANTHUS BARBATUS):* The forskolin extract increases myocardial contractile strength and peripheral vasodilation and may also reduce cardiac preload and afterload, possibly by activating adenylate cyclase (Baumann, 1990).

CHINESE SALVIA, DAN SHEN *(SALVIA MILTIORRHIZA):* This herb was traditionally used in Chinese herbal combinations; it may decrease vascular resistance (Huang, 2000).

VALERIAN *(VALERIANA OFFICINALIS):* This herb was found to dilate pulmonary vascular smooth muscle in cats, probably through a nonselective γ-aminobutyric acid (GABA)-mediated mechanism (Fields, 2003).

EUCOMMIA *(EUCOMMIA ULMOIDES):* Older studies suggest that this herb may reduce blood pressure. There are anecdotal reports of success with it in early cases of hypertension.

UNCARIA *(UNCARIA RHYNCHOPHYLLA):* This relative of cat's claw (both containing the vasoactive alkaloid rhyncophylline) (Shi, 2003) is known as *gou teng* in Chinese medicine. The herb mediates endothelium-

dependent relaxation in spontaneously hypertensive rats in in vitro studies. One extract resulted in peripheral vasodilation in anesthetized dogs (Ozaki, 1990).

Diuretics

Cardioactive herbs were often traditionally classified as diuretics, in many cases because of their effect of increasing renal blood flow secondary to improving ventricular function.

(See the section on urinary system for more information on diuretics.)

DANDELION *(TARAXACUM OFFICINALE):* The German Commission E discovered evidence of a diuretic effect. Oral administration of dandelion extracts had a diuretic effect in rats and mice, and in one study, the effect was assessed as equal to that of furosemide and stronger than juniper berry and horsetail (Bisset, 1994).

PARSLEY *(PETROSELINUM CRISPUM):* This root and fruit was used historically as a diuretic for patients with dropsy.

Nervines

MOTHERWORT *(LEONURUS CARDIACA):* The later Eclectics valued motherwort as a nervine and heart tonic, in addition to its better known effects on women's menstrual functions. It was recommended for "nervous debility" and is used by modern herbalists to treat patients with arrhythmias.

LINDEN *(TILIA PLATYPHYLLOS):* This traditional anxiolytic herb is sometimes used in cardiac formulas, although no clinical trials or animal studies have been undertaken. The dose for humans is $^{3}/_{4}$ to 1 teaspoon (3-5 mL) of the tincture three times daily, or 1 cup of tea (1-2 tsp in 1 cup water) three times daily.

VALERIAN *(VALERIANA OFFICINALIS):* This is a recognized hypnotic herb. Cropley and colleagues investigated heart rate and blood pressure reactions in a group of people presented with stressful mental tasks. Compared with the placebo group, those treated with valerian demonstrated significantly attenuated heart rate and blood pressure changes (Cropley, 2002).

Angiotensin-converting enzyme inhibitors

TRIBULUS (PUNCTUREVINE) *(TRIBULUS TERRESTRIS):* Laboratory animal studies suggest that Tribulus has ACE inhibition activity (Sharifi, 2003b). Heart disease is not a traditional indication for this herb.

DAN SHEN *(SALVIA MILTIORRHIZA):* This herb has shown significant ACE inhibition activity in a rat model of hypertension (Kang, 2002), and is a traditional Chinese herb for blood stagnation and chest pain.

Antiarrhythmics

BERBERINE-CONTAINING PLANTS *(GOLDENSEAL [HYDRASTIS CANADENSIS], COPTIS [COPTIS CHINENSIS], BARBERRY [BERBERIS VULGARIS], OREGON GRAPE [MAHONIA AQUIFOLIUM]):* These herbs were not used traditionally for heart or cardiovascular disease. King's says that goldenseal "appears to stimulate the respiratory and circulatory apparatus, imparting increased tone and power. Arterial tension is augmented, and blood pressure in the capillaries increased, rendering it valuable, like belladonna and ergot, in overcoming blood stasis. Its action upon the nervous system has been compared [with] that of strychnine (Ellingwood, 1919), [although] less energetic, but more permanent. Thus, the tone imparted to the heart muscle is permanent, rather than intermittent or spasmodic." Animal studies show that berberine decreases heart rate and may act like a Class III antiarrhythmic (Riccioppo, 1993; Huang, 1992). Zeng and associates investigated the effects of 1.2 to 2.0 g berberine given daily to people with congestive heart failure who were experiencing ventricular premature complexes (VPCs) or ventricular tachycardia. Compared with people taking placebo, a significantly greater increase was noted in left ventricular ejection fraction, exercise capacity, and the dyspnea–fatigue index, as was a decrease in the frequency and complexity of VPCs. Over the following 24 months, a significant decrease in mortality was observed in these patients as well (Zeng, 2003). Goldenseal root may consist of 0.5% to 6% berberine, and *Coptis rhizome* may contain 4% to 9% berberine. The barberry plant may contain 1% to 3% berberine.

LILY OF THE VALLEY: This herb is recommended by herbalist David Winston for simple arrhythmias, with or without cardiac hypertrophy.

Other herbs with potential antiarrhythmic activity include Broom, Bugleweed, Motherwort, Ailanthus *(Ailanthus altissima),* Cactus, Dogbane *(Apocynum cannabinum),* Adonis *(Adonis vernalis),* Gelsemium *(Gelsemium sempervirens),* Hawthorn, Lobelia seed *(Lobelia inflata),* Pink root *(Spigelia marilandica),* Pulsatilla *(Anemone patens, A. pulsatilla),* Skullcap *(Scutellaria lateriflora),* Veratrum *(Veratrum verde),* and Valerian according to Winston. Adonis, Ailanthus, Dogbane, Gelsemium, Lobelia, Lily of the Valley, Pink root, Pulsatilla, and Veratrum are potentially toxic herbs. Corydalis, Devil's claw, *Panax ginseng, Panax notoginseng,* and *Stephania tetandra* are also used for their antiarrythmic activity.

Anticoagulants

GARLIC *(ALLIUM SATIVUM):* This herb has been shown in many human and animal trials to inhibit platelet aggregation (Rahman, 2000; Ali, 1995; Legnani, 1993; Morris, 1995). Its red blood cell toxicity to cats and dogs in high doses may limit its use to lower doses.

DAN SHEN *(SALVIA MILTIORRHIZA):* This herb inhibits platelet activity, has antithrombin III–like activity, and promotes fibrinolysis (Chan, 2001).

REVIEW OF SPECIFIC CARDIOVASCULAR CONDITIONS

Dilated Cardiomyopathy

Therapeutic rationale

- Optimize cardiac output (increase contractility and reduce cardiac afterload).
- Prevent arrhythmias.
- Decrease oxidative stress.

- Rule out metabolic and nutritional abnormalities, such as hypothyroidism, taurine deficiency, and carnitine deficiency.
- Prevent obesity or cardiac cachexia through proper nutritional support.

David Hoffman's formula for mild congestive heart failure in people consists of the following: 3 parts hawthorn, 1 part ginkgo, 1 part linden, 1 part dandelion leaf, 1 part cramp bark, and 1 part valerian (Hoffmann, 2004). Winston recommends a "Hawthorn Compound" that contains hawthorn flower and berry, ginkgo, lemon balm, linden, prickly ash, bugleweed, and cactus (Winston, 2003).

A prescription for dilated cardiomyopathy follows:

Hawthorn	30% (cardiotonic, coronary vasodilator, hypotensive, antioxidant)
Cactus	20%
Terminalia	20% (cardioprotective, hepatoprotective, mild diuretic)
Dan shen	20% (cardioprotective, hypotensive, anticoagulant, antiplatelet, hepatoprotective)

Another prescription used by the author (BF) for cardiac support is:

Hawthorn	40% (cardiotonic, coronary vasodilator, hypotensive, antioxidant)
Dandelion leaf	20% (diuretic, laxative, cholagogue, antirheumatic)
Ginkgo	20% (PAF inhibitor, antioxidant, circulatory stimulant, cognitive enhancer)
Lemon balm	20% (carminative, antispasmodic, sedative)

Heartworm Disease

Therapeutic rationale

- Kill parasites (adults and microfilaria).
- Reduce intimal damage.
- Control secondary heart failure.
- Prevent thromboembolism with cage rest and administration of aspirin.
- Prevent obesity or cardiac cachexia through proper nutritional support.

BLACK WALNUT *(JUGLANS NIGRA):* This treatment is popular for gastrointestinal parasites, as well as for heartworm disease; no data are available on the latter. Black walnut hull has also been recommended for heartworm prevention at a dosage of approximately 1 capsule of ground herb per day, but long-term safety is unknown. Therapy should be discontinued if diarrhea arises.

GINGER *(ZINGIBER OFFICINALIS):* A dosage of 100 mg/kg of alcoholic extract of ginger, given subcutaneously by 12 injections to dogs infected with heartworm, caused 98% reduction in microfilarial counts and appeared to have some adulticidal activity (Datta, 1987). How this study relates to oral dosing is uncertain.

The authors do not recommend substituting an unproven herbal formula for effective conventional therapy but recognize that some clients and some situations do not support conventional therapy.

A prescription for general support for patients undergoing treatment or posttreatment follow-up or heartworm disease follows:

Hawthorn	40% (cardiotonic, coronary vasodilator, hypotensive, antioxidant)
Dandelion leaf	20% (diuretic, laxative, cholagogue, antirheumatic)
Ginger	20% (carminative, antispasmodic, anti-inflammatory, antiplatelet)
Dan shen	20% (cardioprotective, hypotensive, anticoagulant, antiplatelet, hepatoprotective)

Hypertension

Therapeutic rationale

- Treat underlying disease, if possible.
- Use pharmacologic therapy to reduce blood pressure.
- Manage obesity, if present.
- Recommend other nutrients with antihypertensive effects, such as omega-3 fatty acids.
- Avoid the use of drugs that promote hypertension.

David Hoffman (2004) recommends a general hypertension formula consisting of the following ingredients:

Hawthorn	40%
Linden	15%
Yarrow	15%
Cramp bark	15%
Valerian	15%

A prescription for renal or cardiac hypertension follows:

Hawthorn	20% (cardiotonic, coronary vasodilator, hypotensive, antioxidant)
Yarrow	20% (antispasmodic, mild vasodilator, hypotensive, bitter)
Astragalus	20% (immune enhancing, tonic, cardiotonic, nephroprotective, diuretic, hypotensive)
Withania	40% (tonic, adaptogen, nervine, sedative, anti-inflammatory)

Hypertrophic Cardiomyopathy

Therapeutic rationale

- Relax the myocardium.
- Enhance ventricular filling.
- Control signs of heart failure, such as pulmonary edema.
- Manage arrhythmias and reduce risks for thromboembolism.
- Rule out hyperthyroidism, systemic hypertension, and acromegaly (rare).
- Prevent obesity or cardiac cachexia through proper nutritional support.

A prescription for hypertrophic cardiomyopathy follows:

Dan shen	20% (cardioprotective, hypotensive, anticoagulant, antiplatelet, hepatoprotective)
Motherwort	20% (sedative, antispasmodic, cardiac tonic)

Ginkgo	20% (PAF inhibitor, antioxidant, circulatory stimulant, cognitive enhancer)
Valerian	20% (sedative, hypnotic, antispasmodic, hypotensive, carminative)
Dandelion	20% (diuretic, laxative, cholagogue, antirheumatic)

David Winston's Melissa/Lycopus compound may be useful for these cats; it consists of Motherwort, Bugleweed, and Lemon balm (Winston, 2003).

DERMATOLOGIC HERBS

General Considerations

Many underlying factors, such as genetics, deficient diet, fleas, allergies (including food), endocrine disorders, and others, contribute to skin disease, as recognized in conventional veterinary medicine. These are generally determined during the processes of history taking and diagnosis, and awareness of them helps the clinician to gain an understanding of the pathogenesis of the skin disorder. However, the treatment of patients with skin disorders in herbal medicine draws on some different traditional concepts.

Skin disorders are considered manifestations of deeper disease processes and therefore indicate metabolic imbalance somewhere in the body. Hence, topical herbs are employed judiciously but represent only a superficial approach. It is important to note that the skin should not be treated in isolation but as a tissue that is intimately connected to and affected by other organ systems. In many cases, a skin lesion is considered a valid attempt by the body to discharge or metabolize toxic agents, so paradoxically, medications that suppress this process (e.g., corticosteroids) are sometimes considered counterproductive over the long term.

Traditional and modern phytotherapeutic concepts that are relevant to chronic skin disease and that help to clarify the issues of "toxicity" include toxemia, leaky gut syndrome, and dysbiosis.

Mechanisms of Interest

Topical vulnerary, astringent, and emollient herbs are discussed under the section "Herbs for Topical Use." From a phytotherapy perspective, topical treatment alleviates skin conditions, but for chronic skin disease, systemic treatment is usually necessary.

Toxemia and chronic skin disease

Traditionally, chronic skin disease was considered a sign of internal toxicity that indicated that the body had failed to eliminate fully. In toxemia, normal elimination through the liver, gut, and kidneys is impaired, allowing the accumulation of toxic metabolites. In the case of chronic dermatitis, the eliminative process most frequently impaired is considered the digestive system. The aim of therapy was always to remove toxins by enhancing and supporting the eliminatory functions of the body. The most useful herbs that have been employed traditionally are the alteratives, also known as depuratives or "blood cleansers." These herbs effect changes in metabolic processes within the body and usually have mild laxative or diuretic actions, among others, so it can be seen that the approach of improving "elimination" has some merit if toxemia is present. Other herbs facilitate the various detoxification mechanisms used by the body and can help restore normal metabolism and immune function.

Although this theory of toxemia is a traditional one, perhaps some scientific support can be provided for it. Incomplete digestion, inflammation, and failure of the local immune response (for systemic tolerance) facilitate gut absorption of macromolecules with high antigenicity (Halliwell, 1995). These can bind to immunoglobulin (Ig)E and precipitate mast cell degranulation or activate the complement cascade via the alternate pathway (thus allowing the subsequent development of food sensitivities and allergies). They can also combine with antibodies to form immune complexes that promote inflammation.

Inflammation of the gut from any cause can make the gut more permeable to macromolecules, causing hyperpermeability, or leaky gut syndrome. Predisposing factors for leaky gut include use of nonsteroidal anti-inflammatory agents or steroids, allergy or intolerance to food, and environmental sensitivities. Similarly, impaired liver function can reduce hepatic detoxification and allow toxins and free radical metabolic intermediates to enter the circulation, thereby contributing to widespread cellular damage (including damage within the epithelium).

Food substances and consequently food allergies and food intolerances are typically associated with chronic dermatitis, alongside exposure to common drugs (especially those that impair liver function or inflame the gut wall) and chemicals that enter the body (through the skin, mouth, or lungs). When subclinical allergy occurs, the potential exists for histamine-releasing foods to become mediators of histamine release, thereby initiating clinical disease (Halliwell, 1995).

Thus, although food allergies (involving an immune reaction) are not considered common in veterinary medicine (less than 10% of atopic dogs are considered to have food allergy [Halliwell, 1995]), food intolerance or adverse reactions to food may go unrecognized. In a study of dogs with allergic dermatoses (excluding flea allergy dermatitis) and not considered to have food intolerance or food allergy, 45.7% improved on a commercial chicken and rice elimination diet. Of the dogs that improved, 68.8% were finally diagnosed with atopic dermatitis (Nagata, 1999). Although the mechanism involved was unclear, this demonstrates the importance of dietary manipulation in the treatment of patients with chronic dermatitis, even when it would not seem obvious in conventional veterinary medicine.

Leaky gut syndrome and chronic skin disease

Another concept employed in herbal medicine is that of "leaky gut syndrome." A major task of the intestine is to form a defensive barrier that prevents absorption of damaging substances from the external environment. In

human medicine, inert, nonmetabolized sugars such as mannitol, rhamnose, or lactulose are used to measure the permeability barrier or the degree of leakiness of the intestinal mucosa. Permeability is increased in a number of gastrointestinal tract diseases (such as parasitic infestation, infection, inflammation) and can be increased through trauma, burns, and nonsteroidal anti-inflammatory drugs. The major determinant of the rate of intestinal permeability is the opening or closure of the tight junctions between enterocytes in the paracellular space (Hollander, 1999).

Increasing evidence suggests that a leaky, more permeable bowel wall may lead to translocation of bacteria or endotoxin, which may be an important stimulus for inflammatory cytokine activation (Krack, 2005) and may increase the level of toxic insult to the liver. Leakage of imperfectly digested proteins (peptides) through an incompetent intestinal lining is thought to be the most common cause of environmental sensitivities, acquired food allergies, and an underlying contributing factor to many chronic and degenerative diseases.

Although this syndrome is not yet recognized in veterinary medicine, attention to correcting the "leaky gut" can improve overall health, reduce allergies, and help eliminate one of the major contributing factors to chronic disease.

Dysbiosis theory and chronic skin disease

Related to the theory of the leaky gut syndrome is dysbiosis, which is thought to be a major contributing factor to chronic disease, including skin disorders and food allergies (Fratkin, 1996). It follows the use of antibiotics, other medications, or diets that adversely alter the normal flora, or it may be associated with conditions that allow pathogenic microbes to multiply, producing endotoxins that challenge and deplete the immune system and increase gut permeability (thus predisposing to food allergies and sensitivities). Conditions and symptoms of dysbiosis recognized in human medicine that can be associated with this disturbance include allergies, anxiety, constipation or diarrhea, decreased liver function, decreased pancreatic function, food allergies, muscle pain, pain or swelling in the joints, autoimmune disease, cancer, chemical sensitivities, hyperactivity, chronic hepatitis and pancreatitis, inflammatory bowel disease, malabsorption syndrome, irritable bowel syndrome, and skin conditions such as eczema, psoriasis, urticaria, and acne.

Dysbiosis could be an important unrecognized contributing factor to chronic skin disease, leading to low levels of normal flora (influencing digestion and removal of biodegradable toxins), increased intestinal permeability (toxic overload to liver, lymphatics, interstitial fluids; food sensitivities; autoimmune disease), suppressed immune function, and allergy. Attention to correcting a suspected dysbiosis is worthwhile, and the approach is relatively straightforward.

Therefore, in the treatment of patients with chronic skin disease, whether autoimmune, atopic, infected, or simply chronic, attention must be paid not just to the diagnosis, but to the myriad of contributing factors, such as leaky gut syndrome, dysbiosis, and toxemia, as well as diet, stress levels, drug administration, and so forth. Emphasis is placed on improving systemic health—not just skin health.

When appropriate, herbal interventions may involve the regulation or enhancement of specific body systems, organs, or tissues, or they may require that imbalances be corrected, nutrition optimized, detoxification enhanced, and the energy of the body increased through enhanced vitality (attained with the use of tonics and adaptogens). In chronic disease, an important goal is the stimulation of detoxification, particularly when poor organ function or increased toxic loading is suspected. Detoxification can be achieved by stimulating both the eliminatory organs and the detoxifying processes.

As an informal rule of thumb, chronic skin disease cannot be corrected quickly. The practitioner should allow approximately 3 months' treatment for a condition with duration of 1 year, plus 1 month per each additional year.

Adaptogens

Stress is often a contributing factor to any chronic disease. Adaptogens should be considered if the patient is stressed, anxious, or depressed, in chronic discomfort, and for convalescence. (See Adaptogens in neurology, pain, and behavior section.)

ASHWAGANDHA *(WITHANIA SOMNIFERA):* This agent is a tonic, adaptogen, nervine, and anti-inflammatory.

BUPLEURUM *(BUPLEURUM FALCATUM):* This is an anti-inflammatory, hepatoprotective, renal protective, and tonic treatment.

LICORICE *(GLYCYRRHIZA GLABRA):* This herb is an anti-inflammatory and laxative. It also improves taste.

REHMANNIA *(REHMANNIA GLUTINOSA):* This herb is an anti-inflammatory (useful if the patient is on corticosteroids, or when given following their use).

ELEUTHERO *(ELEUTHEROCOCCUS SENTICOSIS):* This is an immunomodulatory herb.

GOTU KOLA *(CENTELLA ASIATICA):* This herb is a connective tissue regenerator, alterative, nerve tonic, and mild diuretic.

Alteratives/Depuratives

Traditionally, these herbs have been used to detoxify and help eliminatory organs reduce metabolic waste products. Otherwise known as "blood cleansers," they are used to effect a gradual change in chronic disease states, including skin disease. They are said to act by improving the processes of detoxification and elimination, hence they act slowly. A paucity of research data supports their proposed use, but a long tradition of use has been established. Long-term therapy is usually safe and helpful.

BURDOCK ROOT *(ARTICUM LAPPA):* This herb is traditionally used as a "tissue cleanser" to eliminate accumulated toxins; it is used for eczema and septic conditions, as a poultice for boils, and in the management of chronic inflammatory states. It contains inulin

which acts as a prebiotic and may work as a gentle laxative. It also has demonstrated anti-inflammatory activity in vivo (Lin, 1996a), antioxidant activity in vitro (Duh, 1998), and antimicrobial activity in vitro (Holetz, 2002). Wood (2004) recommends it for dry, red, scaly skin with hair loss and overall dry skin. Felter and Lloyd write in *King's American Disensatory* that Burdock is considered an alterative and a tonic, and they recommend its use in psoriasis and other cutaneous affectations.

OREGON GRAPE *(MAHONIA AQUIFOLIUM):* Mahonia is suited to dry, atrophic conditions (rough, dry, scaly skin) when the anabolic function of the liver and the secretory aspect of digestion are compromised. Scudder claimed it "is a blood maker" and a "blood cleanser" that promotes secretion and excretion. It is indicated for dry, scaly, pruritic skin and dandruff (Wood, 2004).

CLEAVERS *(GALLIUM APARINE):* This diuretic and lymphatic is used in skin disease. Cleavers has also been used for dry skin eruptions and as a remedy for ulcers and tumors. Wood (2004) recommends it for skin eruptions that have a neurologic association (resembling neurofibrositis). It is considered a valuable diuretic to assist in the treatment of eczema, seborrhea, and psoriasis. It contains iridoid glycosides that are mildly laxative.

RED CLOVER FLOWERS *(TRIFOLIUM PRATENSE):* Traditionally, red clover has been used for chronic skin disease, specifically for eczema and psoriasis. No scientific data link specific compounds to distinct dermatologic effects.

YELLOW DOCK ROOT *(RUMEX CRISPUS):* Yellow dock is believed to possess gentle purgative and cholagogue properties. Traditionally, it has been used for chronic skin disease, specifically for psoriasis with constipation. Cook, writing in *The Physiomedical Dispensatory* (1869), states that yellow dock is an alterative of the slowly relaxing and stimulating class. It is used in all forms of dry, scaly, itchy, and pustular skin disease.

HEARTSEASE *(VIOLA TRICOLOR):* This herb has traditionally been used for the treatment of patients with eczema, psoriasis, and acne. In folk medicine, it is considered a "blood cleanser." Its anti-inflammatory action may in part be due to the presence of both salicylates and rutin (Willuhn, 1994).

BLUE FLAG *(IRIS VERSICOLOR):* This herb has traditionally used for skin disease, as a "blood purifier and cleanser of toxins" (Meybe, 1988).

SARSAPARILLA (*SMILAX* SPP): European physicians considered this an alterative tonic, blood purifier, diuretic, and diaphoretic (Hobbs, 1988). The ability of Smilax to bind with endotoxins and its antibiotic action may explain its effectiveness.

Herbs with activity within the immune system are also regarded as possessing depurative activity.

ECHINACEA *(ECHINACEA PURPUREA):* This herb has a long history of medicinal use for a wide variety of conditions, primarily infections such as syphilis and septic wounds; it has also been used as an antitoxin for snakebites and blood poisoning (Hobbs, 1994). Traditionally, Echinacea was known as an anti-infective agent that was indicated in bacterial and viral infections, mild septicemia, furunculosis, and other skin conditions such as boils, carbuncles, and abscesses (Bradley, 1992; British Herbal Pharmacopoeia, 1983).

POKE ROOT *(PHYTOLACCA DECANDRA):* King's (Felter, 1898) states that the herb kills scabies mites and is useful for other skin conditions characterized by scaly, vesicular or pustular eruptions, especially those accompanied by lymphatic enlargement. It was recommended for use both locally and systemically in the treatment of patients with skin problems.

Choleretic herbs, such as those listed here, are also considered to have depurative activity:

- Dandelion *(Taraxacum officinale)*
- Fumitory *(Fumaria officinalis)*
- Barberry *(Berberis vulgaris)*
- Globe artichoke *(Cynara scolymus)*

Diuretic herbs that increase detoxification through the urinary tract include the following:

- Dandelion leaf *(Taraxacum officinale)*
- Cleavers *(Gallium aparine)*
- Burdock *(Arctium lappa)*
- Red clover *(Trifolium pratense)*
- Heartease *(Viola tricolor)*

Antiallergy Herbs

The following herbs may help suppress hypersensitivity reactions at any of a number of steps in the process, but their mechanisms of action in vivo are not known. Topical herbs are very useful, but systemic treatment is usually necessary.

NETTLE LEAF *(URTICA DIOICA FOLIA):* This herb, also called *stinging nettles,* induces an allergic skin reaction. Herbalists have traditionally prescribed the juice of the nettle as an antidote to rash. One study found that freeze-dried nettles were helpful for symptoms of allergic rhinitis (Mittman, 1990). The mechanism may be partially due to the presence of quercetin; this herb also has anti-inflammatory activity.

ALBIZIA *(ALBIZIA LEBBECK, ALBIZIA KALKORA):* This plant, also known as mimosa, is an Ayurvedic herb that is used to treat patients with asthma and dermatitis; it is also a traditional Chinese herb that is used as a sedative. In vivo studies on a bark extract of this plant showed antiallergy activity against anaphylaxis (Tripathi, 1979) and atopic allergy (Tripathi, 1979). Albizia has been shown to stabilize mast cell degranulation, depress levels of antiallergy antibodies, and decrease the overaggressive actions of T and B lymphocytes.

BAICAL SKULLCAP ROOT *(SCUTELLARIA BAICALENSIS):* Also called *Huang Qin* in traditional Chinese medicine, this herb has been used traditionally to reduce inflammation and fever. It contains the flavonoids baicalin and wogonin (similar in mechanism of action to quercetin), both of which have antiallergy and free radical scavenging activities (Bochorakova, 2003; Lin, 1996b). Another constituent, baicalein, reduces leukotriene B4 and C4 production by inhibiting lipoxygenase, an action that may lend anti-inflammatory and antiallergy activities (Chang, 1987).

LICORICE *(GLYCYRRHIZA GLABRA):* This herb contains glycyrrhizic acid, which is the major bioactive triter-

pene glycoside of licorice. It possesses a wide range of pharmacologic properties (anti-inflammatory, antiulcer, antiallergic, antidote, antioxidant, antitumor, antiviral, etc.) (Baltina, 2003).

REHMANNIA *(REHMANNIA GLUTINOSA):* This herb has demonstrated antiallergic effects on induced allergic reactions in vivo and in vitro. The aqueous extract reduces plasma histamine levels in a dose-dependent manner. It also dose dependently inhibits histamine release from rat peritoneal mast cells (Kim, 1998).

OTHER HERBS: Other antiallergic herbs include achyranthes, alisma, alpinia, apricot seed, arctium, asarum, astragalus, atractylodes, bupleurum, cardamom, ching pi, cinnamon, citrus, cornus, ephedra (ma huang), galanga, ganoderma, gentian, ginger, ginseng, hoelen, licorice, magnolia, moutan, pinnelia, polyporus, pueraria, rehmannia, scute, stephania, tang-kuei, zedoaria, and ziziphus (Tsung, 1987).

Anti-inflammatory Herbs (Systemic Use)

Anti-inflammatory herbs help to control but not suppress symptoms while longer-term alterative strategies take effect.

EVENING PRIMROSE OIL *(OENOTHERA BIENNIS):* The actions of evening primrose oil are attributable to the essential fatty acid content of the oil and to the involvement of these compounds in prostaglandin biosynthetic pathways. Evening primrose oil contains 8%-10% gamma linolenic acid (GLA), which displaces and competes with more inflammatory fatty acids in cell membranes. Evening primrose oil had inconsistent benefit, improving a portion of patients tested, in multiple clinical trials in dogs and cats (Harvey, 1993a; Harvey, 1993b; Scarf, 1992; Bond, 1992; Scott, 1992; Bond, 1994).

TURMERIC *(CURCUMA LONGA):* This herb has a long history in both Chinese and Ayurvedic medicine as an anti-inflammatory agent. When used orally, curcumin inhibits leukotriene formation, inhibits platelet aggregation, and stabilizes lysosomal membranes, thus inhibiting inflammation at the cellular level (Srimal, 1973). At low levels, curcumin is a prostaglandin inhibitor, and at higher levels, it stimulates the adrenal glands to secrete cortisone (Srivastava, 1985). Powdered turmeric contains 0.6% curcumin (Mukhopadhyay, 1982).

BUPLEURUM *(BUPLEURUM FALCATUM):* The anti-inflammatory activity of bupleurum has been demonstrated by in vivo studies (Chang, 1987); the inhibition of arachidonic acid metabolism by saikosaponins is one of the biochemical mechanisms that has been elucidated (Bermejo, 1998). The potency of anti-inflammatory activity of the saikosaponins is similar to that of prednisolone (Chang, 1987).

LICORICE *(GLYCYRRHIZA GLABRA):* Glycyrrhizin, a major component of *Glycyrrhiza uralensis* (licorice) root, is a saponin that exhibits a number of pharmacologic effects, including anti-inflammation, antiulcer, antiallergy, and anticarcinogenesis (Hsiang, 2002). It has been shown to inhibit the activity of proinflammatory prostaglandins and leukotrienes and appears to have a cortisone-like effect, accounting for its usefulness as an anti-inflammatory (Okimasu, 1981).

GOTU KOLA *(CENTELLA ASIATICA):* This herb is an adaptogen, alterative, and nerve tonic. Triterpenoids are regarded as active principles and are reported to possess wound-healing abilities associated with their stimulating effects on the epidermis and promotion of keratinization. Both asiaticoside and madecassoside are documented to be anti-inflammatory agents (Jacker, 1982). Oral and topical administration of an alcoholic extract of *C. asiatica* for rat dermal wound healing was investigated. The extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increased DNA, protein, and collagen content of granulation tissues; wounds treated with the extract were found to epithelialize faster and the rate of wound contraction was higher, as compared with control wounds. Results showed that *C. asiatica* produced different actions in the various phases of wound repair (Suguna, 1996).

OREGON GRAPE *(BERBERIS AQUIFOLIUM):* Products of lipoxygenase metabolism are known to play a role in the pathogenesis of human psoriasis. Alkaloids in Oregon grape were tested in vitro and were found to inhibit lipid peroxide substrate accumulation by direct reaction with peroxide, by scavenging, or through lipid-derived radicals (Bezakova, 1996).

NETTLE *(URTICA DIOICA):* This traditional herb is used for the treatment of patients with eczema; it is considered to have antiallergic properties and is used to treat itchy skin conditions and insect bites. Nettle leaf extract and caffeic malic acid (the major phenolic component of the extract) were shown to partially inhibit COX- and 5-lipoxygenase (5-LOX)–derived reactions (Obertreis, 1996); also, nettle leaf significantly reduced the release of cytokines in a concentration-dependent manner, and it indirectly decreased PGE_2 synthesis, suggesting an anti-inflammatory effect (Obertreis, 1996).

Antioxidant Herbs

Most herbs have antioxidant activity that is beneficial in reducing oxidative damage associated with inflammation. Herbs that might be useful adjuncts in a formula include Ginger *(Zingiber officinale),* *Ginkgo biloba,* Grapeseed *(Vitis vinifera),* Green tea *(Camellia sinensis),* Reishi *(Ganoderma lucidum),* Rosemary *(Rosmarinus officinale),* Skullcap *(Scutellaria lateriflora),* Milk thistle *(Silybum marianum),* and Turmeric *(Curcuma longa).*

Antipruritics (Systemic)

CHAMOMILE *(MATRICARIA RECUTITA):* The antipruritic effects of diets containing German chamomile on induced scratching in mice have been examined. In mice fed a diet containing 1:2 w/w% of ethyl acetate extract of dried flower of German chamomile for 11 days, scratching behavior was significantly suppressed with no effect on body weight. Inhibitory effects of the dietary intake of German chamomile extract were comparable with those of the antiallergic agent oxatomide (Kobayashi,

2003). The ethyl acetate extract or essential oil of German chamomile showed significant dose-dependent inhibition of induced scratching in mice. The antipruritic effects of the H1 antagonists oxatomide and fexofenadine were only partial in this test. However, the antipruritic effects of these agents were enhanced through combined administration of the ethyl acetate extract of German chamomile (300 mg/kg). Comedication with the ethyl acetate extract, or essential oil of German chamomile, and antihistamines may be more effective for pruritus than either agent alone (Kobayashi, 2005).

TEA *(CAMELLIA SINENSIS):* An open study suggests that consumption of oolong tea helps speed the clearance of atopic dermatitis lesions. A total of 118 people continued their usual medications but also drank oolong tea (10 g steeped in 1000 mL water per day, divided into three doses). Beneficial results were observed after 1 to 2 weeks, and 63% of participants showed marked to moderate improvement in lesions after 1 month. After 6 months, 54% still demonstrated a good response (Uehara, 2001).

Immune-Modulating Herbs

HEMIDESMUS *(HEMIDESMUS INDICUS):* This root is an Ayurvedic herb (Anant Mool, also known as Krishna powder and Indian Sarsaparilla). It is a depurative and tonic that is used to treat patients with chronic skin disease and other conditions such as cough, genitourinary disease, and rheumatism. Oral administration of an ethanol extract decreased activity in both cell-mediated and humoral components of the immune system in mice (Nadkarni, 1976). Its activity is mild and may benefit patients with autoimmune disease by suppressing the Th-2 cell response.

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* This popular herbal medicine is used in Korea, Japan, and China to treat patients with allergic disease. An ethanol extract was tested both in vitro and in vivo to assess murine CD4 T-cell differentiation. Data indicated that astragalus selectively alters Th-1/Th-2 cytokine secretion patterns, which may provide the pharmacologic basis for its clinical applications (Kang, 2004). Astragalus was given to 106 people with herpesvirus keratitis; it changed the state of imbalance of Th-1/Th-2 in these patients and alleviated their immune function disturbance (Mao, 2004).

Nervines

Many animal patients with skin disease display corresponding behavioral signs of anxiety or restlessness. Stress can deplete noradrenaline stores. Adaptogens and nervine herbs may be beneficial. Skullcap *(Scutellaria lateriflora),* Oats *(Avena sativa),* and Saint John's Wort *(Hypericum perforatum)* should be considered.

Effects of Herbal Treatment on Melanin Synthesis

UVA URSI *(ARCTOSTAPHYLOS UVA URSI):* This extract may assist in the treatment of patients with hyperpigmentary disorders because arbutin inhibits melanin synthesis in vitro by inhibiting tyrosinase activity (Matsuda, 1992a).

It should be noted that relatively high levels of melatonin are found in Feverfew flowers *(Tanacetum parthenium);* with 2 µg/g, melatonin (dry weight) levels were reduced by about 30% after fresh leaves were oven-dried. Saint John's Wort flowers *(Hypericum perforatum)* contained about 4 µg/g, and the leaves contained about half that level. Baical skullcap leaves *(Scutellaria baicalensis)* consisted of about 7 µg/g melatonin (Murch, 1997). It should be noted that melatonin can cause marked biological effects, even at very low levels.

DONG QUAI *(ANGELICA SINENSIS):* This herb promoted melanocytic proliferation and enhanced melanin synthesis and the tryosinase activity of melanocytes, which may be the mechanism for validating its clinical usefulness in the treatment of human patients with skin pigmentation problems (Deng, 2003).

Hair Growth

ASIAN GINSENG: A methanol extract of red ginseng promoted hair growth in mouse vibrissal follicles in organ culture. This suggests that *Panax ginseng* possesses hair growth–promoting activity, and that its bioactive components are partially attributable to the ginseng saponin components (Matsuda, 2003).

REVIEW OF SPECIFIC DERMATOLOGIC CONDITIONS

As a starting point, the following prescriptions are suggested. Selection of herbs will depend on pathophysiology of the disorder, as well as the patient and actions and herbs most suited to the individual.

The importance of the connection between the gut and the skin cannot be underestimated. Even in veterinary medicine in the early part of the 20th century, reference was made to the use of aloes for horses and jalap for dogs for eczema, and to the use of alteratives for urticaria. Barbados aloe, aniseed, ginger, gentian, fenugreek, fennel, and linseed meal were common ingredients in alterative physick balls that were designed to improve such conditions in horses (Leeney, 1921).

Dry Skin and Coat (nonpruritic)

In general, dry skin should prompt the practitioner to evaluate dietary fat content first. Flaxseed and other vegetable oils, as well as increased animal fats, easily reverse this simple problem. When dietary influences have been addressed and the problem persists, herbs may be employed.

A prescription for dry skin and dry or coarse coat, as well as brittle nails follows (dose is 1 ml per 5 kg body weight):

Horsetail	20% (contains minerals, including silica)
Bladderwrack	10% (contains iodine; may be useful in subclinical hypothyroidism)
Red clover	20% (alterative)

Burdock	20% (alterative, mildly laxative; contains linoleic acid)
Rehmannia	30% (adaptogen, blood tonic)

"Condition" powders for horses (adapted from those published in 1920 by the Royal College of Veterinary Surgeons):

Gentian	1 part powdered
Ginger	1 part powdered
Fenugreek	1 part powdered
Licorice	1 part powdered

Atopy and Skin Allergies

Therapeutic rationale

- Reduce exposure to known allergens.
- Consider an elimination diet.
- Modulate immune function.
- Reduce allergic pruritus.
- Inhibit mast cell release of histamine.
- Reduce inflammation.

A study from the University of Minnesota College of Veterinary Medicine investigated three herbs for control of pruritus in atopic dogs. Fifty dogs with atopic dermatitis were assessed by both owners and veterinarians and were given placebo or a combination of Licorice, White peony *(Paeonia lactiflora),* and Rehmannia *(Rehmannia glutinosa).* These herbs were chosen as components of a well-tested human product (not now commercially available) on the basis of company (Phytopharm, United Kingdom) bioassay and palatability. Of dogs receiving herbs, 37.5% improved, compared with 13% in the placebo group, and deterioration scores were worse in the placebo group at the final visit. Although neither result reached statistical significance, researchers were encouraged by the results and suggested further study (Nagle, 2001).

Although the modes of action of alteratives are not clear, they are invaluable in the treatment of patients with chronic allergic skin disease. Concurrent conventional therapy may be required initially, and doses may have to be reduced after 4 to 6 weeks. Herbal therapy should be continued for a minimum of 3 months.

A prescription for allergic dermatitis with dry or moist skin lesions follows:

Burdock	20% (depurative, mild laxative, nutritive)
Red clover	20% (alterative)
Cleavers	20% (diuretic, astringent)
Nettle (leaf)	20% (nutritive, circulatory stimulant, anti-inflammatory, diuretic)
Astragalus	20% (immune modulating, tonic, diuretic)

An alternate prescription for atopic dermatitis is:

Baical skullcap	20% (antiallergy, anti-inflammatory, antibacterial, mild sedative, diuretic, bitter)
Nettles (leaf)	20% (nutritive, circulatory stimulant, anti-inflammatory, diuretic)
Burdock	20% (depurative, mild laxative, nutritive)
Licorice	20% (anti-inflammatory, adaptogen. laxative, taste improver)
Astragalus	20% (immune modulating, tonic, diuretic)

Another prescription for atopic dermatitis is:

Rehmannia	25% (blood tonic, immune modulating)
Licorice	10% (anti-inflammatory, adaptogen. laxative, taste improver)
White peony	25% (anti-inflammatory, antiallergic, immune enhancing)
Sarsaparilla	15% (anti-inflammatory, antiseptic)
Yellow dock or Oregon grape	25% (alterative, cholagogue)

David Hoffman (Hoffmann, 2004) has published this prescription for eczema:

Cleavers	33%
Nettles	33%
Red clover	33%

For acute moist dermatitis (or "hot spots"), black or green tea applied topically (in the moistened tea bag, or as tea on a compress, or as a spray) is very useful for reducing inflammation and pruritus.

Autoimmune Skin Disease*

Therapeutic rationale

- Improve systemic health by improving digestion.
- Eliminate triggers (bacterial, viral, vaccine-related, etc.).
- Reduce stress.
- Regulate immune function.

A prescription for autoimmune skin disease follows:

Bupleurum	20% (anti-inflammatory, hepatoprotective, renal protective, tonic)
Echinacea*	20% (immune modulating, anti-inflammatory, antibacterial, antiviral, vulnerary)
Rehmannia	20% (anti-inflammatory, antiallergy, immune modulating)
Burdock	20% (depurative, mild laxative, nutritive)
Licorice	20% (anti-inflammatory, adaptogen, laxative, taste improver)

Chronic Demodectic Mange

Therapeutic rationale

- Improve immunity.
- Reduce bacterial load.
- Improve systemic health, especially gastrointestinal health.
- Nourish the skin.

A prescription is provided:

Echinacea	20% (immune modulating, anti-inflammatory, antibacterial, antiviral, vulnerary)
Burdock	20% (depurative, mild laxative, nutritive)
Blue flag	20% (cholagogue, laxative, diuretic, alterative, lymphatic)
Baptisia	20% (antimicrobial, antipyretic, antiseptic)
Calendula	20% (lymphatic, anti-inflammatory, astringent, vulnerary, cholagogue)

For other ectoparasitic diseases, see section "Herbs for Topical Use".

*See Author's note on page 320.

Authors' note: The use of immune-enhancing herbs in autoimmune disease is very controversial. The German Commission E monograph recommends that Echinacea not be used in patients with autoimmune disease because of the risk that its immune-stimulating effects could lead to exacerbation of autoimmune illness. Despite several adverse event reports associated with the use of Echinacea in patients with autoimmune disease, the risk has not been adequately studied. The British Herbal Pharmacopoeia (1983) and the British Herbal Compendium offer no contraindications for Echinacea. In fact, it is proposed (Bone, 1997) that molecular mimicry by infectious organisms may be causative in autoimmune disease, and that Echinacea may be benefical in decreasing the chronic presence of microorganisms. Echinacea increases phagocytic activity and increases immune surveillance. This may assist the body in eliminating organisms or neutralizing their imbalancing effects on the immune system, thereby downregulating an inappropriate immune response.

Chronic or Recurrent Pyoderma

Therapeutic rationale

- Improve systemic health.
- Improve immunity.
- Reduce bacterial load.

A prescription for immune support and lymphatic drainage follows:

Echinacea	20% (immune modulating, anti-inflammatory, antibacterial, antiviral, vulnerary)
Cleavers	20% (diuretic, astringent)
Astragalus	20% (immune modulating, tonic, diuretic)
Blue flag	20% (cholagogue, laxative, diuretic, alterative, lymphatic)
Calendula	15% (lymphatic, anti-inflammatory, astringent, vulnerary, cholagogue)
Poke root	5% (immune enhancing, lymphatic)

A prescription for deep pyoderma (modified from Weiss, 1988) is given here:

Nettle	10%
Dandelion root and herb	15%
Cascara bark	20%
Senna leaf	15%
Anise fruit	20%
Oregon grape root	20%

See also the section on herbs for topical use, especially pertaining to tea tree oil *(Melaleuca alternifolia)*. Tea tree has been shown in human trials to be beneficial in the treatment of acne and Staphylococcus infections (Martin, 2003), as well as in trials in dogs with dermatitis.

ENDOCRINE HERBS

Many herbs can influence the functioning and metabolism of endocrine organs like the thyroid, or endocrine tissue such as the pancreas; however, the therapeutic effects of these herbs may not be an adequate substitute for the efficacy of hormone replacement like insulin and thyroxine. Although conventional drugs target replacement of various hormone compounds, or regulate their production, herbs may be used to reduce drug doses, regulate drug requirements, improve systemic health, and alleviate the secondary effects of systemic disease that result from endocrine changes. The following herbs have activity relating to the endocrine system but can be prescribed alongside herbs for any other system.

Mechanisms of Interest

Adrenal activity

Adaptogens (discussed under the neurologic system) are key herbs for consideration in conditions affecting the adrenal medulla. Nervine tonics also help to reduce anxiety and stress.

CORDYCEPS *(CORDYCEPS SINENSIS):* In vitro, a water-soluble extract of *C. sinensis* induced a dose-dependent increase in corticosterone production in rat adrenal cells from 1 hour after the addition of the extract up to 24 hours later. It was concluded that the effect was different from that of adrenocorticotrophic hormone (ACTH) (Wang, 1998).

ASIAN GINSENG *(PANAX GINSENG):* Many activities exhibited by *Panax ginseng* have been compared with corticosteroid-like actions, and results of endocrinologic studies have suggested that the ginsenosides may primarily augment adrenal steroidogenesis via an indirect action on the pituitary gland (Ng, 1987). Ginsenosides have increased adrenal cAMP in intact, but not in hypophysectomized, rats, and dexamethasone (which provides positive feedback at the level of the pituitary gland) has blocked the effects of ginsenosides on pituitary corticotropin and adrenal corticosterone secretion (Li, 1987). Ginsenosides may augment adrenocortical steroid production, accounting for its adaptogenic activity (Nocerino, 2000; Rai, 2003b; Kim, 2003). Ginseng saponin was found to act on the hypothalamus or the hypophysis primarily; it stimulated ACTH secretion, which resulted in increased synthesis of corticosterone in the adrenal cortex (Hiai, 1979).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* The alcohol extract of ashwagandha (100 mg/kg twice daily on day 1, 4, or 7) attenuated stress-induced increases in blood urea nitrogen, lactic acid, and adrenal hypertrophy but did not affect changes in thymus weight and hyperglycemia in rats (Dadkar, 1987). Ashwagandha reversed stress-induced increases in plasma corticosterone in rats (Archana, 1999). The adaptogenic activity of a standardized extract of ashwagandha root was investigated in a rat model of chronic stress. Stress-induced significant hyperglycemia, glucose intolerance, increased plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression, and mental depression. These stress-induced changes were attenuated by ashwagandha (25 and 50 mg/kg given orally) administered before stress induction (Bhattacharya, 2003).

LICORICE *(GLYCYRRHIZA GLABRA):* Much has been documented regarding the steroid-type actions of licorice.

Both glycyrrhizin and glycyrrhetinic acid (GA) have been reported to bind to glucocorticoid and mineralocorticoid receptors with moderate affinity, and to estrogen receptors, sex hormone–binding globulin, and corticosteroid-binding globulin with very weak affinity (Tamaya, 1986; Armanini, 1983, 1985). It has been suggested that glycyrrhizin and GA may influence endogenous steroid activity via a receptor mechanism, with displacement of corticosteroids or other endogenous steroids (Tamaya, 1986).

The relatively low affinity of glycyrrhizin and glycyrrhetinic acid for binding to mineralocorticoid receptors, together with the fact that licorice does not exert its mineralocorticoid activity in adrenalectomized animals, indicates that a direct action at the mineralocorticoid receptors is not the predominant mode of action (Stewart, 1987). It has been suggested that glycyrrhizin and GA may exert their mineralocorticoid effects via inhibition of 11β-hydroxysteroid dehydrogenase (11β-OHSD) (Stewart, 1987). 11β-OHSD is a microsomal enzyme complex found predominantly in the liver and kidneys that catalyzes the conversion of cortisol (potent mineralocorticoid activity) to inactive cortisone. Deficiency of 11β-OHSD results in increased concentrations of urinary free cortisol and cortisol metabolites. GA has been shown to inhibit renal 11β-OHSD in rats (Stewart, 1987). It has also been proposed that glycyrrhizin and GA may prevent cortisol from binding to transcortin (Forslund, 1989). One recent case study reports the use of licorice in an Addisonian dog with persistent hyperkalemia. Preliminary results show the dog to be normokalemic after licorice administration (Jarrett, 2005).

ANISEED *(PIMPINELLA ANISUM):* The pharmacologic effects of aniseed are largely due to the presence of anethole, which is structurally related to the catecholamines adrenaline, noradrenaline, and dopamine. Anethole dimers closely resemble the estrogenic agents stilbene and diethylstilbestrol (Albert-Puleo, 1980).

GINKGO *(GINKGO BILOBA):* It has been shown that long-term administration of a *Ginkgo biloba* extract inhibits stress-induced corticosterone hypersecretion through a reduction in the number of adrenal peripheral-type benzodiazepine receptors (PBRs). In addition, ginkgo constituents act at the hypothalamic level and are able to reduce corticotrophic releasing hormone expression and secretion (Marcilhac, 1998). Treatment of rats and adrenocortical cells with ginkgolide B reduced mRNA, protein, and ligand binding levels of the adrenal PBR, leading to decreased corticosteroid synthesis. Results of this study demonstrated that ginkgolide B–activated inhibition of glucocorticoid production is due to transcriptional suppression of the adrenal PBR gene and the authors suggest that this might serve as a pharmacologic tool for controlling excess glucocorticoid formation (Amri, 2003).

Androgenic activity

GINGER *(ZINGIBER OFFICINALE):* An aqueous extract was tested for possible androgenic activity in male rats. It significantly increased the relative weight of the testis, serum testosterone level, testicular cholesterol level, and level of epididymal α-glucosidase activity (Kamtchouing, 2002). Effects on aggression of oral application of 3 mg/day of the ethanolic extracts of ginger were investigated for 6 weeks in intact male mice. The use of ginger showed a dramatic increase in attacks between mice, along with increased spermatozoa count and motility (Homady, 2001).

Antigonadotrophic activity

LYCOPUS *(LYCOPUS EUROPAEUS):* This herb reduces luteinizing hormone, thyroid-stimulating hormone, and testosterone levels, but not levels of prolactin, in rats administered oral treatment. This reduction was pronounced in spite of reduced thyroxine (T4) and triiodothyronine (T3) levels, suggesting a central point of activity of the plant extract (Winterhoff, 1994). The antigonadotrophic activities of *Lycopus* species can be attributed to their phenolic components. These compounds represent precursors of biologically active products that are formed through an oxidation step. Among the oxidation products of phenolic substances, the corresponding quinones are found. It can be demonstrated that the reaction between quinones and unoxidized diphenols yields products with strong antigonadotrophic activity. This type of reaction—the formation of quinhydrones—is proposed to be involved in the formation of various products with antigonadotrophic activity (Gumbinger, 1981).

Antidiabetic activity

ASIAN GINSENG *(PANAX GINSENG):* Hypoglycemic activity has been documented for ginseng and has been attributed to both saponin and polysaccharide constituents. In vitro studies using isolated rat pancreatic islets have shown that ginsenosides promote an insulin release that is independent of extracellular calcium and that uses a different mechanism from that of glucose (Guodong, 1987). In addition, in vivo studies in rats have reported that a ginseng extract increases the number of insulin receptors in bone marrow and reduces the number of glucocorticoid receptors in rat brain homogenate (Yushu, 1988). Both of these actions are thought to contribute to the antidiabetic actions of ginseng.

TURMERIC *(CURCUMA LONGA):* This herb has been used for the treatment of patients with diabetes. One study evaluated turmeric and curcumin in treating rats with induced diabetes. The lower rate of weight gain by diabetic rats, compared with nondiabetic rats, was normalized by oral administration of an aqueous extract of turmeric (1 g/kg) or curcumin (0.08 g/kg) for 21 days. Results revealed a decrease in the cellular leakage of acid phosphatase, alkaline phosphatase, and lactate dehydrogenase into the serum of diabetic animals. Curcumin appeared to be more effective in attenuating diabetes mellitus than turmeric (Arun, 2002).

COMBINATION OF UVA URSI *(ARCTOSTAPHYLOS UVA URSI)*, GOLDENSEAL *(HYDRASTIS CANADENSIS)*, MISTLETOE *(VISCUM ALBUM)*, AND TARRAGON *(ARTEMISIA DRACUNCULUS):* This combination significantly reduced the hyperphagia and polydipsia associated

with streptozotocin–diabetic mice. Treatments were supplied as 6.25% by weight of the diet for 9 days. No effect on insulin or glucose concentrations was observed (Swanston-Flatt, 1989).

CORDYCEPS *(CORDYCEPS SINENSIS):* A study on rats with induced diabetes revealed that the fruiting body—not the carcass of Cordyceps—attenuated diabetes-induced weight loss, polydipsia, and hyperglycemia. This suggested that the fruiting body of Cordyceps has potential as a functional food for patients with diabetes (Lo, 2004). Effects of *C. sinensis* on pancreatic islet B cells of rats with hepatic fibrogenesis were investigated. No change was seen in levels of serum insulin and basal insulin between the test group and the normal group at week 3; however, at week 6 serum insulin and basal insulin were higher in the test group than in the normal group. It was concluded that Cordyceps can increase the basal insulin levels of islets in rats with induced liver fibrosis (Zhang, 2003a).

GINGER *(ZINGIBER OFFICINALE):* The effects of ginger juice (4 mL/kg orally daily, given for 6 weeks) on rats with induced type I diabetes were studied. In normoglycemic rats, 5-HT (1 mg/kg intraperitoneally) produced hyperglycemia and hypoinsulinemia, which were significantly prevented by ginger juice. Treatment with ginger produced a significant increase in insulin levels and a decrease in fasting glucose levels in diabetic rats as well as a decrease in serum cholesterol, serum triglyceride, and blood pressure. The data suggested potential antidiabetic activity of ginger juice in type I diabetic rats, possibly involving 5-HT receptors (Akhani, 2004).

Antihyperglycemic effects

GINSENG *(PANAX GINSENG AND P. QUINQUEFOLIUS):* These herbs have been studied extensively, and data suggest that the antihyperglycemic activity of ginseng may be highly variable. In healthy humans, two batches of American ginseng demonstrated acute postprandial glycemic index lowering efficacy, and a third batch was ineffective, whereas Japanese, Asian red, and Sanchi ginsengs had null effects, and Asian, American wild, and Siberian ginsengs raised glycemia (Sievenpiper, 2004). The dose and the quality of the herb are therefore important, which demonstrates the need for monitoring of patients who are taking herbal medicines.

GYMNEMA *(GYMNEMA SYLVESTRE):* This herb has been found to reduce hyperglycemia in both animal and human studies. Its antidiabetic activity appears to be due to a combination of mechanisms. Animal studies on beryllium nitrate–and streptozotocin–diabetic rats found that Gymnema doubled the number of insulin-secreting β cells in the pancreas and returned blood sugars to almost normal (Prakash, 1986; Shanmugasundaram, 1990). Gymnema increased the activity of enzymes responsible for glucose uptake and utilization (Shanmugasundaram, 1983) and inhibited peripheral utilization of glucose by somatotrophin and corticotrophin (Gupta, 1964). Gymnema has also been found to inhibit epinephrine-induced hyperglycemia (Gupta, 1961).

MADAGASCAR PERIWINKLE LEAF JUICE *(CATHARANTHUS ROSEUS)* AND SEED POWDER OF FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* These herbs were tested for their hypoglycemic actions when used individually and in combination in normal and alloxan-induced diabetic rabbits. Blood glucose was determined in all groups before and after treatment with *C. roseus* (0.5, 0.75, and 1.0 mL/kg) and fenugreek (50, 100, and 150 mg/kg) throughout a 24-hour period, after fasting for 18 hours. The effects were dose dependent with both treatments. The percentage of blood glucose reduction produced by the combination of periwinkle (0.5 mL/kg) and fenugreek (50 mg/kg) was greater than the sum of the individual percentages of blood glucose reduction in both normal and diabetic rabbits, suggesting that the combination produced a synergistic action (Satyanarayana, 2003).

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* This herb and isolated fenugreek fractions have been shown to act as hypoglycemic and hypocholesterolemic agents in both animal and human studies. The dietary fiber composition and high saponin content in fenugreek appear to be responsible for these therapeutic properties (Madar, 2002). Fractions of seeds were given to normal and diabetic dogs for 8 days. Effects on glucose and pancreatic hormones were tested. The lipid fraction of the herb had no effect; the defatted fraction of the herb lowered basal blood glucose, glucagon, and somatostatin and reduced the orally induced hyperglycemia. In diabetic dogs on insulin, the defatted fraction reduced hyperglycemia and glycosuria (Ribes, 1986). In diabetic rats, the inclusion of fenugreek overcame the toxicity of vanadium when given alone. Lower rates of vanadate were needed in combination with fenugreek, and the combined effects were better at restoring the above parameters than was insulin (Dhananjay, 1999).

INULA *(INULA RACEMOSA)* AND GYMNEMA *(GYMNEMA SYLVESTRE):* These (leaf) extracts given alone or in combination were evaluated in the amelioration of corticosteroid-induced hyperglycemia in mice. The extracts in combination were more effective than the individual extracts. The effects were comparable with those of a standard corticosteroid-inhibiting drug, ketoconazole. Because no marked changes in thyroid hormone concentration were observed with the administration of any extracts in corticosteroid-treated animals, it was suggested that these plant extracts may not be effective in thyroid hormone–mediated type II diabetes, but that they would be for steroid-induced diabetes (Gholap, 2003).

BILBERRY *(VACCINIUM MYRTILLUS)* (BILBERRY LEAF TEA): This herb reduced high blood glucose levels in normal and diabetic dogs, even when glucose was concurrently injected intravenously (Allen, 1927). Bilberry extracts are widely used in Europe for the treatment and prevention of secondary eye problems (e.g., diabetic retinopathy cataracts) in people (Murray, 1995); the berry rather than the leaf is most beneficial here. This is a very safe herb that has no known adverse effects.

ALOE *(ALOE VERA):* The dried sap is a traditional remedy for diabetes; it has been reported to reduce blood glucose in patients with type 2 diabetes and in an animal model (Ghannam, 1986). Oral administration of the

juice (prepared from the gel) has been reported to reduce fasting blood glucose and triglyceride levels in patients with type 2 diabetes; the amount used was 1 tablespoon taken twice daily (Bunyapraphatsara, 2003; Yongchaiyudha, 1996).

REHMANNIA *(REHMANNIA GLUTINOSA):* The hypoglycemic and antidiabetic effects of Rehmannia oligosaccharide in glucose-induced hyperglycemic and alloxan-induced diabetic rats were investigated. It was shown that this herb exerted a significant hypoglycemic effect in normal and alloxan-induced diabetic rats. The regulatory mechanism of glucose metabolism was adrenal dependent and was closely related to the neuroendocrine system (Zhang, 2004).

DANDELION *(TARAXACUM OFFICINALE):* In vitro testing of an extract of dandelion revealed insulin secretagogue activity (Hussain, 2004).

Other herbs with hypoglycemic effects

The antihyperglycemic effects of fenugreek *(Trigonella foenum-graceum),* Damania *(Turnera diffusa),* and *Euphorbia prostrata* were studied. Each plant was processed in the traditional way and was intragastrically administered to temporarily hyperglycemic rabbits. Results showed that several plants significantly decreased the hyperglycemic peak or the area under the glucose tolerance curve (Alarcon-Aguilara, 1998).

Other herbs with hyperglycemic effects include agrimony, alfalfa, bugleweed, burdock, celery, corn silk, dandelion, elecampane, eucalyptus, garlic, ginger, ginseng, goat's rue, panax, ispaghula, Java tea, juniper marshmallow, myrrh, nettle, sage, senega, siberian ginseng, tansy (Brinker, 1997).

Hyperglycemic activity

Herbs that may increase blood sugar include Elecampane, *Panax ginseng,* Gotu kola, Licorice, Rosemary, and Tea *(Camellia sinensis).* These herbs may be contraindicated in the treatment of some diabetic patients.

Thyroid-stimulating activity

ASHWAGANDHA *(WITHANIA SOMNIFERA):* A root extract (1.4 g/kg) increased T4 and liver glucose-6-phosphatase in mice and decreased liver lipid peroxidation (Panda, 1999). The same dose rate given for 20 days to mice increased liver superoxide dismutase, glucose-6-phosphatase, and catalase and increased serum 3,3′,5-triiodothyronine (T3) and tetraiodothyronine (T4) (Panda, 1998).

BRAHMI *(BACOPA MONNIERA):* Leaf extracts (200 mg/kg) were investigated in the regulation of thyroid hormone concentrations in male mice. T4 concentration was increased by Bacopa, suggesting a thyroid-stimulating role. Bacopa increased T4 concentration by 41% while decreasing hepatic lipid peroxidation and increasing superoxide dismutase (SOD) and catalase (CAT) activities, thereby showing an antiperoxidative role (Kar, 2002).

BLADDERWRACK *(FUCUS VESICULOSUS):* Bladderwrack (kelp) is often touted as a treatment for patients with hypothyroid disease; however, published supporting evidence is distinctly lacking. The charcoal derived from kelp (under the name of *Aethiops vegetabilis,* or vegetable ethiops) was once used in the treatment of patients with goiter and scrofulous swelling. Experiments of Hunt and Seidell in 1910 presented evidence to show that the extract of this plant is a powerful stimulant for the thyroid gland (Remington, 1918). It may be of greatest value in conditions associated with iodine deficiency.

Thyroid-inhibiting activity

ALOE VERA: An extract (125 mg/kg) was investigated for the regulation of thyroid hormone concentrations in male mice. Serum levels of both T3 and T4 were inhibited by *A. vera* (Kar, 2002).

BUGLEWEED *(LYCOPUS VIRGINICUS):* This herb decreases levels of several hormones in animal models, particularly thyroid-stimulating hormone (TSH) and the thyroid hormone T4 (Wagner, 1970). In rats, an ethanolic extract of *Lycopus europaeus* caused a long-lasting (for a period longer than 24 h) decrease in T3 levels, presumably as a consequence of reduced peripheral T4 deiodination. Pronounced reductions in T4 and TSH concentrations were observed 24 h after application of the extract by gavage (Winterhoff, 1994). *Lycopus virginicus* and *Lycopus europaeus* have the ability to inhibit many of the effects of exogenous and endogenous TSH on the thyroid gland; they inhibit adenylate cyclase in the thyroid and inhibit cAMP, particularly at high doses (Auf'mkolk. 1984b). Aqueous extracts from *L. virginicus* also inhibit extrathyroidal enzymic T4-5′-deiodination to T3 and T4-5′-deiodination. These effects are dose dependent. Rosmarinic acid, ellagic acid, and luteolin-7 β-glucoside are active inhibitory components (Auf'mkolk, 1984a).

LEMON BALM *(MELISSA OFFICINALIS):* In vitro investigation showed lemon balm to disrupt thyroid activity by inhibiting TSH-stimulated adenylate cyclase production. It also produced significant inhibition of TSH binding to its receptor and of antibody binding to TSH. Data suggest that lemon balm may block the binding of TSH to its receptor by acting on both the hormone and the receptor itself (Santini, 2003).

REVIEW OF SPECIFIC ENDOCRINOLOGIC CONDITIONS

Hypoadrenocorticism

Therapeutic rationale

- Correct electrolyte abnormalities.
- Improve adrenal and systemic health and alleviate signs of Addison's disease.
- Supply corticosteroid-like action.

A prescription for adrenal support follows here:

Siberian ginseng	20% (adaptogenic, immunomodulatory)
Astragalus	20% (immune modulating, tonic, cardiotonic, diuretic, hypotensive, antitumor)
Licorice	20% (anti-inflammatory, adaptogen, mineralocorticoid and corticoid-like activity)
Ashwagandha	40% (tonic, adaptogen, nervine, anti-inflammatory, antitumor)

Panax ginseng can be substituted for Siberian ginseng in a debilitated or elderly patient.

Hyperadrenocorticism

Therapeutic rationale

- Reduce production of corticosteroids.
- Improve adrenal and systemic health (including the liver) and reduce signs.
- Improve immunity (and reduce secondary infection).

A prescription for hyperadrenocorticism follows:

Ginkgo	20% (antioxidant, circulatory stimulant, cognition enhancer, may reduce corticosteroid production)
Milk thistle	20% (hepatotonic, antioxidant, hepatoprotective)
Dandelion	20% (diuretic, alterative, laxative, cholagogue)
Rehmannia	20% (renal protective, adaptogen)
Astragalus	20% (immune modulating, tonic, cardiotonic, diuretic, hypotensive, antitumor)

Hyperadrenocorticism (Cushing's Disease) in Horses

In an open trial involving 25 horses and ponies diagnosed with Cushing's disease, chaste tree was administered to animals that should have already been shed. Each of the animals was given a daily dose of *Vitex agnus-castus* for 3 months. The study demonstrated the following: reduced hirsutism—with subsequent reduction in hyperhidrosis—improved energy levels and mood; apparent reduction in the incidence of laminitis; reduced polyuria and polydipsia; and decreased abnormal fat deposits. The results encourage further research into therapeutic effects of *Vitex-agnus castus* in horses (Self, 2003). However, another study showed that *Vitex-agnus castus* extract did not have a beneficial effect in horses with pituitary pars intermedia hyperplasia (equine Cushing's syndrome) (Beech, 2002).

Diabetes Mellitus

Therapeutic rationale

- Improve metabolism of food.
- Use hypoglycemic agents (note that careful monitoring is required because insulin adjustments will be needed).
- Prevent long-term complications.
- Improve systemic health and pancreatic health.

Prescription 1 for diabetes mellitus:

Gymnema	30% (hypoglycemic, pancreatic trophorestorative, astringent, mild diuretic)
Panax	30% (adaptogenic, tonic, hypoglycemic, immunostimulant, hepatoprotective, cardioprotective)
Fenugreek	20% (hypoglycemic, laxative, nutritive)
Bilberry	20% (vasoprotective, antioxidant, anti-inflammatory, astringent)

Prescription 2 for diabetes mellitus:

Bilberry	20% (vasoprotective, antioxidant, anti-inflammatory, astringent)
Gymnema	30% (hypoglycemic, pancreatic trophorestorative, astringent, mild diuretic)
Dandelion	20% (diuretic, alterative, laxative, cholagogue)
Rehmannia	30% (hypoglycemic, renal protective, adaptogen)

Prescription for prevention of complications:

Gymnema	30% (hypoglycemic, pancreatic trophorestorative, astringent, mild diuretic)
Bilberry	20% (vasoprotective, antioxidant, anti-inflammatory, astringent)
Globe artichoke	20% (diuretic, hepatoprotective, choleretic, bitter, hepatic trophorestorative)
Astragalus	30% (immune modulating, tonic, cardiotonic, diuretic, hypotensive, antitumor)

Hyperthyroidism

Therapeutic rationale

- Use relaxing nervines and adaptogens to help prevent the adverse effects of the condition.
- Cardiac tonics may be beneficial.
- Herbs can support the work of conventional medications.

Prescription for feline hyperthyroidism with hyperactivity include the following:

Bugleweed	25% (cardioactive diuretic, reduces heart rate, sedative, thyroxine antagonist)
Motherwort	25% (sedative, cardiotonic)
Hawthorn	25% (cardiotonic, hypotensive, antioxidant)
Passionflower	25% (sedative, nervine, antispasmodic)

Prescription for feline hyperthyroidism with renal disease:

Hawthorn	25% (cardiotonic, hypotensive, antioxidant)
Motherwort	25% (sedative, cardiotonic)
Bugleweed	25% (cardioactive diuretic, reduces heart rate, sedative, thyroxine antagonist)
Rehmannia	25% (adaptogen, renal protective)

Note description of herbs for hypertrophic cardiomyopathy in the section on cardiovascular herbs; the formulas above may be modified by adding lemon balm, Oregon grape, ginkgo, valerian, or pharmacological effect of ethanol extract.

Hypothyroidism

Therapeutic rationale

- No herbs contain thyroxine.
- Stimulate the thyroid, if appropriate, although autoimmune herbs may be more strategic.
- Treat associated disorders: bitters, skin emollients, and circulatory stimulants may be helpful; constipation can be alleviated with mild laxative herbs; antidepressant herbs may be beneficial.

A prescription for hypothyroidism is provided here:

Ginger	10% (bitter, carminative, antispasmodic, anti-inflammatory, circulatory stimulant)
Milk thistle	20% (hepatotonic, antioxidant, hepatoprotective)
Bupleurum	30% (anti-inflammatory, hepatoprotective, renal protective, tonic)

Ashwagandha	40% (tonic, adaptogen, nervine, anti-inflammatory, antitumor)

HERBS FOR GASTROINTESTINAL TRACT DISORDERS

General Considerations

"Let your food be your medicine," said Hippocrates. Throughout history, plants have been our medicine; they have a direct effect on digestion attained via absorption, metabolism, and elimination of plant chemicals, and a direct action achieved through tissue contact in the GI tract. The GI tract is central to systemic health, and a recognized fundamental linkage exists between the gut and systemic health in conditions as wide ranging as asthma, atopy, autoimmune disease, and even arthritis. Visceral reflex connections between the gut and other mucous membranes in the body are employed in herbal medicine, so anything that improves digestion will improve tissues elsewhere in the body.

Considering that the gut plays a significant role in immune function, this is no surprise. Therefore, in herbal medicine, significant emphasis is placed on the health of the digestive system; history taking includes nature of bowel movements and any symptoms related to gut function. Clinically, even mild digestive disturbances, such as burping, mild constipation, inconsistent stools, or excessive flatulence, are always considered significant, even if they are not the reason why a patient presents for consultation.

Mechanisms of Interest

Antacids and antiulcer herbs

A number of herbs counteract stomach acidity and have demonstrated a protective effect against the induction of gastric and duodenal ulcers, as well as efficacy in the treatment of patients with ulcers. These herbs are discussed in the following paragraphs.

Extracts from Lemon Balm *(Melissa officinalis)*, Chamomile *(Matricaria recutita)*, Peppermint *(Mentha x piperita)*, Licorice *(Glycyrrhiza glabra)*, Angelica Root *(Angelica archangelica)*, Milk Thistle *(Silybum marianum)*, and Greater Celandine *(Chelidonium majus)*: Singly and combined, these herbs were tested for their potential antiulcerogenic activity against indomethacin-induced gastric ulcer in rats, as well as for their antisecretory and cytoprotective activities. All extracts produced dose-dependent antiulcerogenic activity associated with reduced acid output and increased mucin secretion, increased prostaglandin E_2 release, and leukotrienes that were decreased in the gastric mucosa. The most beneficial effects were observed with combinations and were comparable with the effects of cimetidine. It was concluded that the cytoprotective effects of the extracts could in part be due to their flavonoid content and free radical scavenging properties (Khayyal, 2001).

Meadowsweet *(Filipendula ulmaria)*: This herb is considered to be a normalizer of acidity in the stomach. Its positive effect on the mucosa is paradoxical because it also contains salicylates. When used in an experimental model of ulcers induced by acetylsalicylic acid (aspirin), meadowsweet, given at rates of 0.7 and 1.25 mL/kg, caused reduced numbers of ulcers by 25.4% and 26.2%, respectively. Injection of the infusion at rates of 0.35 to 15.0 mL/kg accelerated the evacuation of gastric contents, providing better protection of the mucous membrane (Gorbacheva, 2002).

Turmeric *(Curcuma longa)*: Curcuma longa has been commonly used as a traditional remedy for a variety of symptoms such as inflammation, gastritis and gastric ulcer. One study showed that an ethanol extract from *C. longa* specifically inhibits gastric acid secretion by blocking H(2) histamine receptors in a competitive manner (Kim 2005). Intragastric administration of an ethanol extract of turmeric to rats inhibited gastric secretion and protected the gastroduodenal mucosa against chemical, physical, and drug-induced injuries. Turmeric stimulated the production of gastric wall mucus and restored nonprotein sulfides in rats (Rafatullah, 1990). The German Commission E monograph is frequently used as an authoritative source for information on herbal medicine. It lists gastric ulcer, hyperacidity, peptic ulcer as contraindications for use of turmeric, however, newer studies suggest that these cautions are unwarranted.

Bilberry *(Vaccinium myrtillus)*: Anthocyanins have been shown to have antiulcer activity in various experimental models of acute gastric ulcer and in chronic ulcer induced by acetic acid. The mechanism for this may be potentiation of the defensive barriers of the gastrointestinal tract mucosa, such as the secretion of gastric mucus or the stimulation of cellular regeneration (Magistretti, 1988).

Comfrey *(Symphytum officinalis)* and Calendula *(Calendula officinalis)*: This combination was used, alone (137 patients) or in combination with an antacid (33 patients), to treat patients with gastroduodenitis and gastric ulcer. In all, 90% of patients were relieved of pain and the ulcers healed (Chakurski, 1981a). Comfrey is not available in US commercial trade for oral use because of its content of pyrrolizidine alkaloids.

Chamomile *(Chamomilla/Matricaria recutita)*: This extract inhibited ethanol-induced ulceration, and antiulcerogenic activity in rats has been reported for α-bisabolol (Mann, 1986; Szelenyi, 1979).

Milk Thistle *(Silybum marianum)*: Administration of this herb to rats prevented gastric ulceration induced by cold stress. Gastric secretion volume and acidity were not affected, but histamine concentration was significantly decreased. It was suggested that the antiulcerogenic effects of silymarin may be related to inhibition of enzymic peroxidation by the lipoxygenase pathway (Alacrin De Le Lastra, 1992). The protective effects of silymarin and its effects on mucosal myeloperoxidase have been compared with those of allopurinol. Mean ulcer indexes of rats treated with 25, 50, and 100 mg/kg silymarin were significantly lower than those in control rats, although allopurinol was considerably more potent (2.3; 100 mg/kg) (Alarcon De La Lastra, 1995).

DAN SHEN *(SALVIA MILTIORRHIZA):* This herb increased gastric mucosal blood flow in normal dogs. In this way, dan shen supported the integrity of the mucosal barrier and improved its defense function. When aspirin was administered, however, dan shen could only delay the onset of mucosal lesions (Yan, 1990).

FENUGREEK SEEDS *(TRIGONELLA FOENUM-GRAECUM):* These have been shown to have significant ulcer protective effects. The cytoprotective effect of the seeds seemed to be due not only to their antisecretory action but also to their effects on mucosal glycoproteins (Pandian, 2002).

LICORICE *(GLYCYRRHIZA GLABRA):* This herb is well known for its antiulcer action. One mechanism of antiulcer activity involves acceleration of mucin excretion through increased synthesis of glycoprotein at the gastric mucosa, which prolongs the life of the epithelial cells and lengthens antipepsin activity (Dehpour, 1995). Oral administration of deglycyrrhizinated licorice (380 mg, 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antacid or cimetidine treatment (Kassir, 1985).

CORYDALIS *(CORYDALIS AMBIGUA):* In humans with stomach or intestinal ulcer or chronic inflammation of the stomach lining, a 90- to 120-mg extract of corydalis per day (equal to 5-10 g crude herb) was found to improve ulcer repair and alleviate symptoms in 76% of patients (Chang, 1986).

GOTU KOLA *(CENTELLA ASIATICA):* Oral doses of 200 and 600 mg/kg twice daily for 5 days showed significant protection against in a rat model of experimental gastric ulcer; the results were comparable with those elicited by sucralfate. At 600 mg/kg, gotu kola significantly increased gastric juice mucin secretion and increased mucosal cell glycoproteins, signifying increased cellular mucus. It also decreased cell shedding, indicating fortification of the mucosal barrier. Thus, the ulcer protective effect may be due to strengthening of mucosal defensive factors (Sairam, 2001a).

BACOPA *(BACOPA MONNIERA):* When given as a dose of 10 to 50 mg/kg twice daily to rats for 5 days, this herb showed dose-dependent antiulcerogenic effects on various gastric ulcer models. At 20 mg/kg, it showed no effect on acid–pepsin secretion, and it increased mucin secretion; it also decreased cell shedding with no effect on cell proliferation. Bacopa showed significant antioxidant effect. Thus, its gastric prophylactic and curative effects may be due to its predominant effect on mucosal defensive factors (Sairam, 2001b).

Anti-inflammatory, demulcent, and astringent herbs

Many herbs have demonstrated anti-inflammatory activity in various animal models and traditionally are considered anti-inflammatory for the gastrointestinal tract, although few have been studied specifically for their mechanisms in the gut. Demulcent and astringent herbs are included here because they are used traditionally to relieve inflammation through their physical action.

Anti-Inflammatory Herbs

BOSWELLIA *(BOSWELLIA SERRATA):* Extracts of the gum resin possess anti-inflammatory properties. In particular, the boswellic acids inhibit the enzyme 5-lipoxygenase, which is responsible for the production of leukotrienes. Inflammatory bowel disease (IBD) is associated with enhanced leukotriene function, and the benefits of Boswellia in the treatment of patients with chronic colitis (ulcerative colitis) or Crohn's disease have been investigated. A total of 20 patients with chronic colitis received Boswellia gum resin (900 mg/d for 6 wk), and another 10 patients were given sulfasalazine (3 g/d for 6 wk). Of 20 patients treated with Boswellia, 14 went into remission (70%, compared with 40% for sulfasalazine) (Bone, 1999). The safety and efficacy of a Boswellia extract were compared against mesalazine for the treatment of 102 patients with active Crohn's disease in an 8-week, randomized, double-blind study. The authors concluded that the Boswellia extract was as effective as mesalazine (Bone, 2004).

BUTTERBUR *(PETASITES HYBRIDUS):* This herb has been used for hundreds of years to treat patients with gastrointestinal tract complaints. Petasines—the main components of butterbur—inhibit the synthesis of leukotrienes and decrease the intracellular concentration of calcium, which explains the anti-inflammatory and spasmolytic properties of extracts of butterbur (Kalin, 2003).

CHAMOMILE *(MATRICARIA RECUTITA):* The German Commission E has approved the use of chamomile for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract (Blumenthal, 1998).

OTHER HERBS

Other herbs traditionally used for their anti-inflammatory activity in gastrointestinal tract conditions include the following:

- Dong quai *(Angelica sinensis)*
- Baical skullcap *(Scutellaria baicalensis)*
- Calendula *(Calendula officinalis)*
- Wild yam *(Dioscorea villosa)*
- Licorice *(Glycyrrhiza glabra)*
- Meadowsweet *(Filipendula ulmaria)*
- Goldenseal *(Hydrastis canadensis)*
- Devil's claw *(Harpagophytum procumbens)*

Demulcents: Demulcents are used to lubricate and protect the alimentary mucous membrane, but the term is usually applied only to those agents that affect the buccal, pharyngeal, esophageal, and gastric mucosa. Demulcents can be used to protect the mucous membranes before or during administration of irritant substances; to allay irritation and inflammation already caused by chemical or bacterial action, or to act as bulking agents for other drugs and herbs.

Mucilage refers to mucilaginous substances in plants that cause demulcency—usually, polysaccharide gels. These substances may protect mucosal surfaces by adhering to the mucosa, and may also act as a prebiotic, reducing epithelial inflammation by normalizing intestinal flora populations.

Polysaccharides from Marshmallow *(Althaea officinalis),* Ribwort *(Plantago lanceolata), Malva moschata,* or *Tilia cordata* showed only moderate bioadhesion to epithelial tissue, whereas strong adhesive processes were

observed with polysaccharides from Bladderwrack *(Fucus vesiculosus)* and Calendula *(Calendula officinalis),* and the adhesive effects were concentration dependent. Histologic studies of membranes revealed the presence of distinct polysaccharide layers on the apical membrane surface (Schmidgall, 2000).

MARSHMALLOW *(ALTHAEA OFFICINALIS):* This herb contains mucilage polysaccharides (5%–10%) that consist of galacturono-rhamnans, arabinans, glucans, and arabinogalactans (ESCP, 1999). The German Commission E approved the use of root and leaf for irritation of oral and pharyngeal mucosa and associated dry cough, and root for mild inflammation of the gastric mucosa (Blumenthal, 1998).

SLIPPERY ELM *(ULMUS FULVA):* This herb consists of mucilage as a major component and 3% to 6.5% tannin. Traditionally, it has been used for inflammation or ulceration of the stomach or duodenum, convalescence, colitis, and diarrhea. It forms a viscous mucilage with moisture.

LICORICE *(GLYCYRRHIZA GLABRA):* Carbenoxolone, an ester derivative of glycyrrhetinic acid, has been used in the treatment of patients with gastric and esophageal ulcers and is thought to exhibit mucosal protective effects by beneficially interfering with gastric prostanoid synthesis, thereby increasing production of mucus and promoting mucosal blood flow (Guslandi, 1985).

BLADDERWRACK *(FUCUS VESICULOSUS):* The mucilaginous thallus has been used for a long time to treat patients with irritated and inflamed tissues (Newall, 1996)

COMFREY *(SYMPHYTUM OFFICINALIS):* Comfrey is believed to possess vulnerary, cell proliferant, astringent, antihemorrhagic, and demulcent properties. It has been used for colitis, gastric and duodenal ulcers, and hematemesis (Blumenthal, 1998); however, in view of the hepatotoxic properties documented for the pyrrolizidine alkaloid constituents, comfrey should not be taken internally.

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* This herb is stated to possess mucilaginous demulcent, laxative, and nutritive properties and has been used in the treatment of patients with anorexia, dyspepsia, gastritis, and convalescence (Blumenthal, 1998; Bisset, 1994).

Astringents: An astringent such as tannic acid is a compound that precipitates protein. Similar to mucilages, astringents form a temporary film of clotted protein over the mucosal surface that effectively protects it from caustic agents and dulls the sensory nerve endings that are responsible for any reflex hyperexcitability. The precipitate is relatively impermeable to the passage of fluids in either direction (Daykin, 1960). Tannins belong to two main classes. Condensed tannins (flavanols) include catechins, epicatechins, and epigallocatechin gallate, which is found in teas and red wine; they are considered to be very safe. Hydrolyzable tannins, including tannic acid, typically occur in the bark and fruit of trees, such as oak. These tannins are used in the dying and tanning industries and are not found in teas.

It is usually suggested that astringents be used for a limited time (no longer than about 2 weeks). Herbs that are high in tannins can interact with or limit the absorption of some alkaline drugs.

AGRIMONY *(AGRIMONIA EUPATORIA):* This herb contains 3% to 21% condensed tannins and some hydrolyzable tannins (e.g., ellagitannin). The tannin constituents may justify the astringent activity attributed to the herb.

TORMENTIL *(POTENTILLA TORMENTILLA):* The roots of this herb contain up to 20% tannins, primarily condensed tannins and essential oils (tormentol). The root was traditionally used to reduce bowel inflammation associated with diarrhea and as an antidote for consumption of poisons; it is strongly astringent and relieves enteritis and episodes of food poisoning (Blumethal, 1998).

BLACKBERRY *(RUBUS FRUCTOSIS):* The presence of large amounts of tannins gives blackberry leaves and roots an astringent effect that may be useful for treating patients with diarrhea.

CRANESBILL *(GERANIUM MACULATUM):* This herb contains tannins, which hydrolyze to gallic acid, and geranium red (the roots contain 10% to 28% tannins).

OTHER HERBS: Other herbs that contain tannins include Artichoke, Bayberry, Bilberry, Black cohosh, Blue flag, Borage, Cascara, Cassia, Chamomile (German), Cinnamon, Clivers, , Comfrey, Cornsilk, Elder, Ephedra, Eucalyptus, Eyebright, Feverfew, Gentian, Hawthorn, Hops, Horse chestnut, Juniper, Marshmallow, Meadowsweet, Mistletoe, Motherwort, Nettle, Pilewort, Plantain, Poplar, Prickly ash, Raspberry, Rhubarb, Sage, Sassafras, Saw palmetto, Skullcap, Slippery elm, Saint Johns Wort, Tansy, Thyme, Uva ursi, Valerian, Vervain, Willow, Witch hazel, Yarrow, and Yellow dock.

Anthelmintics

In veterinary medicine, before modern anthelmintics became available, Areca *(Areca catechu),* extract of Male fern *(Dryopteris fillix-mas),* kamala, pomegranate (granatum), and santonin (from *Artemisia* spp) were used in different animal species with varying effects. Modern anthelmintics probably pose less of a risk for adverse effects; however, some animal owners prefer to refrain from using drugs and will wish to consider herbal options.

Other issues for consideration include comparative efficacy, safety, risk of zoonoses, resistance, and owner compliance (many protocols involve long-term use). For example, cucurbitine contained in crushed pumpkin seeds is only 55% efficacious against *Taenia saginata* (Pawlowski, 1970), and arecoline hydrobromide, derived from *Areca catechu* (the betel nut palm), is very effective against all kinds of tapeworms; however, emesis and diarrhea are common adverse events. A common procedure was to follow administration of these plant compounds with a purgative, causing diarrhea to expel the affected worms. Because of the difficulty involved in killing intestinal worms without harming the patient, skill was always required in administering these anthelmintics (Mills, 1989).

One of the future directions of herbal anthelmintics involves ethnoveterinary investigation into suitable

plants for helminth control in production animals in tropical countries. For example, *Spondias mombin* has been studied in vivo for evaluation of the therapeutic efficacy of water and alcohol extracts administered to sheep naturally infected with gastrointestinal nematodes. The mean percentage of fecal egg reduction on day 12 in sheep drenched with 500 mg/kg *S. mombin* extract was up to 100% against *Haemonchus* species, *Trichostrongylus* species, *Oesophagostomum* species, *Strongyloides* species, and *Trichuris* species, varying with concentration (Ademola, 2005). In Pakistan, plants identified through ethnoveterinary research were screened for their in vitro anthelmintic activity. In vitro results showed that ginger killed all test worms *(Haemonchus contortus)* within 2 hours postexposure. Most worms exposed to control (normal saline) remained alive until 4 hours postexposure; then, 50% died within 6 hours postexposure. It was concluded that all studied plants had some anthelmintic activity (Zafar, 2001). An experiment was carried out to investigate the anthelmintic activity of papaya latex *(Carica papaya)* against natural infection of *Ascaris suum* in pigs. Pigs given 4 or 8 g of papaya latex per kilogram had worm count reductions of 80.1% and 100%, respectively. Some of the pigs receiving the highest dose of latex showed mild diarrhea on the day following treatment. Otherwise, no clinical or pathologic changes were observed in treated animals (Satrija, 1994). Other herbs that have been traditionally used for their anthelmintic activity in humans and animals are discussed in the following paragraphs.

WORMWOOD (*ARTEMISIA* SPP): These herbs, including *Artemisia absinthium,* include bioactive compounds with some anthelmintic activity. The powdered shoots of *Artemisia herba-alba* were investigated in experimental hemonchosis in Nubian goats. Treatment with 2, 10, or 30 g of Artemisia shoots prevented caprine hemonchosis, suppressing egg production and the development of abomasal lesions (Idris, 1982).

GARLIC *(ALLIUM SATIVUM):* This herb has been used in the treatment of patients with roundworm *(Ascaris strongyloides)* and hookworm *(Ancylostoma caninum* and *Necator americanus)*. Allicin appears to be the anthelmintic constituent; diallyl disulphide was not effective (Kempski, 1967, Soh 1960). Allicin is formed through the action of allinase on alliin, which occurs on crushing fresh garlic. Minced garlic has been reported to be successful in reducing parasitism by *Capillaria* species in carp (Peoa, 1988), but it was unsuccessful as an anthelmintic in the treatment of 12 donkeys, when compared with control and fenbendazole treatment groups (Abells, 1999) (note that whole bulbs were used).

ELECAMPANE *(INULA HELENIUM):* Alantolactone has been used as an anthelmintic in the treatment of patients with roundworm, threadworm, hookworm, and whipworm infection (Reynolds, 1982).

FUMITORY *(FUMARIA PARVIFLORA):* As an ethanol extract, this agent caused a marked reduction in fecal egg count (100%) and 78.2% and 88.8% reduction in adult *Haemonchus contortus* and *Trichostrongylus colubriformis,* respectively, on day 13 posttreatment in lambs; it was as effective as the reference compound pyrantel tartrate (Hordegen, 2003).

BLACK WALNUT *(JUGLANS NIGRA):* A decoction has been used to remove worms from people (Felter, 1898); the oil of black walnut *(Juglans nigra)* is often effectual in expelling worms and has even been known to cause ejection of the tapeworm (Cook, 1869). However, toxicity has been reported in dogs ingesting moldy walnuts, and horses exposed to walnut shavings.

GOLDENSEAL *(HYDRASTIS CANADENSIS):* The effect of hydrastine on the protoscolices of the tapeworm *(Echinococcus granulosus)* has been studied in vitro and in vivo. Hydrastine at 0.3% concentration produced 70% mortality of the larvae in both experiments (Chen, 1991).

OTHER HERBS: Others herbs used historically include the following:

- Tansy *(Tanacetum vulgare)*
- Rue *(Ruta graveolens)*
- Thuja *(Thuja occidentalis)*

Antiemetics

Herbs should not usually be administered orally to animals that are vomiting. They may be administered by enema, if necessary, although conventional injectable medications are probably more appropriate. However, herbs that assist in suppressing emesis include demulcents, which coat, protect, and lubricate the gastric mucosa; local gastric sedatives (antacids and alkaline stomachics), which act through acid neutralization, by coating the gastric mucosa, or by local nerve sedation; and centrally acting antiemetics, which exert their effects by depressing the vomiting center. The aim of antiemetic administration is to suppress the vomiting reflex, thus conserving the animal's strength, preventing loss of nutrients, and preserving the chloride content of the stomach, blood, and tissues. Gastric sedation should not be used to override essential vomition. Once this material has been removed, the reflex can be suppressed (Daykin, 1960). When emesis is centrally initiated, the cause must be diagnosed.

GINSENG *(PANAX GINSENG):* This herb contains saponins that inhibit the serotonin (5-HT) type 3A receptor, which is known to mediate nausea and vomiting and may have an antagonistic action against them (Min, 2003). Ginseng is included in many traditional Chinese formulas aimed at tonifying digestion, but it is not generally used as an antiemetic alone.

GINGER *(ZINGIBER OFFICINALE):* This herb is often advocated as beneficial for nausea and vomiting. In a review of evidence from randomized controlled studies, one study was found for each of the following conditions: seasickness, morning sickness, and chemotherapy-induced nausea; these studies collectively favored ginger over placebo (Ernst, 2000a). A later review of antiemetic therapies by the Cochrane Collaboration found 7 trials of ginger for vomiting in early pregnancy (Jewell, 2006). Studies have documented the antiemetic effects of ginger extract in vivo in dogs (Chang, 1986; Sharma, 1997) and frogs (Kawai, 1994). In dogs, acetone and ethanolic extracts of ginger, administered intragastrically at doses

of 25, 50, 100, and 200 mg/kg, protected against cisplatin-induced emesis (3 mg/kg administered intravenously 30 minutes before ginger extract), compared with control. However, ginger extracts were less effective in preventing emesis than was the 5-HT_3 receptor antagonist granisetron, and they were ineffective against apomorphine-induced emesis (Sharma, 1997). The emetic action of the peripherally acting agent copper sulfate was inhibited in dogs given an intragastric dose of ginger extract, but emesis in pigeons treated with centrally acting emetics such as apomorphine and digitalis could not be inhibited by a ginger extract (Zhou, 1960). These results suggest that ginger's antiemetic activity is peripheral and does not involve the central nervous system. The antiemetic action of ginger has been attributed to the combined action of zingerones and shogaols (Ghazanfar, 1994).

BLACK HOREHOUND *(BALLOTA NIGRA):* Black horehound is stated to possess antiemetic, sedative, and mild astringent properties. Traditionally, it has been used for nausea, vomiting, nervous dyspepsia, and specifically for vomiting of central origin (British Herbal Pharmacopoeia, 1983).

OTHER HERBS: Other herbs that can provide symptomatic relief of nausea include the following:

- Chamomile *(Chamomilla recutita)*
- Fringe tree *(Chionanthus virginicus)*
- Peppermint *(Mentha x piperita)*
- Meadowsweet *(Filipendula ulmaris)*
- Lemon balm *(Melissa officinalis)*

Antimicrobials

Many herbs have direct antimicrobial activity in the gastrointestinal tract. Berberine (contained in goldenseal, Oregon grape root, Coptis root, barberry root bark, and Goldthread bark) and hydrastine (contained in goldenseal only) are some of the best studied for gastrointestinal tract infection; however, most herbs have other properties that should be taken into account, depending on the nature of the condition. For example, berberine also inhibits the activity of enterotoxins.

Berberine is reported to be effective against diarrhea caused by enterotoxins such as *Vibrio cholerae* and *Escherichia coli* (Preininger, 1975). In vivo and in vitro studies in hamsters and rats have reported significant activity for berberine against *Entamoeba histolytica* (Pizzorno, 1985). Berberine is stated to have shown significant success in the treatment of patients with acute diarrhea in several clinical studies. It has been found to be effective against diarrhea caused by *Escherichia coli, Shigella dysenteriae, Salmonella paratyphi* B, *Klebsiella, Giardia lamblia,* and *Vibrio cholerae* (Pizzorno, 1985).

CHAMOMILE *(MATRICARIA RECUTITA):* The oil has been reported to have antifungal activity and antibacterial activity against gram-positive bacteria (ESCP, 1999).

THYME *(THYMUS VULGARIS):* This herb possesses anthelmintic (especially hookworms), antibacterial, and antifungal properties (Meybe, 1988). The antibacterial activities of thymol and thyme oil have been reviewed. Thymol, carvacrol, and thyme oil have antifungal activity against a range of organisms (Mitchell, 1979).

Antiprotozoals

Antiprotozoal agents include Propolis, *Artemisia annua,* berberine-containing herbs, and Euphorbia *(Euphorbia hirta)*. Essential oils may also be effective preventive or curative treatment against several flagellated parasites.

GARLIC *(ALLIUM SATIVUM):* The essential oils obtained from garlic bulbs were investigated in vitro on *Tetratrichomonas gallinarum* and *Histomonas meleagridis* in poultry, and it appears that these oils may be useful as chemotherapeutic agents against several poultry parasites (Zenner, 2003).

CHAPARRAL *(LARREA MEXICANA):* Amoebicidal action against *Entamoeba histolytica* has been reported for a chaparral extract (0.01%). This action may be attributable to the lignin constituents, which are documented as both amoebicidal and fungicidal (Fronczek, 1987).

EUPHORBIA *(EUPHORBIA HIRTA):* In vitro amoebicidal activity versus *Entamoeba histolytica* has been reported for a *Euphorbia hirta* decoction (Basit, 1977).

OTHER HERBS: *Sophora flavescens, Sinomenium acutum, Ulmus macrocarpa, Pulsatilla koreana,* and *Quisqualis indica* were effective against *Eimeria tenella* in broiler chicks (Youn, 2001).

Antiviral herbs

Several herbs (such as *Echinacea* species, *Thuja occidentalis, Uncaria tomentosa, Phyllanthus amarus, Tabebuia avellanedae,* and *Hypericum perforatum*) may have antiviral activity, but few have been investigated for their antiviral activity against gastrointestinal viruses.

TORMENTIL ROOT *(POTENTILLA ERECTA):* This extract in controlled doses shortened the duration of rotavirus diarrhea and decreased the requirement for rehydration solution in children with rotavirus diarrhea (Subbotina, 2003); it may be useful in rotaviral infection in animals.

Bitters, sialagogues, and stomachics

Bitters, sialogogues, and stomachics refer to herbs that improve a patient's digestion and appetite by increasing saliva production (sialogogue) or increasing gastric secretion (stomachics); they frequently are bitter tasting (hence, "bitters"). A stomachic is an herb that stimulates gastric function, gastric secretion, and gastric motility; the term refers to many of the bitters. In low doses, they act as "stomach tonics" to improve appetite and upper digestive function.

The taste of bitterness is an extremely common feature of many herbs; it has a major pharmacologic action, which is to stimulate the bitter receptors inside the mouth. These, in turn, send signals via the gustatory nerve (Mills, 1997) to promote the release of gastrointestinal hormones; they also have effects on other physiologic functions. Work published in 1915 by Moorhead revealed that a tincture of the herb Gentian *(Gentiana lutea)* given by mouth or directly into the stomach of cachectic dogs caused a marked increase in appetite. Only

when gentian was given by mouth (i.e., tasted) did it cause a marked increase in gastric secretion of acid and pepsin content, and this effect occurred only after normal feeding. These effects provide rational explanations for the traditional use of bitters for liver and digestive complaints, poor appetite, debility, and a wide range of other conditions. It has been postulated that bitters applied to the mouth before a meal have a priming effect on upper digestive function, which is most marked in states in which digestion is below optimum. The increase in digestive function is probably mediated by a nerve reflex caused by the bitter taste buds and involves an increase in vagal stimulation (ACP, 1999). Vagal stimulation causes an increase in gastric acid secretion, a transient rise in gastrin, an increase in pepsin secretion, a slight increase in gallbladder motility, and priming of the pancreas.

Bitters can be used to (1) stimulate the appetite (anorexia or poor appetite), (2) increase the flow of digestive juices, (3) reduce the risk of enteric infection and improve the microenvironment of the gut, (4) promote bile flow, (5) regulate the secretion of insulin and glucagons, and (6) stimulate repair of the gut wall lining; bitters are not necessarily contraindicated in ulcer or other erosive conditions. In short, the action of bitters can be seen to enhance the whole upper digestive function and to improve assimilation of nutrients into the system.

In traditional medicine, this property was highly regarded as leading to a real tonic improvement in health. Bitters were seen as "cooling," that is, reducing fever by switching blood flow to the breakdown of food and reducing toxin resorption in such conditions, but in a more general way, improving nourishment at the expense of "circulatory heat." Bitters were therefore prescribed in "hot" conditions—those in which the patient feels the heat; the patient experiences thirst; the tongue is dry and red; and nervous agitation, restlessness, and tension are observed. The bitter option is one of the most central choices facing the herbalist (Mills, 1989).

Because they act locally on the taste buds, bitters must be administered in the form of a tea, powder, or tincture. Tablets, pills, and capsules bypass the taste buds. They should be administered 5 to 15 minutes before feeding, or should actually be mixed in with food. Dogs and cats usually object to the taste, and meat or meat extracts are probably more useful as salivary or gastric stimulants. In convalescing cattle and horses, gentian can be mixed with bran mashes (Daykin, 1960).

The two most famous bitters are Gentian and Wormwood *(Artemisia absinthium),* the latter of which is the central ingredient in Angostura bitters.

GENTIAN *(GENTIANA LUTEA):* Elevation of gastric secretion by up to 30% has been reported following the administration of gentian tincture to dogs. An infusion given orally to sheep as a single daily dose (5 g) stimulated enzyme secretion in the small intestine. A root extract (12 mg/kg/d) applied by gavage to rats for 3 days elevated bronchosecretion. A standardized extract perfused into the stomachs of anesthetized rats increased gastric secretion in a dose-dependent manner. Lower doses caused no changes in gastric pH, whereas higher doses increased pH from 4.25 to 4.85. A dose of 0.5 mL/kg did not affect the incidence of gastric ulceration in rats (EMEA, 2002). In an open, uncontrolled study, a single dose of an alcoholic extract of gentian (equivalent to 0.2 g) given to 10 healthy volunteers was reported to result in stimulation of gastric juice secretion (Glatzel, 1967). Gallbladder emptying was increased and prolonged while protein and fat digestion was enhanced. A total of 19 patients with inflammatory conditions of the gastrointestinal tract (e.g., colitis, Crohn's disease, nonspecific inflammation) and elevated secretory immunoglobulin A (IgA) concentrations and 8 healthy individuals were treated with gentian tincture (3 × 20 drops/d) for 8 days. IgA concentrations decreased in both groups (ESCP, 1999).

OTHER HERBS: Other herbs that can be used for their "bitterness" include the following:

- Oregon grape *(Berberis aquifolium)*
- Barberry *(Berberis vulgaris)*
- Bupleurum *(Bupleurum falcatum)*
- Burdock *(Arctium lappa)*
- Forskohlii *(Plectranthus forskholi)*
- Wild yam *(Dioscorea villosa)*
- Echinacea species
- Fringe tree *(Chionanthus virginicus)*
- Fumitory *(Fumaria officinalis)*
- Goldenseal *(Hydrastis canadensis)*
- Chamomile *(Matricaria recutita)*
- Picrorrhiza *(Picrorrhiza kurroa)*
- Baical skullcap *(Scutellaria baicalensis)*
- Dandelion (*Taraxacum officinale folia* and *radix*)
- Thyme *(Thymus vulgaris)*
- Prickly ash *(Zanthoxylum clava-herculis)*
- Ginger *(Zingiber officinale)*
- Yellow dock *(Rumex crispus)*

Carminatives and spasmolytics

Carminatives cause the expulsion of gases from the stomach via eructation and have also been used in flatulent colic to assist in the evacuation of gases from the large intestine. These compounds cause mild irritation of the gastrointestinal tract mucosa, which results in vasodilation. This is probably responsible for the well-known "warm feeling" that follows the swallowing of these compounds. Other actions that result are the relaxation of the gastrointestinal tract musculature, but particularly the cardiac sphincter, for a period of up to 30 minutes, which probably plays a large part in releasing gases from the stomach. The antispasmodic action of some of these, especially ginger, is due to the same factors, which give the carminative effect. The rhythm and tone of peristalsis may be initially increased, but this is often followed by a decrease in movement, which helps in relaxing colic spasms (Daykin, 1960).

ANISEED OIL *(PIMPINELLA ANISUM):* This herb (200 mg/L) was shown to antagonize carbachol-induced spasms in a guinea pig tracheal muscle preparation.

CHAMOMILE *(MATRICARIA RECUTITA):* The spasmolytic activity of chamomile has been attributed to

apigenin, apigenin-7-O-glucoside, and α-bisabolol, all of which have activity similar to that of papaverine (Bruneton, 1995).

CARDAMOM OIL: The antispasmodic activity of this herb was determined from a rabbit intestine preparation, using acetylcholine as agonist. Results proved that cardamom oil exerts its antispasmodic action through muscarinic receptor blockage (al-Zuhair, 1996).

FENNEL SEED OIL *(FOENICULUM VULGARE):* This herb has been shown to reduce intestinal spasms and enhance motility of the small intestine. In a randomized, placebo-controlled trial fennel seed oil emulsion was compared with placebo in infantile colic. One study suggested that fennel seed oil emulsion is superior to placebo in decreasing the intensity of infantile colic (Alexandrovich, 2003).

LAVENDER *(LAVANDULA ANGUSTIFOLIA):* This herb is said to have carminative, antiflatulence, and anticolic properties. Lavender also exhibits spasmolytic activity on guinea pig ileum and rat uterus in vitro, which is most likely to be mediated through cAMP—not through cyclic guanosine monophosphate (Lis-Balchin, 1999).

THYME *(THYMUS VULGARIS):* In vitro antispasmodic activity of thyme and related herbs has been associated with the phenolic components of the volatile oil and with the flavonoid constituents; their mode of action is thought to involve calcium channel blockage (Cruz, 1989).

PEPPERMINT *(MENTH X PIPERITA):* Peppermint oil is used to relieve the symptoms of irritable bowel syndrome, relaxing intestinal smooth muscle by reducing the availability of calcium (Beesley, 1996). In a trial of 50 children with irritable bowel syndrome, patients received 187-374 mg daily of a pH-dependant, enteric coated peppermint oil preparation, or placebo. Seventy one percent of those receiving peppermint oil experienced improvement in abdominal pain, as opposed to 43% of those administered placebo ($p < 0.002$) (Kline, 2001). Grigoleit et al (2005) monitored the gastrointestinal effects of peppermint oil in 269 people. Peppermint administration resulted in a substantial spasmolytic effect (Grigoleit, 2005). Menthol in peppermint oil is thought to have the strongest effect in suppressing smooth muscle contraction (Grigoleit, 2005b).

LEMON BALM *(MELISSA OFFICINALIS):* An ethanol extract of lemon balm leaves inhibited histamine- and barium-induced contractions of guinea pig ileum in vitro (200 mg/mL); an aqueous extract was inactive (Itokawa, 1983).

LICORICE *(GLYCYRRHIZA GLABRA):* The spasmolytic activity of licorice has been demonstrated in vivo (guinea pig, rabbit, and dog) and appears to be due to the flavonoids liquiritigenin and isoliquiritigenin (Chandler, 1985).

OTHER HERBS: Other carminatives and spasmolytics are listed here:

- Ginger *(Zingiber officinale)*
- Rosemary *(Rosmarinus officinalis)*
- Cinnamon *(Cinnamomum zeylanicum)*
- Catnip *(Nepeta cataria)*
- Cramp bark *(Viburnum opulus)*

Cholagogues and choleretics

Cholagogues stimulate release of bile already formed in the liver and possibly stimulate contraction of the gallbladder. Cholagogue activity is generally a characteristic of bitters but can be attributed to other plant constituents as well. Cholagogues are traditionally prescribed for "cleansing of the liver" and may aid bile movement into the gastrointestinal tract. They are often combined with laxatives (and formerly emetics) and make up an important part of the eliminative regimen; they are useful in the treatment of liver disease and wider liver dysfunction (Mills, 1989).

Choleretics stimulate bile production by hepatocytes, and most have effective cholagogue properties as well. Contraindications for choleretics and cholagogues include obstructed bile ducts (e.g., cancer of the bile duct or pancreas), jaundice following hemolytic disease, and acute or severe hepatocellular disease (e.g., viral hepatitis, septic cholecystitis, intestinal spasm, or ileus or liver cancer). Strongly choleretic herbs include Goldenseal *(Hydrastis canadensis),* Barberry *(Berberis vulgaris),* and Greater celandine *(Chelidonium majus)*. It should be noted that bitter herbs can cause nausea in patients with liver damage, so they should be avoided until after hepatic restoratives have been used.

ANDROGRAPHIS *(ANDROGRAPHIS PANICULATA):* Andrographolide produces a significant dose-dependent (1.5-12 mg/kg) choleretic effect (4.8%-73%), as evidenced by increases in bile flow, bile salt, and bile acids in conscious rats and anesthetized guinea pigs. Paracetamol-induced decreases in volume and contents of bile were prevented significantly by andrographolide pretreatment. It was found to be more potent than silymarin, a clinically used hepatoprotective agent (Shukla, 1992).

CHAMOMILE *(MATRICARIA RECUTITA):* This oil has been reported to increase bile secretion and concentration of cholesterol in the bile following the administration of 0.1 mL/kg by mouth to cats and dogs (Ikram, 1980).

OREGON GRAPE *(MAHONIA AQUIFOLIUM),* GOLDENSEAL *(HYDRASTIS CANADENSIS),* BARBERRY *(BERBERIS VULGARIS):* Clinical studies have shown berberine to stimulate bile and bilirubin secretion (Pizzorno, 1985).

DANDELION *(TARAXACUM OFFICINALE):* Bile secretion was doubled in dogs by a decoction of fresh root (equivalent to 5 g dried plant); similar activity has been observed for rats (ESCP, 1999).

GLOBE ARTICHOKE *(CYNARA SCOLYMUS):* Globe artichoke leaf extract not only increases choleresis and, therefore, cholesterol elimination, but it has also been shown to inhibit cholesterol biosynthesis (Kraft, 1997b).

OTHER HERBS: Other herbs include Greater celadine *(Chelidonium majus),* Turmeric *(Curcuma longa),* Agrimony *(Agrimonia eupatoria),* Calendula *(Calendula officinalis),* Fringe tree *(Chionanthus virginicus), Picrorrhiza kurroa,* Gentian *(Gentiana lutea),* Yellow dock *(Rumex crispus),* Milk thistle *(Silybum marianum),* Wormwood *(Artemisia absinthium),* Licorice *(Glycyrrhiza glabra),* Peppermint *(Mentha x piperita),* and Ginger *(Zingiber officinale).*

Hypolipidemic and hypocholesterolemic activity

A few herbs have been well studied for their lipid- and cholesterol-lowering effects and may have some application in veterinary treatment.

GARLIC *(ALLIUM SATIVUM):* The cholesterol- and lipid–lowering effects of garlic and its constituents have been documented in several animal models (e.g., rabbits, rats, chickens, pigs) of atherosclerosis, hypercholesterolemia, and hyperlipidemia (Koch, 1996). The cholesterol-lowering effect of garlic is thought to be dose related; proposed mechanisms of action include inhibition of lipid synthesis and increased excretion of neutral and acidic sterols (Lau, 1983; Fulder, 1989). The potential for causing Heinz body anemia in dogs and cats may limit the dose size and duration of treatment in these species.

GLOBE ARTICHOKE *(CYNARA SCOLYMUS):* Hypolipidemic, hypocholesterolemic, and choleretic activities are well documented for globe artichoke leaf extract. Luteolin was considered to be one of the most important constituents for this effect, and it was suggested that a possible mechanism of action might be indirect inhibition of hydroxymethylglutaryl-CoA reductase (HMG-CoA) (Gebhardt, 1998). Several other experimental studies have documented lipid-lowering effects for globe artichoke leaf extract and cynarin in vivo (Kraft, 1997b; Fintelmann, 1996) and have shown benefit in human clinical patients (Thompson, 2003; Lupatelli, 2004).

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* Hypocholesterolemic activity has been reported for fenugreek in rats (Sharma, 1986) and alloxan-diabetic dogs (Ribes, 1984). Activity has been attributed to the fiber and saponin fractions, with reduction in cholesterol but not in triglyceride concentrations (Ribes, 1984).

OTHER HERBS: Other herbs with hypolipidemic activity include Myrrh and Senega (both hypolipidemic in vivo). Other herbs with hypocholesterolemic activity include alfalfa, bilberry, capsicum, black cohosh, ginger, ispaghula, milk thistle, plantain, tansy, and skullcap. It should also be noted that Gotu kola has shown hypercholesterolemic activity.

Hepatoprotective and hepatorestorative herbs

A number of herbs have demonstrated hepatoprotective and hepatorestorative (restore liver parenchyma) activity.

MILK THISTLE *(SILYBUM MARIANUM):* After poisoning with *Amanita phalloides* in beagles, silibinin administration (50 mg/kg) 5 and 24 hours after intoxication markedly reduced hemorrhagic necrosis induced in the liver and more effectively prevented death in all of the silibinin-treated dogs compared with controls (Vogel, 1984). The active principle silymarin protects when given 60 minutes before intoxication with phalloidine, or 10 minutes after intoxication. However, as the time span between administration of the toxic substance and the start of treatment increases, so the efficacy of silymarin decreases; after 30 minutes, its curative effect is negligible (Desplaces, 1975). Silymarin was tested in dogs that were subjected to carbon tetrachloride (CCl_4) intoxication, which leads to damage of the liver. The protective effects of silymarin were manifested by the significantly lower aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and by the insignificantly reduced extent of lesions in the liver parenchyma, compared with the control CCl_4-intoxicated group (Paulova, 1990). In another study, beagles were divided into 5 groups, and given 85 mg/kg Amanita phalloides lyophilizate orally. The 5 groups, after receiving Amanita extract, were then administered either no treatment (as a control group), prednisolone 30 mg/kg iv at 5 and 24 hours, cytochrome C 50 mg/kg iv at 5 and 24 hours, penicillin G 1000 mg/kg iv at 5 hours, or silymarin 50 mg/kg iv at 5 hours and 30 mg/kg iv at 24 hours. Blood was sampled at 5, 24, 48, 96 and 192 hours and changes in liver enzymes were monitored. At 24 hours post Amanita administration, GPT and GOT levels of the control group averaged over 4000 U/l while those of the silymarin group remained under 60 U/l, slightly lower than the penicillin group and significantly lower than those dogs administered prednisone or cytochrome C. At 48 hours, the control groups' values had returned to near normal with the exception of GPT, which averaged 2250 U/l. The prednisone group transaminase values continued to climb rather than resolve, and the other groups, including the silymarin group, remained in normal ranges (Floersheim, 1978). Studies were conducted on the effects of silybin on the biological activities of Kupffer cells in regenerating livers of rats subjected to partial hepatectomy; results showed that silybin increased the mitotic activity of Kupffer cells (Magliulo, 1979).

GLOBE ARTICHOKE *(CYNARA SCOLYMUS):* In vivo hepatoprotectivity against tetrachloromethane–induced hepatitis has been documented for globe artichoke leaf extract (500 mg/kg) administered orally to rats 48 hours, 24 hours, and 1 hour before intoxication (Adzet, 1987). A hepatoregenerating effect has also been described for an aqueous extract of globe artichoke leaf administered orally to rats for 3 weeks following partial hepatectomy (Maros, 1966). Regeneration was determined in globe artichoke–treated rats, compared with controls, by stimulation of mitosis and increased weight in the residual liver when animals were sacrificed.

DAN SHEN *(SALVIA MILTIORRHIZA):* This herb has been traditionally used in chronic hepatitis and hepatic fibrosis. It protects rat hepatocytes against CCl_4-induced necrosis (Hase, 1997).

SCHISANDRA *(SCHISANDRA CHINENSIS):* This herb is effective in protecting the liver from harmful toxins, and it may stimulate liver repair (Shiota, 1996; Ohtaki, 1996).

ANDROGRAPHIS *(ANDROGRAPHIS PANICULATA):* Hepatoprotective effect was studied on acute hepatitis induced in rats. Treatment of rats before galactosamine administration or after paracetamol challenge leads to complete normalization of toxin-induced increase in the levels of hepatic biochemical parameters, and significantly ameliorates toxin-induced histopathologic changes in the livers of experimental rats (Handa, 1990).

ASIAN GINSENG *(PANAX GINSENG):* Oral administration (250-500 mg/kg) accelerated liver regeneration and

ameliorated liver injury after hepatectomy in dogs (Kwon, 2003).

ANISEED OIL *(PIMPINELLA ANISUM):* When given to rats (100 mg/kg given subcutaneously), this herb stimulated liver regeneration after partial hepatectomy (ESCP, 1999).

CHAMOMILE *(MATRIACRAIA RECUTITA):* The ability of the volatile oil of Chamomile to regenerate liver tissue in partially hepatectomized rats has been attributed to the azulene constituents (Mann, 1986).

OTHER HERBS: Other hepatoprotective and hepatorestorative herbs include the following:

- Phyllanthus *(Phyllanthus amarus)*
- Picrorrhiza *(Picrorrhiza kurroa)*
- Dandelion root *(Taraxacum officinale)*
- Burdock *(Articum lappa)*
- Bupleurum *(Bupleurum falcatum)*
- Turmeric *(Curcuma longa)*

Liver tonics, hepatotonics

Liver tonics include those with choleretic, cholagogue, hepatoprotective, or hepatorestorative properties, as described previously.

Laxatives and aperients

Aperient: *Aperient* is the traditional term for a mild laxative that increases stool moisture to promote bowel movements. These plants often contain soluble fibers and oligosaccharides such as inulin and are mild in their effect. They are used traditionally to aid digestion and assimilation and are frequently cholagogue or choleretic in their action. They include the following:

- Fringe tree *(Chionanthus virginicus)*
- Fumitory *(Fumaria officinalis)*
- Licorice *(Glycyrrhiza glabra)*
- Dandelion root *(Taraxacum officinale)*
- Fenugreek *(Trigonella foenum-graecum)*
- Burdock *(Articum lappa)*
- Oregon grape *(Berberis aquifolium)*
- Barberry *(Berberis vulgaris)*
- Rehmannia *(Rehmannia glutinosa)*

Laxatives include mechanical stimulants, bulk purgatives, irritant purgatives, and neuromuscular purgatives. Mechanical stimulants like paraffin oil may hinder absorption of nutrients by coating the mucosa. Chronic constipation or impaction will not benefit and may be aggravated; in small animals, liquid paraffin may actively encourage the continued existence of fecoliths because the oil facilitates the passage of soft feces past solid masses.

Bulk laxatives increase the volume of intestinal contents, causing distention of the intestines, which induces a reflex that initiates contraction of the musculature and an increase in the power and speed of peristalsis. Wheat bran, plantain seeds (psyllium), and seaweeds fall into this group. The swelling properties of mucilage in herbs also enable it to absorb water in the gastrointestinal tract, thereby increasing the volume of the feces and promoting peristalsis. These laxatives have only mild stimulant effects and are particularly useful when sharp foreign bodies (e.g., needles, sharp bones, stones) have been swallowed. Bulk laxatives lower transit time through the gastrointestinal tract and therefore may delay the absorption of other drugs.

Vegetable oils are probably the most efficient and safe of the direct irritant purgatives. As a group, they act by combining in a saponification process with alkaline bile salts of the small intestine. This process produces monobasic, dibasic, and tribasic soaps that exert irritant effects. Glycerol is a by-product of this process and is useful in lubricating and breaking up fecal masses; it also assists in defecation by exerting strong osmotic pressure to retain fluid within and possibly attract fluid into the intestinal lumen. The soaps produced by these oils differ in their irritant properties, so olive oil produces oliveic acid, castor oil ricinoleates, and linseed oil linoleates and linolenates—all of which are relatively strong irritants. Small quantities of stearates and palmitates are also produced (Daykin, 1960).

The effect is seen within 4 to 8 hours in smaller species and in 12 to 18 hours in the horse. An almost complete clearance of the intestines results when these oils are used. Defecation is temporarily suspended until sufficient bulk reaches the colon again; therefore, oleaginous purgatives are not recommended for chronic constipation.

Indirect irritant purgatives contain precursors that are broken down to anthrones and anthraquinones, which themselves pass unchanged through the colon; there, they exert an irritant action and stimulate intestinal movement. Systemic absorption is limited, especially in the case of whole anthraquinone glycosides. Their main effects probably involve stimulation of active chloride secretion, which is electrochemically and osmotically balanced by an increase in sodium and water secretion—an effect that is counteracted by morphine, with 5-HT as a likely mediator.

Neuromuscular Purgatives: A separate effect of anthraquinones is observed in increasing gut motility of the bowel musculature—a response that may be more sensitive than changes in secretion. Bowel flora metabolism has been firmly implicated in the action of sennosides in the gut (Mills, 1997). The primary members of this group are aloes, cascara, Senna *(Cassia angustifolia),* and rhubarb (rhizome).

ALOE *(ALOE BARBADENSIS):* This was the most widely used anthracene purgative until synthetic anthraquinones were introduced into veterinary medicine. The emodins (anthraquinones) of Aloes are excreted in the large intestine and are of greatest value in those animals that suffer from impaction of the large intestine. The horse with its numerous colon flexures and its decrease in diameter at the pelvic flexure benefits from this type of purgative. Purgation in the horse is delayed for at least 18 hours. In other animals, the action is far more rapid (Daykin, 1960). The glycosides are metabolized by glycosidases in the intestinal flora to form active anthrones. The laxative action is due to increased motility of the large intestine attained by inhibition of the Na^+/K^+ pump and chloride ion channels; enhanced fluid secretion occurs because of stimulation of secretion of mucus and chloride ion (ESCP, 1997).

SENNA POD *(CASSIA ANGUSTIFOLIA):* At very small doses, this herb produces sublaxative effects, whereby bowel motions are made comfortable, normal, and soft. At larger doses, it produces a laxative or purgative effect. The effects of sennosides on colonic motility were investigated in eight conscious dogs. Oral sennosides (30 mg/kg) inhibited colonic motility for 12 to 18 hours after a 3- to 6-hour delay and were associated with giant contractions and diarrhea. The minimal oral dose of sennosides needed to produce such changes varied from 5 to 15 mg/kg. Intracolonic sennosides at the minimal effective dose and at 30 mg/kg reproduced the effects of oral sennosides, but with a shorter latency (0.5-1.5 h). This study suggested that colonic motor actions of sennosides are mediated through local prostaglandin synthesis because they were blocked by cyclooxygenase inhibitor and reproduced by PGE_2 (Staumont, 1988).

PARSLEY *(PETROSELINUM CRISPUM):* The mechanism of action for the purported laxative effects of parsley has been investigated. In rat colon, an aqueous extract of parsley seeds significantly reduced net water absorption from the colon, as compared with controls. Results suggest that parsley acts by inhibiting sodium and consequently water absorption through inhibition of the Na^+/K^+ pump, by stimulating the NaKCl transporter, and by increasing electrolyte and water secretions (Kreydiyyeh, 2002).

RHUBARB *(RHEUM OFFICINALE):* The laxative action of anthraquinone derivatives is well recognized. Rhubarb also contains tannins, which exert an astringent action. At low doses, rhubarb is stated to act as an antidiarrheal because of its tannin components, whereas at higher doses, it exerts a cathartic action (Meybe, 1988).

PSYLLIUM (ISPAGHULA/METAMUCIL) *(PLANTAGO OVATA):* In addition to its stool bulking effects, psyllium exhibits cholinergic activity. Mild laxative action has also been reported in mice administered iridoid glycosides, including aucubin (Inouye, 1974). Four-week supplementation of a fiber-free diet with ispaghula seeds (100 or 200 g/kg) was compared with that of husks and wheat bran in rats (Leng-Peschlow, 1991). The seeds increased fecal fresh weight by up to 100% and fecal dry weight by up to 50%. Total fecal bile acid secretion was stimulated, and β-glucuronidase activity reduced, by ispaghula. The study concluded that ispaghula acts as a partly fermentable dietary fiber supplement that increases stool bulk, and that it probably has metabolic and mucosa-protective effects.

OTHER HERBS: Other laxative herbs include the following:

Cascara *(Rhamnus purshiana)*	Hydroxyanthracene constituents
Eyebright *(Euphrasia officinalis)*	Iridoids
Plantain *(Plantago major)*	Iridoids (much less than senna)
Yellow dock *(Rumex crispus)*	Hydroxyanthracene constituents
Buckthorn *(Rhamnus frangulara)*	Hydroxyanthracene constituents
Butternut *(Juglans cinerea)*	Hydroxyanthracene constituents

Pancreatic protectives and trophorestoratives

These herbs have some affinity for pancreatic tissue and aid chronic and acute pancreatic conditions.

FRINGE TREE *(CHIONANTHUS VIRGINICUS):* This traditional herb is advocated for pancreatic disease, inflammatory or otherwise, and for diabetes (Felter, 1898)

ALOE *(ALOE VERA):* The constituent emodin (also found in other herbs) is a potent agent in the management of clinical and experimental acute pancreatitis. In induced pancreatitis in rats, the serum amylase level was decreased significantly in the emodin-treated group compared with controls. It was concluded that emodin might upregulate gene expression, which subsequently increases DNA synthesis and protein content and thus accelerates pancreatic repair and regeneration (Gong, 2002). Emodin in combination with baicalein has significant therapeutic benefit in severe acute pancreatitis in rats (Zhang, 2005).

DANDELION *(TARAXACUM OFFICINALE):* This herb (10 mg/kg orally) reduced IL-6, a principal mediator of acute phase response and TNF-α production during cholecystokinin-induced acute pancreatitis in rats (Seo, 2001).

REVIEW OF SPECIFIC GASTROINTESTINAL TRACT CONDITIONS

In the following symptoms or conditions, the underlying pathophysiology is assumed to be known. However, it is not uncommon for the veterinary clinician to be presented with a case in which a definitive diagnosis is not made. These are ideal cases for herbal medicine, which can be used to treat the presenting signs. For this reason, both signs and disease conditions of the gastrointestinal tract are listed.

One of the primary considerations in gastrointestinal tract disease is how to avoid aggravating the condition by giving something orally. However, in the authors' experience, the oral route is the main route of administration, with only a handful of adverse events recorded. Many herbs can be given as teas rectally, particularly when vomiting is a major issue.

In human medicine, increasing attention is being paid to physiological, emotional, cognitive and behavioral components of chronic GI disease (Mulak, 2004); stress may similarly impact GI problems in animals and can be addressed with nervines and adaptogens. Attention to diet, probiotics, and contributing or perpetuating factors is essential, as is consideration of conventional treatment.

Colic

Therapeutic rationale

- Identify the cause and relieve obstructions, if applicable.
- Relieve pain.
- Reduce spasm.
- Relieve gas.

The main herbal agents for consideration are spasmolytics, carminatives, nervines, and analgesics (see neu-

rologic section). Fennel *(Foeniculum vulgare),* Chamomile *(Matricaria recutita),* Peppermint *(Mentha x piperita),* Cramp bark *(Viburnum opulus),* and Ginger *(Zingiber officinale)* are well indicated and usually work best when incorporated in a formula (tincture or tea), although a tea of one or two herbs may be sufficient for mild cases.

For example, colic in infants is a common problem in human medicine. For 1 week, 33 healthy infants 2 to 8 weeks of age with colic were given an herbal tea that contained extracts of chamomile, vervain, licorice, fennel, and balm mint; 35 infants were given a placebo drink that included no herbs. At the end of treatment, the colic improvement score was significantly better with herbal tea. Colic was eliminated in 19 infants given herbal tea and in 9 given placebo. No adverse events were reported in either group (Weizman, 1993).

David Hoffmann recommends dill, fennel, chamomile, lemon balm, peppermint, catnip, linden, and red clover for colic. For mild colic in cats or dogs, one should consider using chamomile tea, 1 teaspoon to 1 tablespoon every half-hour. In the author's experience, this is a gentle, readily available herb that provides anti-inflammatory, antispasmodic, carminative, antimicrobial, and bitter actions. It is very useful when stress is a feature of the history, and it is especially useful in German shepherds with stress-induced diarrhea.

For mild colic in veterinary staff, peppermint or chamomile tea, 1 cup sipped every 2 to 3 hours, should be prescribed.

A prescription for recurrent colic signs in small animals that should be given twice daily over 2 to 3 weeks might include the following:

Chamomile	40% (carminative, anti-inflammatory, bitter, spasmolytic, mild sedative)
Fennel	20% (carminative, antimicrobial, anti-inflammatory)
Cramp Bark	20% (bitter, antispasmodic, sedative, astringent)
Licorice	20% (adaptogen, antispasmodic, mild laxative, antiulcerogenic, taste improver)

For mild colic in horses, one historical formula follows:

Aloe	33% (1 oz)
Buckthorn	33% (1 oz)
Ginger	33% (1 oz)

This should be prepared as powders dissolved in a pint of water and given as a drench (Manning, 1883).

Colitis

(See also "Inflammatory Bowel Disease.")

Therapeutic rationale

- Eliminate parasites.
- Reduce inflammation and infection.
- Rule out food allergy—consider an elimination diet.
- Manage stress.

The primary actions that should be considered involve anti-inflammatory, spasmolytic, and nervine herbs. Astringents may be necessary when bleeding is a sign; demulcents and mucilages can reduce mucosal irritation, and vulnerary herbs enhance healing. Immune system support and antimicrobial herbs may be needed when infection is present.

When pain is evident controlling spasm is probably more important than correcting epithelial defects, so peppermint oil is among the most important herbs for consideration. Two drops per 2 oz can be added easily to a tincture.

Herbs to be considered include agrimony, wild yam, angelica, calamus, ginger, licorice, chamomile, lavender, bayberry, turmeric, and fiber-containing herbs such as psyllium, flaxseed, or slippery elm.

Weiss (1988) recommends chamomile, tormentil, and senna in equal parts but also notes that local topical treatments may be most valuable. Herbs used as retention enemas include chamomile, tormentil, and a stimulant "tonic" herb that would enhance secretory activity, such as calamus or red clover. Saint John's Wort can also be used as a vulnerary, and licorice can be used as an anti-inflammatory.

A prescription for colitis follows:

Cramp bark	20% (bitter, antispasmodic, sedative, astringent)
Chamomile	20% (carminative, anti-inflammatory, bitter, spasmolytic, mild sedative)
Marshmallow	20% (demulcent, vulnerary)
Licorice	20% (adaptogen, antispasmodic, mild laxative, antiulcerogenic, taste improver)
Calendula	20% (antimicrobial, anti-inflammatory, astringent, spasmolytic, vulnerary, cholagogue)

Peppermint oil, 1 drop per 25 mL of formula (antispasmodic, carminative, antiemetic)

If stress is involved, one should consider the use of nervines such as skullcap, valerian, or lime blossom and adaptogens such as Eleuthero or *Withania somnifera*.

In an open trial, 24 patients with chronic nonspecific colitis were treated with an herbal combination of *Taraxacum officinale, Hypericum perforatum, Melissa officinalis, Calendula officinalis,* and *Foeniculum vulgare*. As a result of treatment, spontaneous and palpable pains along the large intestine disappeared in over 95% of patients by the 15th day of treatment. Defecation occurred daily in patients with obstipation syndrome, but a combination of *Rhamnus frangula, Citrus aurantium,* and *Carum carvi* was added to the herbal combination already described. Defecation was normalized in patients with diarrhea syndrome. The pathologic admixtures in feces disappeared (Chakurski, 1981b). The inclusion of nervine herbs in this formula should be noted.

A double-blind, randomized, placebo-controlled trial of the efficacy and safety of aloe vera gel for the treatment of patients with mildly to moderately active ulcerative colitis was undertaken in 44 patients given oral aloe vera gel 100 mL twice daily for 4 weeks (2:1), or placebo. Aloe produced a clinical response more often than placebo; it also reduced histologic disease activity and appeared to be safe (Langmead, 2004a).

An open-label, parallel-group, multicenter, randomized clinical trial to assess the efficacy and safety of *Plantago ovata* (psyllium) seeds as compared with mesalamine in maintaining remission was conducted in patients with ulcerative colitis. A total of 105 patients with ulcerative colitis who were in remission were randomized into groups to receive treatment with *P. ovata* seeds (10 g twice daily), mesalamine (500 mg three times daily), and *P. ovata* seeds plus mesalamine at the same doses. The primary outcome was maintenance of remission for 12 months. After 12 months, the treatment failure rate was 40% in the *P. ovata* seed group, 35% in the mesalamine group, and 30% in the *P. ovata* plus mesalamine group. A significant increase in fecal butyrate levels was observed after *P. ovata* seed administration. It was concluded that *P. ovata* seeds may be as effective as mesalamine in maintaining remission in patients with ulcerative colitis (Fernandez-Banares, 1999).

The use of wheat grass *(Triticum aestivum)* in the treatment of patients with ulcerative colitis has been investigated in a randomized, double-blind, placebo-controlled study. A total of 23 patients with active distal ulcerative colitis were randomly allocated to receive 100 mL of wheat grass juice or a matching placebo daily for 1 month. Treatment with wheat grass juice was associated with significant reductions in overall disease activity; treatment appeared effective and safe when given as a single or adjuvant treatment for distal ulcerative colitis (Ben-Arye, 2002).

Constipation

Therapeutic rationale

- Increase systemic hydration and exercise.
- Increase stool bulk (if appropriate, pelvic narrowing would be a contraindication).
- Increase gastrointestinal tract lubrication.
- Use gentle aperients to stimulate peristalsis.
- Suppress spasm when appropriate.
- Improve liver function.

If laxative herbs are needed, initial treatment with bulk-forming (mucilage-containing) herbs such as flax seed or psyllium seed is usually appropriate. Attention to systemic hydration is important in the use of these herbs because they lead to water reabsorption into the intestine. Use of anthraquinone-containing herbal laxatives is generally safe and effective. However, they are best used as a last resort after obvious factors, such as hydration status, diet, and exercise, have been addressed. These herbs have a tendency to cause flatus and can aggravate discomfort. Because they cause emptying of the bowel, it is not uncommon for the client to believe that the animal is still constipated if it does not have a bowel movement for a day or two after use. If needed, modest doses of Senna, Butternut, and Cascara may be used.

A prescription for constipation is provided here:

Licorice	30% (adaptogen, antispasmodic, mild laxative, antiulcerogenic, taste improver)
Marshmallow	20% (demulcent, vulnerary)
Cascara	40% (mild purgative)
Yellow dock	10% (gentle purgative, cholagogue)

Tincture: Give 1 mL per 10 lb twice daily in food for 3 weeks.
Tea: Give 1 dessert spoonful twice daily in food for 3 weeks. Repeat, if necessary.

Megacolon in cats: Marsden in (Wynn, 2003) recommends the following formula for megacolon in cats (proportions are modified):

Cascara	60%
Ginger	10%
Licorice	30%

0.2 mL per 5 kg twice daily

Manning (1883) published the following recipes for constipation in cattle:

Laxative clyster (for obstinate constipation):

- 3-4 quarts warm water
- 8 oz linseed oil
- 1 tablespoon common salt

Stimulating clyster (for inactive rectum and small intestine with gas or loaded with feces):

- 3 quarts thin mucilage of slippery elm bark or linseed tea
- 1 teaspoonful pure cayenne

or

- $^1/_2$ tablespoon powdered ginger
- 3 quarts boiling water

Diarrhea

Therapeutic rationale

- Maintain hydration.
- Normalize intestinal motility.
- Reduce mucosal inflammation.
- Eliminate parasites.
- Rule out food allergies.
- Restore bowel flora.

Depending on the cause of diarrhea, herbs to be considered may have demulcent properties or anti-inflammatory, spasmolytic, astringent, or antimicrobial activity.

For simple, mild diarrhea of nonspecific origin, one should consider *Hydrastis canadensis* (goldenseal). It inhibits enterotoxins and is most useful for gastrointestinal tract infection and giardiasis. *Geranium maculatum* (cranesbill) contains tannin and is a gentle astringent and almost a specific for mild diarrhea. *Hamamelis virginiana* (witch hazel) is an astringent and anti-inflammatory for nonspecific diarrhea. *Harpagophytum procumbens* (devil's claw) has a traditional use in nonspecific diarrhea as a bitter tonic and anti-inflammatory herb.

Matricaria recutita (chamomile) is ideal for inflammation or spasm of the digestive tract, especially with nervous diarrhea, travel sickness, and anxiety. *Filipendula ulmaria* (meadowsweet) has astringent properties and, according to Grieves (1931), is almost a specific for children's diarrhea. King's Dispensatory (Felter, 1898) reports that it is effective in debility and convalescence from diarrhea. *Chelidonium major* (greater celadine) is used in China to treat patients with enteritis and abdominal pain.

In a prospective, double-blind, randomized, multicenter, parallel-group study, children (6 months to 5.5 years of age) with acute, uncomplicated diarrhea received apple pectin and chamomile extract (n = 39) or placebo (n =

40), in addition to rehydration and realimentation diet. After 3 days, the diarrhea had ended significantly more frequently in the pectin/chamomile group than in the placebo group, and pectin/chamomile reduced the duration of diarrhea significantly by at least 5.2 hours. Parents expressed their contentment more frequently (82%) with pectin/chamomile than with placebo (60%) (de la Motte, 1997).

Many cats and dogs with simple diarrhea respond to a combination of probiotics and slippery elm powder ($^1/_4$ teaspoon per 10 lb, or 5 kg twice daily) administered with water or fresh food.

Preweaning diarrhea is a very common disease in piglets. Oral administration of 0.5 g of Ko-ken-huang-lien-huang-chin-tang (pueraria, coptis, scute, and licorice combination) to piglets at 1 day of age was effective in reducing the incidence of gastrointestinal tract infection and increasing body weight gain during the first 10 days of life (Lin, 1988).

A prescription for nonspecific diarrhea in animals is provided here:

Goldenseal	20% (antimicrobial, mucous membrane tonic, stomachic)
Marshmallow	20% (demulcent, vulnerary)
Cramp bark	20% (bitter, antispasmodic, sedative, astringent)
Chamomile	20% (carminative, anti-inflammatory, bitter, spasmolytic, mild sedative)
Agrimony	20% (astringent, bitter tonic)

Tincture: Give 1 mL per 10 lb twice daily in food for 3 weeks.

A historical recipe for an astringent enema for scours in cattle is as follows:

1 tablespoon bayberry bark
3 quarts boiling water

Digestive Weakness

Veterinarians are sometimes presented with a general picture of intestinal disturbance. Bloating, flatulence, mild diarrhea, mild constipation, mild abdominal pain, mucus in the stool, and anorexia or fussy eating habits, as well as borborygmus and pica, can all be evidence of inherent "digestive weakness" and dysbiosis (an alteration in normal bowel flora, leading to bowel function changes). Poor digestion in animals may also be largely nonclinical but can contribute to other conditions, such as food intolerance or allergies, constipation, dysbiosis, and nutrient deficiencies (and skin problems). Herbalists suspect that many chronic diseases begin with subclinical poor digestive function. Herbs that improve upper digestive function include bitters, carminatives, pungent herbs to stimulate gastric secretions, choleretics, and cholagogues.

A prescription for digestive weakness is provided:

Barberry	20% (alterative, mild laxative, cholagogue, liver and digestive tonic antiseptic)
Ginger	10% (carminative, antispasmodic, anti-inflammatory)
Dandelion	20% (laxative, cholagogue, bitter)
Licorice	20% (adaptogen, antispasmodic, mild laxative, antiulcerogenic, taste improver)
Eleuthero	30% (adaptogen, immune modulatory)

Use alcohol or glycerin tinctures for best results; alternatively, use teas.

Tincture: Give 1 mL per 10 lb twice daily in food for 3 weeks.

Emaciation

If emaciation is due to anorexia, one should consider using gentian or some of the bitters and stomachics. Also, consideration should be given to adaptogens and nutritive herbs like ashwagandha, alfalfa, nettle, and others. Of course, the predisposing cause of emaciation must be identified and addressed.

Flatulence

Therapeutic rationale

- Identify food intolerances and hypersensitivities.
- Improve digestibility.
- Rule out dysbiosis, bacterial overgrowth, and pancreatic insufficiency.

Carminative herbs are used to relieve gas and gas pain. These include anise seed, fennel, cardamom, peppermint, cilantro, bergamot, lavender, hyssop, and chamomile. Spasmolytic herbs such as wild yam and cramp bark may also be useful.

Perianal Fistula

An association may be found between colitis and perianal fistula; food sensitivities and allergies should be ruled out. One should consider using immune-modulating herbs, astringent, and vulnerary herbs. Two herbs used in human furunculosis are *Baptisia tinctoria* (wild indigo) and *Potentilla erecta* (tormentil).

Prescription for perianal fistula:

Barberry	30% (alterative, anti-inflammatory, mild laxative, liver tonic, digestive tonic, antiseptic)
Echinacea	20% (immunostimulant, anti-inflammatory, antibacterial, vulnerary)
Marshmallow	20% (demulcent, vulnerary)
Licorice	10% (anti-inflammatory, adaptogen, taste improver, antiulcerogenic)
Astragalus	20% (immune enhancing, tonic)

Gallbladder Disorders

Therapeutic rationale

- Use mild bitter herbs to improve digestion and gallbladder function.
- Spasmolytic and carminative herbs can be used to relieve pain.
- Regulate bowel function simultaneously.

Agents of value include anti-inflammatories, hepatic tonics, antispasmodics, and antimicrobial herbs. Caution

should be used with choleretic herbs that improve bile flow and cholagogue herbs that stimulate gallbladder motility; these may increase peristalsis and therefore worsen discomfort. Only mild choleretics and cholagogues should be used.

Weiss (1988) suggests that, in treating gallbladder disease, a therapeutic triad to guide the prescription should involve a specific biliary remedy that includes a carminative and an antispasmodic, as well as a supporting laxative. His example formula is as follows:

Peppermint (as a cholagogue)	50%
Melissa (sedative adjuvant)	20%
Fennel seed (carminative)	20%
Buckthorn bark (laxative)	10%

Another example given by Weiss (1988) is composed of 10% caraway seed, 10% fennel seed, 30% peppermint, 20% yarrow, 20% everlasting flower, and 15% senna. Other herbs that are included in his formulas are wormwood, milk thistle, blessed thistle, and dandelion.

A prescription for cholecystitis is provided:

Barberry	20% (alterative, mild laxative, liver and digestive tonic, antiseptic)
Globe artichoke	10% (bitter tonic, choleretic, cholagogue, hepatic tonic)
Wild yam	20% (spasmolytic, anti-inflammatory, cholagogue)
Milk thistle	20% (hepatotonic, antioxidant)
Dandelion	30% (laxative, cholagogue)

Gastritis

Therapeutic rationale

- Reduce inflammation.
- Identify and remove the cause.
- Control nausea and vomiting.
- Rule out bacterial infection.

A number of herbs have demonstrated therapeutic effects on the stomach and may be particularly useful in the prevention of gastritis or gastric ulcers associated with some conventional medicines. Herbs to consider include Licorice, Chamomile, Dan shen, Fenugreek, Goldenseal, Thyme, and Cat's claw. If bacterial infection (such as *Helicobacter*) is suspected, Goldenseal, Barberry, and Grapeseed extract may be added. Garlic, on the other hand, may exacerbate gastritis and worsen gastric ulceration (see Garlic monograph in Chapter 24).

One formula advocated for gastritis by Hoffmann (1992) is provided here (proportions slightly modified):

Comfrey root	30%
Marshmallow root	30%
Meadowsweet	30%
Goldenseal	10%

Administer as a tea.

Prescription for simple gastritis:

Chamomile flowers 50.0 g, 1 teaspoon to 1 cup boiling water, or

Chamomile tincture, 10 to 20 drops in $^1/_2$-glass lukewarm water.

Chamomile is easily accepted by small animals with gastritis as a tea or a diluted tincture.

Prescription for chronic gastritis:

Meadowseet	40% (antiulcerogenic, antacid, anti-inflammatory, astringent)
Marshmallow	30% (demulcent, vulnerary)
Chamomile	30% (carminative, spasmolytic, anti-inflammatory, cholagogue, antiallergic, mild sedative, and vulnerary)

Or, a simple infusion can be prepared of equal parts fennel seeds, peppermint leaves, melissa leaves, and calamus (sweet flag); 1 teaspoon to 1 cup in boiling water should be given.

Gastroenteritis

Therapeutic rationale

- Treat infection (viral, bacterial, protozoal, etc.).
- Reduce inflammation.
- Control nausea and vomiting.

The prescription should include astringent herbs if the problem is acute, as well as anti-inflammatory and antimicrobial herbs. If the patient is vomiting, one should consider delivery of herbal teas via enema.

Prescription for gastroenteritis, given as tea or tincture (no vomiting):

Marshmallow	20% (demulcent, vulnerary)
Meadowsweet	30% (antiulcerogenic, antacid, anti-inflammatory, astringent)
Goldenseal	20% (antimicrobial, mucous membrane tonic, stomachic)
Angelica root	20% (warming, bitter, carminative, spasmolytic)
Agrimony	10% (astringent, bitter, cholagogue)

Gastric Dilation

The gastric dilation–volvulus (GDV) syndrome in the dog is considered to be multifactorial; however, an association between GDV and inflammatory bowel disease has been raised as a possibility, on the basis of an evaluation of the correlation between GDV and preexisting gastrointestinal tract disease (Braun, 1996). Prevention in large-breed dogs is desirable, and prevention of recurrence post-GVD may be aided by herbal medicine, along with appropriate diet and lifestyle changes. The most important herbs to be included are the carminatives, stomachics, bitters, and anti-inflammatories. Along with dietary and lifestyle management, the following formula should be considered.

A preventative prescription for GDV:

Fennel	25% (carminative, antimicrobial, anti-inflammatory)
Peppermint	25% (antispasmodic, carminative, antiemetic)
Chamomile	25% (carminative, spasmolytic, anti-inflammatory, cholagogue, antiallergic, mild sedative, and vulnerary
Dandelion	25% (laxative, cholagogue)

One should give 1 mL per 5 kg to large-breed dogs in divided doses in food; for long-term use, 3 weeks on and 1 week off the formula is recommended, with chamomile

tea during the rest week given at a half-cup twice daily with food.

Giardia

Numerous medicinal herbs, including Berberine-containing herbs (Coptis, Goldenseal, Oregon grape, Barberry), show promise. For example, a group of 42 human patients with giardia received 10 mg/kg/d of berberine orally for 10 days. A total of 90% had negative stool specimens after treatment, although a small number relapsed 1 month later. Results compared favorably with those of the other three antigiardial drugs that were investigated (Gupte, 1975). Others, such as Indian Long Pepper *(Piper longum),* the Ayurvedic formulation consisting of Indian Long Pepper and Palash *(Butea monosperma),* and propolis, also showed antigiardial activity (Hawrelak, 2003). Flavonoid-containing herbs, including Oregano *(Origanum vulgare),* Guava leaves *(Psidium gujava),* Mango leaves *(Mangifera indica),* and plantain leaves *(Plantago major),* demonstrated antigiardial activity equal to tinidazole (Ponce-Macotela, 1994). Probiotics are well indicated, as is a low-fat diet (Giardia trophozoites depend on bile acids for survival). Wheat germ may also be therapeutic (human dose 2 g, or 1 tsp three times daily).

Prescription for chronic or recurrent giardiasis:

Goldenseal	20% (antimicrobial, mucous membrane tonic, stomachic)
Meadowsweet	20% (antiulcerogenic, antacid, anti-inflammatory, astringent)
Cramp bark	20% (bitter, antispasmodic, sedative, astringent)
Echinacea	20% (immunostimulant, anti-inflammatory, vulnerary)
Marshmallow	20% (demulcent and vulnerary)

Although conventional medicines (e.g., metronidazole) may be effective, herbal medicine may help to alleviate the signs and duration of infection.

Gingivitis/Periodontal Disease

Therapeutic rationale

- Identify the cause.
- Treat accompanying dental or periodontal disease.
- Reduce inflammation.
- Treat infection and inflammation.

Herbs with potential use in the treatment of patients with periodontal disease include antimicrobials, vulnerary herbs, and anti-inflammatory herbs. Astringents may help reduce bleeding, and circulatory stimulants might improve circulation of blood to the gums. Immune system support should be considered, given the potential for systemic effects caused by bacteremia. Traditionally, propolis, marshmallow, aloe, calendula, Echinacea, witch hazel, goldenseal, myrrh, balm of gilead, coptis, spilanthes, and other herbs have been used.

One study investigated the treatment of patients with chronic catarrhal gingivitis with polysorb-immobilized calendula. The results of this use for periodontal disease in clinic cases showed the greatest effect of calendula after treatment (Krazhan, 2001). Epigallocatechin gallate (EGCG), the main constituent of green tea polyphenols, has been reported to have inhibitory effects on the activity and expression of matrix metalloproteinases (MMPs) that are involved in alveolar bone resorption in periodontal disease (Yun, 2004). Likewise, baicalin inhibits metalloproteinases, which suggests that baicalin and plants that contain high levels of it may play an important role in preventing and treating periodontal disease (Li, 2004).

Centella asiatica and *Punica granatum* have been investigated for periodontal healing following scaling and root planing in adult human patients with periodontitis. Study results showed significant improvement in pocket depth and attachment level in test sites when compared with placebo sites at 3 months, and with placebo and control sites at 6 months. Results indicate that local delivery with *C. asiatica* and *P. granatum* extracts plus scaling and root planing significantly reduced the clinical signs of chronic periodontitis (Sastravaha, 2003).

Methanol extracts of *Hamamelis virginiana* and *Arnica montana* and, to a lesser extent, *Althaea officinalis* were shown to possess antimicrobial activity and may be useful as topical medications in periodontal prophylaxis (Iauk, 2003). Similarly, a perilla seed *(Perilla frutescens)* extract was examined for its antimicrobial activity against oral cariogenic bacteria. Luteolin, one of the components of perilla seed, showed the strongest antimicrobial effect among the phenolic compounds; therefore, perilla seed may be used to prevent dental caries and periodontal disease (Yamamoto, 2002).

Prescription for periodontal disease/gingivitis for internal use:

Echinacea	30% (immunostimulant, anti-inflammatory, vulnerary)
Baptisia	20% (antimicrobial, antiseptic)
Baical skullcap	30% (anti-inflammatory, antibacterial, antiallergic)
Devil's claw	20% (anti-inflammatory, analgesic, bitter tonic)

For topical use: For small animals, consider a flush with fresh, cooled green tea twice daily, and add the remaining tea to food.

Halitosis

Halitosis may have three main causes: dental or periodontal disease, gastric disease, or rhinitis/sinusitis. If it is due to poor digestion, one should consider starting treatment with bitters like *Gentiana lutea* (gentian) or stomachics.

Inflammatory Bowel Disease

(See also "Colitis.")

Therapeutic rationale

- Rule out parasites.
- Reduce inflammation.
- Address food allergy and food intolerance.
- Identify and remove behavioral or stress triggers.

The cause or causes of inflammatory bowel disease (IBD) remain obscure. Food allergy or intolerance contributes in many dogs and in up to 66% of cats. Antigens that have been implicated include parasites, dietary proteins, and bacteria, including commensal species. In cats with chronic IBD, triaditis (an associated inflammation of liver and pancreas) may also develop. Herbal agents indicated include astringents, demulcents, vulneries, carminatives, antispasmodics, and nervines, as well as immune system support (antiallergy herbs should be considered). Herbs frequently recommended for human patients with IBD include catnip, chamomile, sarsaparilla, belladonna, bayberry, turmeric, wild yam, and agrimony.

It has been suggested that reactive oxygen metabolites produced by inflamed colonic mucosa may contribute to the pathogenesis of the disease. In one in vitro study, slippery elm, devil's claw, Mexican yam, tormentil, and wei tong ning (a traditional Chinese medicine) scavenged superoxide dose dependently, so they may deserve a role in treatment of IBD (Langmead, 2002). In another in vitro study, the inflammatory action of aloe vera gel provided support for the proposal that it may have a therapeutic effect in IBD (Langmead, 2004b).

A formula consisting of Bilwa *(Aegle marmelos),* Dhanyak *(Coriandrum sativum),* Musta *(Cyperus rotundus),* and Vala *(Vetiveria zizanioides)* was evaluated for its activity against IBD. The formulation showed significant inhibitory activity against IBD induced in rat models; the activity was comparable with that of prednisolone (Jagtap, 2004).

A prescription for IBD follows:

Chamomile	20% (carminative, anti-inflammatory, vulnerary, bitter, spasmolytic, antiallergic, cholagogue, mild sedative)
Calendula	20% (antiseptic, anti-inflammatory, astringent, spasmolytic, vulnerary, cholagogue)
Meadowsweet	20% (antiulcerogenic, antacid, anti-inflammatory, astringent)
Astragalus	20% (immunomodulatory)
Baical skullcap	20% (anti-inflammatory, antibacterial, antiallergic)

One should give 1 mL per 5 kg for large-breed dogs in divided doses in food.

An emollient clyster published by Manning (1883) for cattle was:

2 oz slippery elm bark
2 quarts boiling water

Irritable Bowel Syndrome

Therapeutic rationale

- Rule out food allergy.
- Manage stress/behavioral triggers.

It is estimated that 10% to 15 % of dogs with chronic large bowel diarrhea have irritable bowel syndrome (IBS). IBS has an unclear cause and, in humans, stress, anxiety, and psychological issues are common triggers, along with possible food intolerance. In animals, stressful episodes such as boarding or shows can be linked to onset of clinical signs. Food intolerance may also contribute, and leaky gut and poor liver function should be ruled out. Signs may include constipation or diarrhea, or alternating between these two. The colon is generally more sensitive than normal, so key signs include urgency to defecate, cramping, and diarrhea.

Spasmolytic herbs, including chamomile, cramp bark, peppermint, and bayberry, and nervine herbs, especially chamomile, should be used for nervous dogs with stress-related diarrhea. The presence of mucus implies inflammation, and gastrointestinal anti-inflammatory and astringent herbs, like meadowsweet, might be considered. Other herb classes for consideration when appropriate include hepatic, choleretic, antimicrobial, and demulcent herbs.

A modern Chinese herbal formula significantly improved symptoms of irritable bowel syndrome in a randomized controlled trial in human patients (Bensoussan, 1998). This trial compared patients given placebo, individualized Chinese herbal prescriptions, and standard formula. Initially, both treatment groups improved significantly compared to the placebo group; at follow-up 14 weeks later, only those receiving individualized prescriptions maintained improvement.

Standard Chinese herbal formula in Bensoussan trial

Dang Shen	*Codonopsis pilosulae*	7 gm
Huo Xiang	*Agastaches seu pogostemi*	4.5 gm
Fang Feng	*Ledebouriella sesiloidis*	3 gm
Yi Yi Ren	*Coicis lacryma-jobi*	7 gm
Chai Hu	*Bupleurum Chinense*	4.5 gm
Yin Chen	*Artemisia capillaris*	13 gm
Bai zhu	*Atractylodes macrocephalae*	9 gm
Hou Po	*Magnolia officinalis*	4.5 gm
Chen Pi	*Citrus reticulata*	3 gm
Pao Jiang	*Zingiber officinalis*	4.5 gm
Qin Pi	*Fraxinus rhynchophylla*	4.5 gm
Fu Ling	*Poria cocos*	4.5 gm
Bai Zhi	*Angelica daihurica*	2 gm
Che Qian Zi	*Plantago asiatica*	4.5 gm
Huang Bai	*Phellodendron amurense*	4.5 gm
Zhi Gan Cao	*Glycyrrhiza uralensis*	4.5 gm
Bai Shao	*Paeonia lactiflora*	3 gm
Mu Xiang	*Aucklandia lappa*	3 gm
Huang Lian	*Coptis sinensis*	3 gm
Wu Wei Zi	*Schisandra chinensis*	7 gm

Hoffmann suggests the following formula for IBS (proportions modified):

Bayberry	25%
Mugwort *(Artemisia vulgaris)*	15%
Chamomile	15%
Peppermint	15%
Wild yam	15%
Valerian	15%

A simplified prescription for IBS:

Chamomile	25% (carminative, anti-inflammatory, vulnerary, bitter, spasmolytic, antiallergic, cholagogue, mild sedative)
Passionflower	25% (sedative, antispasmodic, anodyne)
Calendula	25% (antiseptic, anti-inflammatory, astringent, spasmolytic, vulnerary, cholagogue)
Marshmallow	25% (vulnerary and demulcent)

Liver Hypofunction

Phytotherapeutic and naturopathic thinking recognizes a condition wherein the liver functions below optimum, even when no clinical evidence of liver disease or damage is apparent. Because the liver plays an important role in detoxification and many other metabolic processes, a poorly functioning liver can broadly affect health.

Signs of a poorly functioning liver might include food or drug intolerance, chronic constipation, fat intolerance, and poor digestion; poor liver functioning may contribute to chronic skin disease, autoimmune disease, allergies, IBD, and cancer.

Depending on severity and signs, treatment of patients with subclinical liver dysfunction should include hepatoprotective and hepatorestorative herbs, especially if a history of liver damage or exposure to liver toxins or drug toxicity is reported. Choleretic herbs, such as artichoke and dandelion, are also included to improve liver function, especially if digestion is compromised. Choleretics aid detoxification and may be useful in chronic skin disease and cancer, as may long-term prednisolone therapy. Depuratives such as burdock and yellow dock may also be considered.

A prescription to aid liver function:

Schisandra	20% (hepatoprotective, nervine tonic, adaptogen)
Dandelion root	20% (laxative, cholagogue)
Milk thistle	20% (hepatotonic, hepatoprotective, antioxidant)
Panax ginseng	20% (adaptogen, anti-inflammatory, antiallergic, immune enhancing)
Burdock	20% (alterative, bitter, mild laxative)

Another simple liver formula might consist of equal parts milk thistle, turmeric, artichoke, and schisandra.

An initial recommended dosage is 1 mL per 5 kg, given daily to twice daily.

Hepatitis

Therapeutic rationale

- Identify precipitating cause.
- Suppress inflammation to reduce fibrosis.

Knowledge of the underlying pathophysiology of particular hepatic disorders is important if treatment will be tailored for the individual case. Primary herbs for consideration in liver disease include barberry, milk thistle, dandelion, Oregon grape, bupleurum, fringe tree, artichoke, phyllanthus, turmeric, and schisandra. Antimicrobial, antiviral, and immune-enhancing herbs may be necessary. When fibrosis is a concern, hepatotrophorestorative herbs are an important part of strategic treatment. Hepatoprotective herbs given to minimize liver damage may include bupleurum, dandelion root, globe artichoke, and milk thistle. One should consider using milk thistle and schisandra in more concentrated forms, perhaps by giving tablet forms in addition to a formula. Because of the high prevalence of viral hepatitis, the human herbal literature lists antiviral herbs such as picrorrhiza, but these syndromes have not been documented in veterinary medicine at this writing. Immune-enhancing herbs such as *Astragalus membranaceus* (astragalus) and antimicrobial herbs such as *Echinacea* may still be appropriate for acute or chronic infection. For toxic insults to the liver, Schisandra and milk thistle should be considered.

The general liver health formula of herbalist Christopher Hobbs consists of milk thistle, artichoke, dandelion root, turmeric, skullcap, and California coast sage. David Winston's thistle compound for liver problems (Winston, 2003) contains dandelion root, watercress, blessed thistle, milk thistle, turmeric, and Oregon grape.

Hoffmann's chronic hepatitis formula (Hoffmann, 2004) consists of the following (proportions slightly modified):

Dandelion root	25%
Milk thistle	25%
Echinacea	20%
Mugwort	15%
Fringe tree	15%

A veterinary prescription for hepatitis :

Bupleurum	20% (hepatoprotective, anti-inflammatory, tonic)
Schisandra	20% (hepatoprotective, nervine tonic, adaptogen)
Milk thistle	20% (hepatotonic, hepatoprotective, antioxidant)
Panax ginseng	20% (adaptogen, anti-inflammatory, antiallergic, immune enhancing)
Astragalus	20% (immunomodulatory)

Another prescription is:

Milk thistle	20%
Artichoke	20%
Oregon grape	30%
Echinacea	30%

The recommended dosage is 1 mL per 5 kg, given daily to twice daily.

Megacolon

See "Constipation."

Parvovirus

Therapeutic rationale

- Maintain hydration.
- Control systemic bacterial infection via translocation from compromised gut.
- Maintain nutritional support.

Dogs with parvoviral enteritis may benefit from antiviral herbs, astringent herbs, and mucosal support provided by mucilaginous herbs. Herbs should be delivered via enema if administered to vomiting dogs. African plants *Bauhinia thonningii, Boswelia dalzielii, Detarium senegalensis*, and *Dichrostachys glomerata* inhibited replication of canine parvovirus in vitro (Kudi, 1999).

Stomatitis

Therapeutic rationale

- Control plaque.
- Identify other inciting causes, where possible.
- Control inflammation and bleeding.
- Control pain.

Classic herbs for gum disease include myrrh, goldenseal, sage, coptis, propolis, and calendula. For bleeding gums, astringent herbs (tormentil, agrimony) or yunnan pai yao can be used as needed. Echinacea is an antimicrobial herb, but it also acts as a local anesthetic. Weiss (1988) provides formulas that contain tormentil, sage, and arnica, and also recommends that lidocaine be added to one formula for pain.

One suggested formula follows:

Tormentil	30%
Echinacea	20%
Propolis	20%
Sage	20%
Myrrh	10%

Marsden has recommended Hoxsey formula for animals that present with an energetically "hot" constitution (Wynn, 2003), along with other formulas:

Agrimony	6 parts
Yellow dock	2 parts

Administer 0.2 mL/5 kg twice daily.

Or

Sarsaparilla	2 parts
Burdock	2 parts
Agrimony	3 parts
Yellow dock	1 part

Give 0.2 mL/5 kg twice daily.

Vomiting and Nausea

Therapeutic rationale

- Identify cause.
- Provide gastrointestinal tract rest in acute cases.
- Allow vomiting to remove offending material, if the cause is believed to be local.

Herbs traditionally used for symptomatic treatment of nausea in human medicine include ginger, gentian, goldenseal, peppermint, licorice, lavender, catnip, chamomile, and wild yam. Peppermint and ginger are probably the most effective.

Ulcers, Gastric or Intestinal

Therapeutic rationale

- Identify cause.
- Reduce formation of hydrogen ions.
- Protect ulcerated tissue.

The primary herbs used traditionally for gastrointestinal tract ulceration are chamomile and gotu kola, which appear to enhance healing of the ulcers and should be given on an empty stomach. Astringent herbs such as meadowsweet can be used but are of secondary importance. Mucilaginous herbs such as marshmallow or slippery elm may help protect ulcerated surfaces and, if used, should follow the vulnerary chamomile or gotu kola. See "Antiulcer Herbs."

HERBS FOR MUSCULOSKELETAL DISORDERS

General Notes

Musculoskeletal disorders result in loss of function and pain. This is generally associated with joint irregularities (hypermobility, instability, arthrosis, bony proliferation, ligamentous thickening) and muscle changes (spasms, both acute and chronic; atrophy). Goals of therapy include normalizing joint and muscle function and controlling pain. Joint instability itself may require surgical intervention; however, herbal analgesics and anti-inflammatory herbs may be useful in acute situations. In chronic situations, chondroprotectives, anti-inflammatories, alteratives, and analgesics are required. In older patients and those with chronic joint disease, muscle spasm is a dramatic but rarely recognized clinical finding. Deep palpation of thoracic, lumbar, and upper limb muscles reveals sensitivity that indicates massage therapy and antispasmodic herbs. Other useful therapies include physiotherapy, as well as chiropractic treatment and acupuncture.

In earlier times, arthritis was sometimes viewed as resulting from abnormal accumulations of metabolic toxins, which could be cleared with dietary changes, diuretics, and hepatics. There may be reason to connect toxin accumulation with pain and inflammation, and the more modern concept of "leaky gut" can explain why herbalists generally direct some efforts toward normalizing gut function, as well as directly addressing joint and muscle pain and inflammation. Leaky gut occurs in animals that may be older and stressed because of chronic pain or disease, especially when steroids and nonsteroidal anti-inflammatory drugs (which may often lead to mucosal inflammation) change normal gut permeability. When the gut mucosa is altered in this way, large proteins such as food as well as bacterial, and self antigens may gain access to the submucosa and possibly even the portal circulation. The normal gut is responsible for making primary immune responses, but it also makes significant neuroendocrine responses, including the production of serotonin, benzodiazepines, glutamate, enkephalins, nitric oxide, and dopamine. The end clinical response is increased immune responsiveness, systemic inflammation and perhaps altered behavior (Figure 20-2).

Mechanisms of Interest

Antirheumatics

Veterinarians are not prone to use the term *rheumatism,* and most are not searching for it in the clinic. Chronically arthritic animals use other body regions to compensate for pain and suboptimal function. In the case of hip dysplasia, for instance, most animals exhibit sensitivity on palpation of thoracic and lumbar muscles. Treatment of the primary problem may or may not resolve the

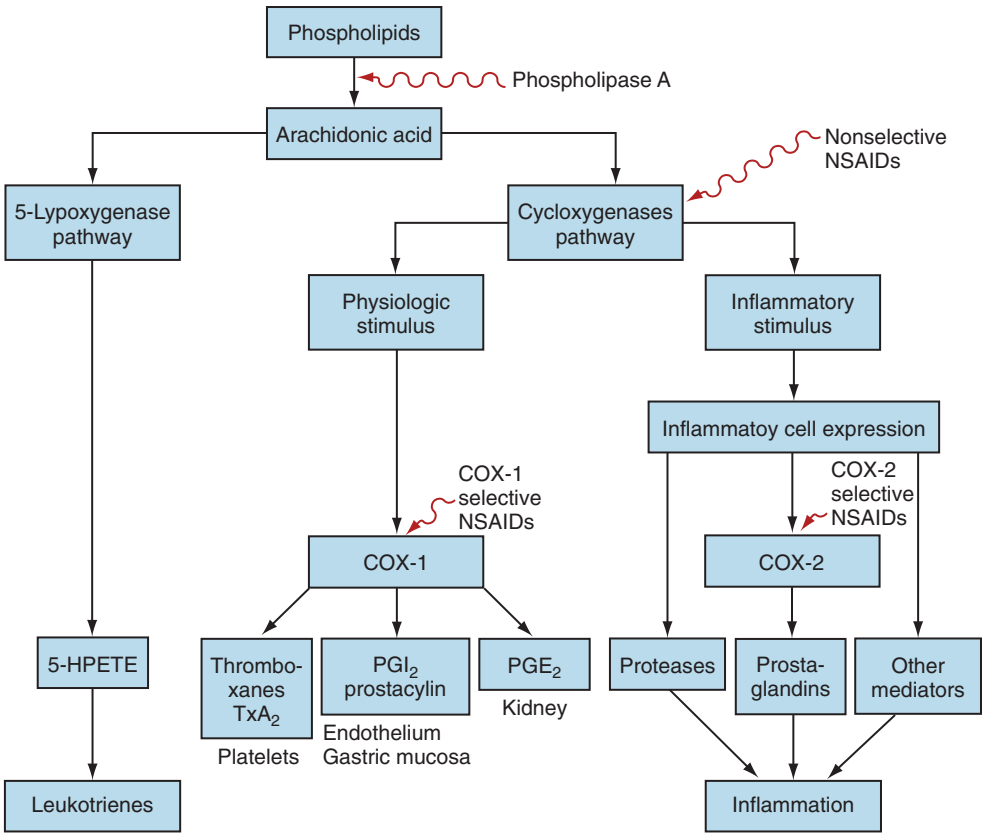

Figure 20-2 Inflammatory pathways and sites for herb interventions.

painful muscle spasms that limit mobility in these animals. Massage and other physical therapies can be very helpful, but herbs can provide a variety of therapeutic actions, including antispasmodic, anti-inflammatory, and circulatory enhancement to these areas. Most of the herbs that are useful in treating "rheumatic" animals are discussed below by putative mechanism, but the entire list given by Hoffmann (2004) is long and includes the following: yarrow, angelica, celery seed, burdock, uva ursi, arnica, horseradish, wormwood *(Artemisia absinthium),* mugwort, birch, brassica, cayenne, blue cohosh, black cohosh, wild yam, boneset, gravelroot, meadowsweet, bladderwrack, wintergreen, guaiacum, devil's claw, blue flag, juniper, Oregon grape, bogbean, bayberry, parsley, poke, aspen, rosemary, yellow dock, willow, sarsaparilla, feverfew, dandelion, nettle, cramp bark, prickly ash, and ginger.

Anti-inflammatory agents

These herbs appear to inhibit the inflammatory processes that accompany degenerative processes, immune-mediated events, and other inflammatory and traumatic conditions.

DEVIL'S CLAW *(HARPAGOPHYTUM PROCUMBENS):* This plant is used in traditional African medicine for arthritis. Studies suggest that devil's claw may suppress prostaglandin E_2 (PGE_2) synthesis and nitric oxide production by inhibiting lipopolysaccharide-stimulated enhancement of cyclooxygenase (COX)-2 and inducible nitric oxide synthase mRNA expression. Human clinical trials show that it is clearly effective in the treatment of low back pain.

MEADOWSWEET *(FILIPENDULA ULMARIA):* This was the first source identified for commercial production of salicin, a nonselective COX-1 and COX-2 inhibitor.

WILLOW BARK (*SALIX ALBA* AND OTHER SALIX SPECIES): Willow contains high levels of salicin, a nonselective COX-1 and COX-2 inhibitor. *Betula* (Birch) species are also recognized as having significant salicin levels in their barks.

FEVERFEW *(TANACETUM PARTHENIUM):* Clinical trial evidence for use of feverfew in osteoarthritis is not yet convincing (Ernst, 2000b). A well-studied constituent, parthenolide, specifically binds to and inhibits IKK-beta, which is involved in cytokine-mediated signaling. Parthenolide and other constituents also apparently inhibit COX expression and have various other effects on a variety of eicosanoids. Feverfew powder (more so than its extracts) has antiserotonergic activity (Mittra, 2000).

NETTLE *(URTICA DIOICA):* In his review, Ernst (2000) describes unpublished data from a randomized controlled trial in which a stew of aerial parts of the plant was effective for pain, but a concentrated juice containing 10 times more of the presumed active ingredient (lipoxygenase inhibitor caffeoyl malic acid) was not. Nettle inhibits

the activity of NF-kappa-B (Riehemann, 1999), and proprietary extracts of nettle were found to suppress the activity matrix metalloproteinases, which enhance degradation of extracellular matrix in joint cartilage (Schulze-Tanzil, 2002).

GINGER *(ZINGIBER OFFICINALIS):* This has been recommended for anti-inflammatory effects through eicosanoid modulation, as it inhibits the activity of both cyclooxygenase and lipoxygenase. The few studies done may suggest some such activity (Bliddal, 2000).

BOSWELLIA *(BOSWELLIA SERRATA):* Boswellia may reduce pain and inflammation through its activity as a lipoxygenase inhibitor. In bovine serum albumin-induced arthritis, boswellic acids reduced inflammatory cell infiltrates (Sharma, 1989). One study showed that boswellic acids have activity against 5-lipoxygenase, but that they did not affect 12-lipoxygenase or cyclooxygenase (Ammon, 1993). An open, multicenter (10 veterinarians) clinical trial was performed with a resin extract of *Boswellia serrata* (BSB108, product of Bogar AG). A total of 29 dogs with signs of chronic joint and spinal disease were enrolled; 25 had radiologic signs of osteoarthritis and "degenerative conditions." BSB108 was administered in the diet at a dose of 400 mg/10 kg body weight daily for 6 weeks. Of 24 eligible dogs, the investigators believed that 71% of them showed improvement. A statistically significant reduction in severity and resolution of typical clinical signs, such as intermittent lameness, local pain, and stiff gait reported after 6 weeks, were observed in individual animals; however, no control group was included. Adverse effects were rare and mild, consisting only of brief episodes of diarrhea and flatulence (Reichling, 2004).

TURMERIC *(CURCUMA LONGA):* This has been used in Ayurvedic medicine for arthritis and other types of pain, and in Chinese medicine for abdominal pain, and is often found in formulas with Boswellia. Human clinical trials have demonstrated some anti-inflammatory activity (Chainani-Wu, 2003). A clinical trial using similar species of turmeric—Indian turmeric *(C. domestica)* and Javanese turmeric *(C. xanthorrhiza)*—was conducted with 61 client-owned dogs with arthritis. The dogs were evaluated by veterinarians and owners, then were administered a placebo or a standardized extract containing 20 mg curcuminoids, 50 mg *C. xanthorrhiza* volatile oil, and 150 mg *C. domestica* essential oil. The dose used was 2 capsules per 10 kg body weight twice daily. Veterinary evaluations were statistically significantly in favor of the turmeric preparation over placebo, but force plate analysis and owner evaluations were not. Investigators noted that minor adverse effects occurred in the turmeric group, including a peculiar smell that may have compromised the blinding of the clinical evaluators (Innes, 2003).

YUCCA *(YUCCA SCHIDIGERA):* This herb is popular but not well studied. One proposed mechanism of action involves the suppression of gut bacterial endotoxin production by saponins, which thus removes a supposed suppressor of proteoglycan synthesis. One study suggested that a single constituent, Yuccaol C, reduced inducible nitric oxide synthase expression via the transcription factor NF-kappa-B (Marzocco, 2004).

WILD YAM, OR MEXICAN YAM *(DIOSCOREA VILLOSA):* This herb has traditionally been used for pain control. It contains diosgenin, which has been used as a precursor in the manufacture of commercial corticosteroids. Diosgenin does not appear to be converted to glucocorticoid by mammalian systems, so plant sterols may have effects that are like or unlike mammalian steroids. One study showed that extracts of a Japanese yam inhibited production of COX-2 and nitric oxide synthase (Kim, 2004).

GUGGUL *(COMMIPHORA MUKUL):* Clinical investigations have shown that guggul reduced pain and stiffness and improved function in older patients with osteoarthritis of the knee. Guggul was administered in capsule form (500 mg concentrated exact delivered three times daily) along with food. No adverse effects were reported during the trial (Singh, 2003b).

ARNICA *(ARNICA MONTANA):* This strong herb inhibits the activation of NF-kappa-B (Klaas, 2002). It is usually used only topically, or orally in homeopathic doses. An open multicenter clinical trial was conducted to determine the safety and efficacy of an *Arnica montana* fresh plant gel, applied twice daily, in 79 people with mild to moderate osteoarthritis of the knee. After 3 and 6 weeks, significant decreases in scores for pain, stiffness, and function scales showed significant reductions at these time points, with only one allergic reaction. (Knuesel, 2002). A preparation like this may be useful in horses, but dogs would have to be prevented from licking the gel because of its oral toxicity. Arnica was also investigated in a double-blind trial with 37 humans undergoing bilateral endoscopic carpal tunnel release surgery. Patients were administered homeopathic Arnica orally and arnica gel topically. A significant reduction in pain was noted after 2 weeks in the Arnica-treated group (Jeffrey, 2002).

GUAIACUM *(GUAIACUM OFFICINALE):* This herb has been listed as a traditional analgesic, but one study suggested that it has anti-inflammatory activity (Duwiejua, 1994).

BOGBEAN *(MENYANTHES TRIFOLIATA):* This plant contains unusually high levels of betulinic acid, a potent anti-inflammatory agent (Patočka, 2003).

OTHER HERBS: Other anti-inflammatory agents suggested in traditional herbal texts include Angelica *(Angelica archangelica),* Celery *(Apium graveolens),* Blue cohosh *(Caulophyllum thalictroides),* Black cohosh *(Actea racemosa),* Wintergreen *(Gaultheria procumbens),* and Quaking aspen *(Populus tremuloides).*

Analgesics

Analgesics alleviate pain without causing loss of consciousness, although they may also have central nervous system effects that affect awareness. (Analgesic herbs are discussed further under neurologic and behavioral herbs.)

CORYDALIS *(CORYDALIS YANHUSUO, C. TURTSCHANINOVII, C. TECUMBENS, AND C. INCISA):* These herbs account for part of traditional Chinese herbal combinations for pain. Although a specific mechanism of

action has not been well described, authorities state that continued use leads to tolerance and to cross-tolerance with opioids.

JAMAICAN DOGWOOD *(PISCIDEA ERYTHRINA):* This herb is not well studied, but early laboratory animal studies suggested some spasmolytic and possible sedative effects. *King's American Dispensatory* opined that it had a central pain-relieving action.

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* Although it is better known as an antidepressant, this herb has exhibited analgesic and anti-inflammatory activities in laboratory animals; two other *Hypericum* species *(H. cordatum* and *H. caprifoliatum)* have shown antinociceptive activity, possibly via opioid systems, in laboratory animal pain models (Viana, 2003). Antidepressants are recognized elements of pain control in human medicine, and they may act through a number of pharmacologic actions; for example, by blocking reuptake of noradrenaline and 5-hydroxytryptamine through direct and indirect actions on opioid receptors; inhibiting histamine, cholinergic, 5-hydroxytryptamine and *N*-methyl-D-aspartate receptors; inhibiting ion channel activity; and blocking adenosine uptake (Sawynok, 2001).

CALIFORNIA POPPY *(ESCHSCHOLTZIA CALIFORNICA):* This plant has not been well investigated for analgesic properties, but the U.S. Dispensatory of 1918 claimed it to be a powerful but safe soporific and analgesic, containing small amounts of morphine and other alkaloids. Rolland et al (2001) showed analgesic effects in mice.

INDIAN PIPE *(MONOTROPA UNIFLORA):* This has also been used for pain control and is said to have mild dissociative effects.

Spasmolytic agents

Although spasmolytic agents are generally thought to apply more to smooth muscle (such as in the gastrointestinal, reproductive, respiratory, and urinary tracts), skeletal muscle may also be relieved of spasm, probably because of central effects.

BLACK COHOSH *(ACTAEA RACEMOSA):* The single constituent, cimicifugoside, was recently shown to selectively inhibit N-acetylcholine receptor–mediated responses in bovine chromaffin cells (Woo, 2004). No other studies related to pain or spasm could be located.

VALERIAN *(VALERIANA OFFICINALIS):* Older German studies indicate that valerenic acid is spasmolytic and relaxes muscles (Wagner, 1979; Bisset, 1994).

CRAMP BARK *(VIBURNUM OPULUS):* This herb and other *Viburnum* species have shown the ability to reduce smooth muscle spasm in a number of in vitro studies (Cometa, 1998; Calle, 1999; Nicholson, 1972). Whether they also have skeletal muscle effects has not been investigated.

OTHER HERBS: Other herbs used for their spasmolytic effects include Black haw, Skunk cabbage, Lobelia, Myrrh, Skullcap, and Kava kava.

Alteratives

Alterative herbs cause a change in a chronic condition, or tend to restore to health ["without sensible evacuations," according to *Webster's Dictionary*]. Traditional lore had it that these herbs were blood purifiers that supported toxin elimination. Modern medical science may also conceive of these herbs as supplying nutritional elements or acting as immune modulators, enhancing liver detoxification activity, antioxidants, anti-inflammatories, or normalizing gut function or gut bacterial populations.

BURDOCK *(ARCTIUM LAPPA):* This herb has shown antioxidant and anti-inflammatory activities in laboratory animal studies (Lin, 1996a). The root is also high in starch (especially inulin), which accounts for its mild laxative effect, and may improve gut bacterial populations.

BLUE FLAG *(IRIS VERSICOLOR):* This herb is usually used for liver disease (chronic skin and musculoskeletal diseases are often treated with the same alteratives for many of the same reasons). The herb is traditionally considered to be hepatic, cholagogue, diuretic, laxative, and anti-inflammatory.

OREGON GRAPE *(MAHONIA AQUIFOLIUM):* The components jatrorrhizine and magnoflorine are powerful antioxidants (Rackova, 2004). The aporphine alkaloids isothebaine and isocorydine showed relaxant properties in the rat aorta (Sotnikova, 1997). This herb is a traditional hepatic, laxative, and cholagogue.

YELLOW DOCK OR CURLY DOCK *(RUMEX CRISPUS):* This herb is a traditional hepatic, cholagogue, and mild laxative. Studies on other species of Rumex *(R. maritima, R. patientia,* and *R. saggitatus)* show anti-inflammatory activity in laboratory animal and in in vitro studies (Islam, 2003; Suleyman, 2001; Jager, 1996).

SARSAPARILLA (*SMILAX* SPP): Various species of *Smilax* have shown immune modulatory and anti-inflammatory activities in laboratory animal studies of chronic inflammation (Lu, 2003; Jiang, 2003; Ageel, 1989).

POKEWEED *(PHYTOLACCA AMERICANA):* This strong plant is not used often for patients with arthritis but may be a powerful immune modulant or anti-inflammatory agent. It was an important plant for rheumatism in American folk medicine

Circulatory stimulants

Traditional circulatory stimulants are generally warming and pungent herbs, the peripheral effects of which can sometimes be seen in nearly immediate sweating. Practically speaking, these herbs probably have anti-inflammatory AND analgesic effects.

CAPSICUM *(CAPSICUM ANNUUM):* This herb has been used orally as a traditional circulatory stimulant. Capsaicin is the best known analgesic compound in this pepper, and it is the parent compound of a group of vanillyl fatty acid amides. It acts specifically by depleting stores of substance P from sensory neurons; it has been used successfully in the treatment of rheumatoid arthritis, osteoarthritis, peripheral neuropathies, and fibromyalgia, and is applied topically. Capsicum oleoresin, however, contains more than 100 volatile compounds and may have a variety of other actions. Other capsaicinoids have anti-inflammatory activity, inhibiting activation of NF-kappa-B and certain events in T-cell activation (Sancho, 2002).

PRICKLY ASH *(ZANTHOXYLUM AMERICANUM):* This traditional circulatory stimulant has not been examined for activity in musculoskeletal pain. The Eclectics used it primarily for muscular rheumatism and neuromuscular problems. Other species of *Zanthoxylum* have shown antinociceptive and antispasmodic activities in laboratory animals and in in vitro studies (de Moura, 2002; Rahman, 2002).

OTHER HERBS: Ginger has been reviewed in the anti-inflammatory herb section.

Diuretics

Diuretics have traditionally been considered important to help eliminate end products of metabolism and inflammatory by-products. Although the plants discussed in this section have diuretic activity, it is unclear that this is a primary mechanism for consideration in patients with musculoskeletal disease, because they also appear to work via other mechanisms.

YARROW *(ACHILLEA MILLEFOLIUM):* This herb and other species of yarrow contain anti-inflammatory principles, including sterols, flavonoids, and sesquiterpenes.

CELERY *(APIUM GRAVEOLENS):* This traditional remedy is used for gout, a type of inflammatory arthritis that develops in people with accumulation of uric acid in the joints. Celery seed has a reputation for increasing urinary uric acid excretion, but studies have not confirmed this. One group did identify multiple compounds in celery seed that inhibited both COX-1 and COX-2 activity, as well as compounds that had antioxidant activity (Momin, 2002).

BONESET *(EUPATORIUM PERFOLIATUM):* A component of Joe Pye Weed *(E. purpureum)* has been shown to have anti-inflammatory activity (Habtemariam, 2001). Other species of *Eupatorium* have shown antinociceptive activity that is not related to opioids (Clavin, 2000). No relevant studies were found for use of boneset.

Nervines

See the neurologic and behavioral herb section.

Nervines may be effective in reducing the stress associated with chronic pain. The herbs listed here have other actions that have been described previously.

- Celery *(Apium graveolens)*
- Jamaica dogwood *(Piscidia erythrina)*
- Valerian *(Valeriana officinalis)*

Other herbs

Other herbs that have been used for their effects on the musculoskeletal system include Blue vervain, Butterbur, Chamomile, Hops, Skunk cabbage, Valerian, Willow bark, and Wood Betony.

Review of Specific Musculoskeletal Conditions

Musculoskeletal pain and inflammation

The formulas given here are simply starting points and should be customized (in content and dose) for the patient's condition. These formulas may be dosed at approximately 0.25-1.0 mL per 10 lb two to three times daily.

A prescription for early osteoarthritis or presurgical patients with anti-inflammatory and analgesic activity follows:

Devil's claw	25%
Meadowsweet	25%
Ginger	25%
Ashwagandha	25%

A stronger formula, used only after chondroprotectives, massage, exercise, and milder formulas have failed, is provided here:

Devil's claw	30%
Corydalis	30%
Prickly ash	30%
Sarsaparilla	10%

Formulas similar to those above can be considered for the following conditions.

Cranial cruciate ligament rupture

Complete rupture of the ligament will probably require surgery for best results, but partial tears may be managed with anti-inflammatory herbs and physical therapy. Analgesics or acupuncture may be necessary for animals undergoing physical therapy.

Luxating patella

Anti-inflammatory herbs are useful if the condition is of low grade and surgery is not required. Severe arthritis of the stifle may require more integrated therapy with anti-inflammatory, antispasmodic, analgesic, and alterative herbs, as well as acupuncture and physical therapy.

Myopathy

Owners of animals with diseases such as feline congenital myotonia, Devon Rex myopathy, Scotty cramp, German shepherd fibrotic myopathy, Labrador stress syndrome, and other unusual muscle diseases frequently seek herbal and other therapies when conventional medicine fails their pets. These animals may benefit from spasmolytic and nervine herbs. Cramp bark, black haw, valerian, Jamaica dogwood, wild yam, and prickly ash might be candidates for these patients.

Osteoarthritis

Anti-inflammatory herbs are frequently used for osteoarthritis. The most popular are Boswellia, Ginger, Devil's claw, Meadowsweet, and Yucca. For chronic arthritis, analgesic, spasmolytic, nervine, and alterative herbs may be used.

One Chinese herbal combination tested in dogs appeared effective (Bonnett, 1996). In a study of 143 clinical canine patients in four groups, a proprietary Chinese herbal combination was compared with Devil's claw combination, aspirin, and placebo. The Chinese herbal prescription contained White peony, Licorice, Epimedium, Oyster shell, Reishi mushroom, Isatidis, and Corydalis. The Chinese herbal combination and aspirin groups experienced significant improvement according to owner

and veterinary evaluation, whereas the response to Devil's claw combination was equivalent to the placebo response (Bonnett, 1996). The specific formula used in this study is not commercially available, but similar combinations can be formulated on request by reputable Chinese pharmacies.

A prescription for relief from osteoarthritis:

Devil's claw	20%
Corydalis	20%
Saint John's Wort	20%
Ashwagandha	40%

Osteochondrosis

Acute osteochondrosis requires surgery, but the consequence of this disease is osteoarthritis. See the section on osteoarthritis for suggested herbs.

Panosteitis

Analgesic herbs may be helpful in this condition. Boneset has a reputation for relieving deep bone pain. Boneset has a specific indication for deep "bone" pain and may be useful in a formula as well. *King's American Dispensatory* describes the indications for boneset in this way: "Its popular name, "boneset," is derived from its well-known property of relieving the deep-seated pains in the limbs which accompany [influenza], and colds and rheumatism. Often, this pain is periosteal, and if neuralgic in character, or due to a febrile condition, eupatorium will relieve it. But it is not a remedy for periosteal pain due to inflammation or to organic changes in the periosteum."

Muscular rheumatism (old age stiffness)

Merriam Webster Online defines rheumatism as, "any of various conditions characterized by inflammation or pain in muscles, joints, or fibrous tissue." Herbs that may be helpful for this kind of pain include prickly ash, valerian, and the viburnums (Black haw and Cramp bark).

Rheumatoid arthritis

Patients with rheumatoid arthritis may benefit from immune modulators, alteratives, and anti-inflammatory herbs. One plant that has been shown to have activity in rheumatoid arthritis patients is *Tripterygium wilfordii* (Tao, 2000); however, the adverse effects have led researchers to try to isolate a safer single constituent (triptolide). Other herbs for consideration are those with anti-inflammatory and analgesic activities.

These may include bogbean, meadowsweet, wild yam, guaiacum, valerian, celery seed, angelica, and Saint John's wort.

Spondylosis deformans

Although many still consider this a nonpainful condition, we disagree. Anti-inflammatory herbs may be useful, but circulatory stimulants and analgesics may be more useful. These might include capsicum, prickly ash, valerian, boswellia, peony, and yucca.

Trauma

Arnica is a specific remedy for trauma. It is a very strong herb and, if used orally, is generally administered in homeopathic (or low-dose) form. Arnica ointments are available for topical use but may be toxic if the animal licks the area.

Rabbits with induced impacted vertebrae and spinal cord injury that were treated with dan shen *(Salvia miltiorrhiza),* compared with controls, demonstrated less serious damage histologically. It was concluded that dan shen injection has some protective effect on spinal cord injury in its early stage (Ni, 2002).

Fracture repair

In addition to conventional treatment, one may consider using dan shen *(Salvia miltiorrhiza).* Dan shen was used in an experimental group of rabbits with induced bone defects. It increased osteoblast activity to a greater extent than did controls, and it stimulated synthesis of protein in fibroblasts. Dan shen caused early formation of dense callus, and microscopic examination revealed increased activity of osteoblasts. It was concluded that dan shen could improve mandibular bone fracture healing (Lin, 1992).

HERBS FOR PAIN AND NEUROLOGIC AND BEHAVIORAL DISORDERS

General Considerations

In no other system is it so obvious that plants and animals coevolved to use each other for conducting the business of life—beyond mere nutrition. Plant and animal physiologic master plans developed in concert, sometimes during battles (as plants developed defenses against herbivores) but seemingly to everyone's benefit in the end. Plants learned to use animals for reproduction (for a surprising read, *The Botany of Desire* is highly recommended). Animals have receptors for plant chemicals—opioid receptors, named for the opium poppy, as well as cannabinoid receptors, benzodiazepine receptors, and vanilloid receptors (for cayenne's constituent, capsaicin). Many plants can have an effect on animal consciousness and pain perception. Veterinarians have learned many of these in poisonous plant lists. For herbalists, these plants may provide additional tools with which to treat patients with abnormal behavior, seizures, neuromuscular disease, and pain.

In traditional herbal medicine, any plant that affects the nervous system is called a *nervine.* A nervine can therefore encompass several kinds of therapeutic activity. For example, an herbalist might prescribe a nervine to calm and sedate a patient who exhibits hyperactivity or anxiety, or a nervine may be prescribed for a depressed patient, to restore a sense of well-being. In veterinary neurology, one of the most important contributions that herbal medicine can make is in "strengthening" the nervous system. Nervines can be broadly classified into three main groups, although many nervine herbs have overlapping activity.

1. Nervine relaxants have sedating, hypnotic, or calming and anxiolytic activity, and many have antispasmodic activity. Relaxant nervines are prescribed for anxiety, hyperactivity, and sleeplessness and restlessness. They

include herbs such as valerian, lavender, hops, passionflower, and lemon balm. Nervine relaxants include antispasmodic nervines that are prescribed for muscle cramping or twitches, such as smooth muscle spasm of the colon, bronchi, stomach, bladder, and so forth. An example is chamomile, which is used for painful spasm of the gastrointestinal tract.

2. Nervine stimulants may be beneficial in a depressed or hypoactive nervous system. Rarely needed in veterinary medicine, these herbs are widely used by people and include coffee, tea, cola (kola nut), and guarana; all can induce anxiety and tension. Stimulating nervines are prescribed for low-energy states, lethargy, and depression. Saint John's wort can be useful for mild depression; also, this group may include the cognition-enhancing herbs outlined later.
3. Nervine tonics can restore tissues directly (see later) by contributing to tissue repair, or they may help reduce the effects of undue stress on the body; these include adaptogens, nervine trophorestoratives, and most herbs that reduce anxiety and stress. One example is *Ginkgo biloba,* which appears to work by promoting vasodilation in the brain, thus improving oxygenation to brain tissue. Others include Saint John's wort and Oats.

Although these classifications may appear paradoxical, in all cases of neurologic or behavioral imbalance, the goals of herbal medicine are fundamentally the same: to nourish the nervous system and restore and balance activity. The following herbs may give veterinary herbalists additional tools for use in treating patients with abnormal behavior, seizures, neuromuscular disease, and pain; their mechanisms of action are presented.

Mechanisms of Interest

Nervine relaxants

BLACK COHOSH *(ACTAEA RACEMOSA):* Most Eclectic uses of black cohosh as a nervine were associated with menstrual or menopausal disorders in women, and it is difficult to separate the antispasmodic and analgesic effects within traditional literature. King's (Felter 1898) has this to say of Black cohosh: "exerts a powerful influence over the nervous system, and has long been favorably known as a remedy for chorea. It may be used alone or with specific valerian, equal parts. Its action is slow, but its effects are permanent. It has been used successfully as an antispasmodic in hysteria, epilepsy when due to menstrual failures, asthma and kindred affections, periodical convulsions, nervous excitability, pertussis, delirium tremens, and many other spasmodic affections."

HOPS *(HUMULUS LUPULUS):* This traditional sedative is used for neuralgia, insomnia, excitability, priapism, mucous colitis, and, specifically, for restlessness associated with nervous tension headache or indigestion. The German Commission E approved its use for mood disturbances such as restlessness and anxiety, as well as for sleep disturbances (Blumenthal, 1998). King's describes hops this way: "They are principally used for their sedative or hypnotic action—producing sleep, removing restlessness, and abating pain, but which they often fail to accomplish." Whole extracts of hops were generally administered for this purpose in the form of ale or porter. The Eclectics preferred a powdered extract called *lupulin,* and found it much more reliable. Early laboratory animal and human clinical studies showed no sedative effects (Hansel, 1967; Stocker, 1967). Later studies showed that one auto-oxidation product had strong sedative properties in animals (Wohlfart, 1983; Hänsel, 1980; Wohlfart, 1982). This is an aromatic principle, and the authors warned that it may be present in traditional hops pillows, but not in many herb extracts. However, it has also been suggested that isovaleric acid residues present in hops may contribute to its sedative action in mice. Hops extract administered intraperitoneally 30 minutes before a series of behavioral tests resulted in dose-dependent suppression of spontaneous locomotion at a dose of 250 mg/kg for up to 1 hour (Lee, 1993).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* The alkaloid root extract (ashwagandholine) exhibited a taming effect and had a mild depressant (tranquilizer) effect on the central nervous system of monkeys, cats, dogs, rats, and mice (Malhotra, 1965). Glycowithanolides of withania (10 and 20 mg/kg/day, intraperitoneally, for 21 days) induced a dose-related increase in superoxide dismutase, catalase, and glutathione peroxidase activity in rat brain; this effect was comparable to the benefit of deprenyl (Bhattacharya, 1997). Sitoindosides VII through X and withaferin-A were studied on brain cholinergic, glutamatergic, and gamma-aminobutyric acid (GABA)ergic receptors in rats. Results suggested that the compounds preferentially affect events in the cortical and basal forebrain cholinergic signal transduction cascade. The drug-induced increase in cortical muscarinic acetylcholine receptor capacity might explain in part the cognition-enhancing and memory-improving effects of extracts from *Withania somnifera* observed in animals and humans (Schliebs, 1997). GABA binding was inhibited by 20% with 5 µg Withania root extract and completely by 1 mg. This extract increased Cl influx, which was blocked by bicuculline and picrotoxin and was enhanced by diazepam. These results suggest that the *W. somnifera* extract contains an ingredient that has a GABA-mimetic activity (Mehta, 1991). Withania has been used to stabilize mood in patients with behavioral disturbances.

ZIZYPHUS SEED *(ZIZYPHUS SPINOSA):* The flavonoids and saponins were tested for sedative activity. All compounds tested potentiated hexobarbital-induced hypnosis and reduced ladder climbing and caffeine-induced hyperactivity. It was found that these compounds produced sleep but were not anticonvulsants or muscle relaxants (Shin, 1981). Jujuboside A (JuA), a major constituent of the seed, has inhibitory effects on the glutamate-mediated excitatory signal pathway in the hippocampus and probably acts through its anticalmodulin action (Zhang, 2003b).

MOTHERWORT *(LEONURUS CARDIACA):* This herb has not been investigated for its nervine qualities. King's describes its indications as "nervous excitability, all chronic diseases attended with restlessness, wakefulness, disturbed sleep. . . . It is adapted to cases of nervous debil-

ity with irritation, nervous unrest, tendency to choreic or spasmodic movements."

CHAMOMILE *(MATRICARIA RECUTITA):* The dried flower heads of chamomile are used in folk medicine to prepare a spasmolytic and sedative tea. Laboratory animal studies suggest that this plant has some sedative activity (Della Loggia, 1981). The essential oil of chamomile improved mood in a human clinical trial (Roberts, 1992). King's describes the indications as "nervous irritability, with peevishness, fretfulness, discontent, and impatience; sudden fits of temper during the catamenial period; muscular twitching; morbid sensitiveness to pain." This herb was considered most important for children and for those who exhibited signs that were out of proportion to the actual pain that was experienced. The text also notes that the nervine effects of Chamomile are more marked at low (drop) doses than at typical herb doses.

LEMON BALM *(MELISSA OFFICINALIS):* Laboratory animal studies have shown that Lemon balm has sedative activity (Bisset, 1994). Two randomized, placebo-controlled, double-blind, balanced-crossover studies investigated the effects of a standardized extract in healthy people who received single doses of 300, 600, 900, 1000, or 1600 mg or a placebo at 7-day intervals. Cognitive performance was assessed immediately before dosing and at 1, 2.5, 4, and 6 hours thereafter. Calmness (self-assessed) was increased after the lowest doses, and alertness was decreased following the higher doses. Higher doses improved memory performance, however (Kennedy, 2002; Kennedy, 2003b). In a subsequent study, this group showed that in healthy humans, 300 mg or 600 mg of standardized extract increased calmness and decreased alertness in the face of stress, but the speed of mathematical processing was increased at the lower dose (Kennedy, 2004). Patients with agitation due to severe dementia were administered a lotion with essential oil of Melissa or a placebo aromatherapy lotion. In this study, there was significant improvement in agitation and quality of life indices for those being treated with Lemon balm (Ballard, 2002). The Eclectics considered the plant stimulant and diaphoretic.

CATNIP *(NEPETA CATARIA):* This herb was used by the Eclectics for headaches and nervous irritability. It was also used as an antispasmodic, and Cook's *Physiomedical Dispensatory* (1869) calls it a "diffuse nervine and antispasmodic of much service." Laboratory animal studies have produced somewhat conflicting results regarding sleep time and activity. Two studies suggest that components of catnip have some sedative activity. Catnip oil (500 mg/kg) and nepetalic acid (62.5 mg/kg) were found to significantly increase sleep time in mice. Rats showed a significant decrease in performance in avoidance studies after intraperitoneal injections of catnip oil (500-750 mg/kg), nepetalic acid (125-250 mg/kg), and the nepetalactone-enriched fraction (500-750 mg/kg) (Harney, 1978). The alcohol extract of catnip showed a biphasic effect on the behavior of young chicks, increasing the number of chicks who slept at low and moderate doses (25-1800 mg/kg), while high dose levels (i.e., above 2 g/kg) led fewer chicks to sleep (Sherry, 1979). On the other hand, Massoco and colleagues (1995) fed mice catnip at 10% of their dietary intake and discovered amphetamine-like activity. A case report described a single child who ate a large amount of catnip and was obtunded (Osterhoudt, 1997). Aydin (1998) determined that nepetalactone (a component of *Nepeta cataria* and other species of *Nepeta*) had specific activity at some opioid receptor subtypes. Unique behavioral reactions of cats have been observed in the presence of catnip. The chemosensory stimulus evoking the catnip reaction is undoubtedly mediated through the main olfactory system. These behaviors, include sniffing and chewing as associated with oral appetitive behavior, rolling and rubbing characteristic of female sexual behavior, batting the catnip source characteristic of play behavior, and a type of kicking associated with predatory behavior. These behavioral reactions occur randomly and intermittently (Hart, 1985).

PASSIONFLOWER *(PASSIFLORA INCARNATA):* The methanol leaf extract was evaluated for various central nervous system (CNS) effects in experimental animals. This extract exhibited significant sedative, anticonvulsant, and CNS-depressant activities at a dose of 200 mg/kg in mice. The extract also exhibited analgesic and anti-inflammatory activities against induced pain and induced edema, respectively, in experimental animals (Kamaldeep, 2003).

JAMAICA DOGWOOD *(PISCIDIA PISCIPULA,* FORMERLY *PISCIDEA ERYTHRINA):* Ellingwood's *Materia Medica* (1919) describes this herb's indications as follows: "In susceptible patients, it will control pain and relieve general distress. It is distinctly a nerve sedative, and overcomes nervous excitability and also reflex irritability. It is an antispasmodic of much power in mild cases." It is also known for its ability to induce deep, restful sleep. Laboratory animal studies suggest that this plant has some sedative activity (Della Loggia, 1981). The herb is toxic in high doses (producing seizures and cardiorespiratory arrest) and probably is not appropriate for long-term use. The human dose of the fluid extract recommended by King's (Felter, 1898) is 10 drops to 2 fluid drachm (approximately 7 mL) daily, but doses recommended by the *British Herbal Compendium* are higher: 2 to 4 g of dried root bark, 5 to 15 mL of the tincture (1:5 in 45%), or 2 to 8 mL of the liquid extract (1:1 in 60%) three times daily (Bradley 1992).

PULSATILLA *(PULSATILLA VULGARIS,* FORMERLY *ANEMONE PULSATILLA):* This herb is also called European pasqueflower, Meadow anemone, and Windflower. The 1918 US Dispensatory summarizes the available anecdotes and literature on this herb, saying that it leads to progressive paralysis and that there is contradictory information on any effect on the heart; it does not list nervousness or anxiety as an indication. On the other hand, King's describes the specific indications for Pulsatilla to include "nervousness and despondency, sadness, unnatural fear, tendency to weep, morbid mental excitement, marked depression of spirits, pain, with debility, nervousness . . ." The US Dispensatory related the fatal dose for the rabbit as 200 mg/kg and for the guinea pig as 0.16 g/kg. This reference provided a dose for humans of from $^{5}/_{6}$ to $1^{1}/_{2}$ grains (0.05-0.096 g) divided daily.

SKULLCAP *(SCUTELLARIA LATERIFLORA):* King's lists the specific indications for Skullcap as "Nervousness, attending or following acute or chronic diseases, or from mental or physical exhaustion, teething, etc.; nervousness manifesting itself in muscular action; tremors, subsultus, etc.; hysteria, with inability to control the voluntary muscles; functional cardiac disorders of a purely nervous type, with intermittent pulse." The 1918 US Dispensatory proclaimed it devoid of medicinal effects, but evidence is accumulating that it may indeed act as a mild nervine. Scutellarin and ikonnikoside bind a 5-HT receptor subtype (Gafner, 2003). The plant contains baicalin and baicalein, which bind the benzodiazepine site of the GABA A receptor (Awad, 2003).

LINDEN *(TILIA PLATYPHYLLOS):* This is a mild traditional nervine that was more popular in Europe than in the United States. The Eclectics considered the flowers a stimulant and nervine, as well as a remedy for mild hysteria. No studies were found on the putative medicinal effects of Linden.

VALERIAN *(VALERIANA OFFICINALIS):* The 1918 US Dispensatory discusses valerian as follows: "Valerian is used as a sedative to the higher nerve centers in conditions of nervous unrest, hysteria, hypochondriasis, neuralgic pains, and the like." There is fairly good evidence for valerian as a hypnotic; clinical trials have shown that it can decrease sleep latency and nocturnal awakenings and improve subjective sleep quality (Beaubrun, 2000), but the evidence for a sedative effect is less strong. In laboratory animal studies, valerian extracts appear to influence GABAergic neurons, including increased release of GABA, decreased GABA reuptake, and decreased GABA degradation. Studies in rats and mice have shown sedative and anticonvulsant activities for whole plant extracts, as well as for valerenic acids, valepotriates, and the volatile oil (Schulz, 2001). Cats given 10 mg of valepotriates by stomach tube showed decreased restlessness, fear, and aggressive behaviors (Eickstedt, 1969).

MISTLETOE, EUROPEAN *(VISCUM ALBUM):* This herb is classed as a nervine by some herbalists. The Eclectic literature evolved from originally calling the herb a *narcotic,* used for calming seizures (in King's 1898), to calling it *toxic* and possibly indicated most often for heart disorders (Felter, 1922). Modern studies concentrate on its immune modulating and antineoplastic effects. It cannot be recommended as a nervine for animals without additional studies or experience.

GOTU KOLA *(CENTELLA ASIATICA):* In vivo studies in mice and rats using brahmoside and brahminoside, given by intraperitoneal injection, have shown a CNS-depressant effect. These compounds were found to decrease motor activity, increase hexobarbitone sleeping time, and slightly decrease body temperature; they were thought to act via a cholinergic mechanism (Ramaswamy, 1970).

Herbs with anxiolytic activity

CALIFORNIA POPPY *(ESCHSCHOLZIA CALIFORNICA):* Rolland and associates investigated the anxiolytic effects of an aqueous extract in mice. Doses of 25 mg/kg were anxiolytic when measured by standard anticonflict tests. Additional behavioral effects were noted at doses of 100 mg/kg and 200 mg/kg, and no adverse effects were noted when the herb was administered intraperitoneally and orally (Rolland, 1991). This extract was evaluated for benzodiazepine, neuroleptic, antidepressant, antihistamine, and analgesic properties. Investigators concluded that the extract had an affinity for benzodiazepine receptors, and that it had peripheral analgesic effects (Rolland, 2001).

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* Saint John's wort extracts have been shown in multiple laboratory animal studies to bind at GABA A and GABA B receptors, to inhibit GABA reuptake, to evoke GABA release, and to exert anxiolytic-like effects that are blocked by the benzodiazepine antagonist flumazenil (Skalisz, 2004; Beijamini, 2003a; Beijamini, 2003b; Zanoli, 2002; Perfumi, 2002; Flausino, 2002). The Eclectics mentioned that it had sedative properties but did not make much use of the plant for this purpose. A modern application may be its use in the treatment of obsessive-compulsive disorder. The mechanism of action of Saint John's wort is postulated to be inhibition of the synaptosomal uptake of serotonin. Twelve subjects were evaluated with a primary diagnosis of obsessive-compulsive disorder of at least 12 months' duration. Treatment lasted for 12 weeks, with a dose of 450 mg of 0.3% hypericin twice daily. Weekly and monthly evaluations were conducted. A significant change from baseline to endpoint was found, which occurred at 1 week and continued to increase throughout the trial. At endpoint, 5 of 12 were rated much or very much improved, 6 were minimally improved, and 1 had no change (Taylor, 2000). Saint John's Wort induces CYP3A4 and P-glycoprotein, and has been shown to reduce blood levels of alprazolam (Madabushi, 2006).

LAVENDER (*LAVANDULA* SPP): This herb is listed as a calming agent in some herbal texts, but the Eclectic *Materia Medicas* all describe it as a stimulant. A clinical trial examining the effects of inhaled lavender oil suggests that it increases arousal but decreases stress (Motomura, 2001). A study of plant-derived essential oils that possess an anticonflict effect in mice showed that the anxiolytic diazepam, as well as lavender essential oil, increased response rate during the alarm period and demonstrated an anticonflict effect in the same manner (Umezu, 2000).

WITHANIA *(WITHANIA SOMNIFERA):* One study investigated the anxiolytic and antidepressant actions of the glycowithanolides (WSG), isolated from withania roots, in rats. WSG (20 and 50 mg/kg) was administered orally once daily for 5 days, and the results were compared with those elicited by the benzodiazepine lorazepam (0.5 mg/kg, intraperitoneally) for anxiolytic studies, and by the tricyclic antidepressant imipramine (10 mg/kg, intraperitoneally), for antidepressant investigations. WSG induced an anxiolytic effect, comparable with that produced by lorazepam, and both WSG and lorazepam reduced rat brain levels of tribulin, a marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazol. WSG also exhibited an antidepressant

effect, comparable with that induced by imipramine (Bhattacharya, 2000).

CHAMOMILE *(MATRICARIA RECUTITA):* Study of the aqueous extract detected several fractions with significant affinity for the central benzodiazepine receptor and isolated apigenin in one fraction. Apigenin showed anxiolytic activity in mice without sedation and muscle relaxant effects or anticonvulsant action. A 10-fold increase in dosage produced a mild sedative effect (Viola, 1995). Individual flavonoids contained in chamomile have also been shown to have anxiolytic and antispasmodic activities (Paladini, 1999; Bisset, 1994).

PASSIONFLOWER *(PASSIFLORA INCARNATA):* Laboratory animal (Bisset, 1994) and human clinical trial evidence indicates that Passionflower has anxiolytic activity. Various extracts, including methanol and water extracts of Passionflower whole plant and plant parts, have been evaluated for their anxiolytic activity in mice. The methanol extracts of leaves, stems, flowers, and whole plant exhibited anxiolytic effects at 100, 125, 200, and 300 mg/kg, respectively. The roots were practically devoid of anxiolytic effects (Dhawan, 2001). A double-blind randomized trial in 36 patients compared the efficacy of Passionflower extract with that of oxazepam in the treatment of patients with generalized anxiety disorder. Patients were allocated in a random fashion for a 4-week trial: 18 to the Passionflower 45 drops/day plus placebo tablet group, and 18 to the oxazepam 30 mg/day plus placebo drops group. Both were effective in the treatment of patients with generalized anxiety disorder with no significant difference between the two protocols. Oxazepam showed a rapid onset of action but significantly more problems related to impairment of job performance. The results suggested that Passionflower is an effective drug for the management of generalized anxiety disorder with a low incidence of impaired job performance (Akhondzadeh, 2001b). Dhawan and colleagues (2003, 2004) have investigated a benzoflavone of Passionflower with particularly potent CNS depressant activity.

KAVA KAVA *(PIPER METHYSTICUM):* Good evidence suggests that Kava is anxiolytic (Pittler, 2003; Basch, 2005), and it is generally agreed that the risk/benefit ratio (despite recent reports of hepatotoxicity) is good compared with that of anxiolytic drugs (Clouatre, 2004). The mechanisms thought to be operative include blockade of voltage-gated sodium channels, enhanced GABA A receptor binding, diminished excitatory neurotransmitter release due to calcium channel blockade, reduced neuronal reuptake of norepinephrine, monoamine oxidase (MAO)-B inhibition, and thromboxane A2 synthesis suppression, the latter of which antagonizes GABA A receptor function (Singh, 2002). The Eclectics did not seem to recognize this herb as anxiolytic but did note pain-relieving properties and diuresis. Felter listed the specific indications as "irritation, inflammation, or debility of the urinary passages; chronic catarrhal inflammations; vesical irritation and inflammation; vesical atony; painful micturition, strangury, and dysuria." With consideration of its accepted anxiolytic properties and traditional indications for diuresis, urinary tract pain, and inflammation, kava seems particularly appropriate for cases of feline interstitial cystitis, in addition to short-term use for other conditions in which anxiety is present.

SKULLCAP *(SCUTELLARIA LATERIFLORA):* One animal and one human clinical trial have suggested that the plant has anxiolytic effects (Awad, 2003; Wolfson, 2003).

BAICAL SKULLCAP *(SCUTELLARIA BAICALENSIS):* The constituent wogonin was investigated. Oral wogonin (7.5-30 mg/kg) elicited an anxiolytic response, similar to diazepam. However, the anxiolytic effects of wogonin were not accompanied by the sedative and muscle relaxant adverse effects that are typical of benzodiazepines (Hui, 2002).

BACOPA *(BACOPA MONNIERI):* One study investigated the anxiolytic activity of a standardized extract (bacoside A content 25.5% ± 0.8%) of Bacopa at doses of 5, 10, and 20 mg/kg, given orally in rats, and results were compared with those elicited by lorazepam at 0.5 mg/kg, given intraperitoneally. In all test parameters, Bacopa produced dose-related anxiolytic activity that was qualitatively comparable with that of lorazepam. Significant results were attained, usually at 10 and 20 mg/kg. Bacopa did not produce any significant motor deficit (Bhattacharya, 1998).

GINGER *(ZINGIBER OFFICINALIS)* AND GINKGO *(GINKGO BILOBA):* The anxiolytic effects of a range of doses (0.01-10 mg/kg) of combination preparations containing different mixture ratios of standardized extracts of ginkgo leaf and ginger root have been tested in rats by means of a maze test. Compared with controls, rats treated with the combination preparation (mixture ratio of ginger extract to ginkgo extract, 2.5 : 1; 1 mg/kg, intragastrically) spent increased amounts of time in the open arms of the maze, whereas the behavior of rats treated with preparations of mixture ratios of 1 : 1 and 1 : 2.5 did not change (Hasenörhl, 1998). Zingicomb, a preparation consisting of ginger and *Ginkgo biloba* extracts, administered intragastrically has anxiolytic-like properties. A study assessed the effects of acute treatment with this preparation on inhibitory avoidance learning. The influence of zingicomb on avoidance conditioning was investigated in rats treated intragastrically with vehicle or 0.5, 1, 10, or 100 mg/kg zingicomb 60 minutes before the trial. When tested 24 hours after training, rats that had received 10 mg/kg zingicomb exhibited significantly longer step-through latencies than did vehicle-treated animals. In contrast to conventional anxiolytic drugs, which tend to have amnesic properties, zingicomb is a potent anxiolytic agent that may facilitate performance on a learning task (Topic, 2002).

ASIAN GINSENG *(PANAX GINSENG):* The anxiolytic activities of the white and red varieties of ginseng were investigated in rats and mice and compared with those of diazepam. Pilot studies indicated that single-dose ginseng had little to no acute behavioral effects; so, the two varieties of ginseng were administered orally at two dose levels twice daily for 5 days, and diazepam (1 mg/kg intraperitoneally) was administered acutely. White and red varieties of ginseng (20 and 50 mg/kg) showed posi-

tive results when tested against several paradigms of experimental anxiety. Both were effective in maze tests, and they reduced conflict behavior in thirsty rats and during footshock-induced fighting in paired mice. Ginseng also attenuated pentylenetetrazol-induced decrease in rat brain MAO activity, confirming its anxiolytic activity. The effects of white and red ginseng (50 mg/kg × 5 days) were comparable with those of diazepam (Bhattacharya, 1991).

Hypnotics

Insomnia is an occasional complaint that is usually reported in elderly animals. These animals may well be experiencing "sundowner syndrome"—increasing agitation and confusion in the evening, seen in patients with Alzheimer's disease. Medical problems such as hypertension, hyperthyroidism, pain, and other disorders also must be considered. Traditional hypnotics do not always have a chemical sleep-inducing effect; in some cases, these plants are anxiolytic and help calm people, leading to better sleep. It is unknown whether this is applicable to animals.

California Poppy *(Eschscholzia californica):* The US Dispensatory of 1918 describes it as "a powerful soporific and analgesic, which is free from the disadvantages of opium," and laboratory animal studies (described earlier, in the section on relaxants) suggest that it does have anxiolytic properties. In one study (Rolland, 1991), investigators found that the extract induced sleep at doses above 100 mg/kg. It may act via benzodiazepine receptors (Rolland, 2001).

Hops *(Humulus lupulus):* The aromatic principles in hops may have sedative activity, thus enhancing sleep. (See discussion of hops in the section on nervine relaxants.)

Wild Lettuce *(Lactuca virosa):* King's claims that 20 to 30 grains (1.3-1.9 g) of the dried sap of wild lettuce "will cause a dog to sleep." It was said to be insufficiently investigated but used primarily as a calmative and hypnotic. The human dose for the tincture was 30 to 60 drops. No supporting studies could be found.

Passionflower *(Passiflora incarnata):* The Eclectics found Passionflower useful for inducing sleep from mental overwork; this reflects the anxiolytic effect better than a specific hypnotic effect, for which no data can be found.

Kava Kava *(Piper methysticum):* This herb has been shown to assist people with anxiety in falling to sleep (Lehrl, 2004). A total of 61 patients were administered 200 mg of the standardized extract WS 1490 or a placebo in a multicenter, randomized, double-blind, placebo-controlled trial. According to sleep and anxiety questionnaires, 4 weeks of treatment resulted in statistically significant improvement.

Jamaica Dogwood *(Piscidia piscipula):* This herb had a reputation for inducing deep and restful sleep. (Also see the section on anxiety.)

Valeria *(Valeriana officinalis):* Fairly good evidence has been found that indicates that valerian is a hypnotic. Clinical trials have shown that it can decrease sleep latency and nocturnal awakenings and improve subjective sleep quality (Beaubrun, 2000); however, the evidence for a sedative effect is less strong. In laboratory animal studies, valerian extracts appear to influence GABAergic neurons, including increased release of GABA, decreased GABA reuptake, and decreased GABA degradation.

Chamomile *(Matricaria chamomilla):* Intraperitoneal administration to mice of a lyophilized infusion of chamomile decreased basal motility and exploratory and motor activities and potentiated hexobarbital-induced sleep. These results demonstrated that in mice, chamomile depresses the central nervous system (Della Loggia, 1982).

Anesthetics

Clove Oil *(Syzygium aromaticum):* This was tested for anesthesia induction, recovery time, hematology, and stress indicators in gilthead sea bream and rainbow trout and was compared with 2-phenoxyethanol. Results showed only slight differences in anesthetic efficiency and physiologic effects, and suggested that clove oil does not block cortisol response to stress in fish, as do other anesthetics (Tort, 2002; Vykusova, 2003). In a similar study, clove oil (85%–95% eugenol) was only slightly less effective than quinaldine and more effective than benzocaine, MS-222, and 2-phenoxyethanol. Clove oil had a much calmer induction to anesthesia than did quinaldine, along with a recovery time that was 2 to 3 times longer (Munday, 1997). The anesthetic effects of clove oil–derived eugenol were studied in juvenile rainbow trout. Times to induction and recovery from anesthesia were measured and compared with those of MS-222. Eugenol induced anesthesia faster and at lower concentrations than did MS-222, and recovery times for eugenol were 6 to 10 times longer. Clove oil eugenol was determined to be an acceptable anesthetic for use in aquaculture and aquatic research. It was found that 40 to 60 ppm eugenol induced rapid anesthesia, with a relatively short time for recovery in juvenile trout (Keene, 1998). Juvenile rabbitfish were anesthetized and their length and weight recorded on three separate occasions. Fish were fed shortly afterward, and no mortality was observed. Clove oil appeared to be highly effective as a fish anesthetic with potentially few or no adverse effects (Soto, 1995).

Lavender *(Lavandula officinalis):* The local anesthetic activity of the essential oil of lavender was investigated and compared with that of the essential oils of *Citrus reticulata* and *C. limon.* Tests were also performed on the components of lavender essential oil, linalool, and linalyl acetate. The essential oil of lavender, linalyl acetate, and linalool (0.01-10 µg/mL)—but not the Citrus essential oils—reduced electrically evoked contractions of rat phrenic hemidiaphragm. In the rabbit, conjunctival reflex test treatment with a solution of essential oil of lavender, as well as linalyl acetate and linalool, confirmed the local anesthetic activity that had been observed in vitro (Ghelardini, 1999).

Kava *(Piper methysticum):* This herb has been reported to have analgesic activity (Jamieson, 1990) and was used by the Eclectics as a local anesthetic.

Antispasmodics

Antispasmodic herbs are listed in neurologic *Materia medicas* for their ability to relax skeletal muscle tension and reduce the consequences of stress, such as asthmatic bronchiolar constriction and intestinal/colonic spasm. Anxiolytics can be employed, but some herbs have specific activity on smooth and skeletal muscle.

KAVA KAVA *(PIPER METHYSTICUM):* The kavapyrone, kavain, has been shown in vitro to inhibit contraction (and relax precontracted muscle) in vascular and gastrointestinal smooth muscle, possibly by interfering with Ca^{2+} channels (Martin, 2002; Seitz, 1997).

BAICAL SKULLCAP *(SCUTELLARIA BAICALENSIS):* This agent has shown smooth muscle relaxant properties (Usow, 1958). Recent in vitro studies in vascular and respiratory smooth muscle suggest a different effect, depending on the dose of the flavonoid baicalein (Ajay, 2003; Miyamoto, 1997).

VALERIAN *(VALERIANA OFFICINALIS)*: This is a potent smooth muscle relaxant in feline pulmonary vasculature, probably via GABA-mediated mechanisms (Fields, 2003). Isovaltrate, valtrate, and valeranone caused suppression of peristaltic contractions in guinea pig ileum in vivo (Hazelhoff, 1982).

CRAMP BARK *(VIBURNUM OPULUS)* AND BLACK HAW *(VIBURNUM PRUNIFOLIUM):* These herbs probably have similar properties in that both are used as antispasmodics for uterine cramps. King's says that Cramp bark is useful in asthma, spasms, and cramps of the limbs as well. Tests in guinea pigs, rats, and human uteri suggest that Black haw has smooth muscle relaxant properties (Horhammer, 1965; Horhammer, 1966).

JAMAICA DOGWOOD *(PISCIDIA PISCIPULA):* Ellingwood (1919) recommended the plant for gallstone, renal, and intestinal colic. Some studies have shown spasmolytic activity (Della Loggia, 1988; Costello, 1948).

OTHER HERBS: Others include California poppy, Motherwort, Lobelia, Lemon balm, Peppermint, Catnip, Aniseed, Rosemary, Sage, Bloodroot, Tilia, Licorice, Peony, Passionflower, Parsley, Thyme, Verbena, and Ginger.

Adaptogens

The original definition of adaptogen was as follows (Panossian, 1999):

1. The adaptogenic effect is nonspecific in that the adaptogen increases resistance to a very broad spectrum of harmful factors ("stressors") of different physical, chemical, and biological natures;
2. An adaptogen is said to have a normalizing effect, that is, it counteracts or prevents disturbances brought about by stressors; and
3. An adaptogen must be innocuous to have a broad range of therapeutic effects without causing any disturbance (other than very marginally) to the normal functioning of the organism.

More recently, a theory has been advanced to explain that changing levels of mediators such as nitric oxide (NO), platelet-activating factor (PAF), catecholamines, cortisol, and PGE_2 are held in tighter homeostatic control, unlike the wide swings that a normal stress response brings with it (Panossian, 1999).

Herbalists believe, in addition, that adaptogens must work through the hypothalamic-pituitary-adrenal axis, differentiating them from other function regulators, such as immune stimulants. Adaptogenic herbs are especially useful for mitigating the effects of stress in overworked horses and dogs, run-down production animals such as dairy cows, and perhaps chronically stressed dogs and cats that exhibit anxiety-related behaviors, or for elderly or chronically ill animals to help counteract lethargy and weakness. These herbs have been investigated for use in enhancing performance in healthy athletes—early clinical trials in humans suggested the effect, but more recent high-quality studies do not support this use.

ELEUTHERO, SIBERIAN GINSENG *(ELEUTHEROCOCCUS SENTICOSIS):* Animal studies showed a "protein anabolic" effect (Kaemmerer, 1980). One study of mice that ingested different ginseng infusions in comparison with water showed no increase in stamina or longevity, and no difference in survival, under major environmental stress (Lewis, 1983). Another showed that various extracts increased swimming time and attenuated the rise in blood corticosterone (Kimura, 2004). Mouse studies also suggest that Eleuthero can enhance cellular and humoral immunity (Rogala, 2003). Elderly human patients given Eleuthero experienced temporary improvements in social functioning that were measured at 4 weeks but did not last to 8 weeks of the trial (Cicero, 2004). Hartz and associates examined 96 people with chronic fatigue who had been given Eleuthero or placebo and found no statistically significant differences between groups (Hartz, 2004). Some animal studies and one human study in athletes (Gaffney, 2001) showed that Eleuthero actually increased hormonal indices of stress. In a controlled study of 1000 Siberian factory workers, a 50% reduction in illness and a 40% reduction in lost workdays were noted over 1 year (Bone, 2003).

ASIAN GINSENG *(PANAX GINSENG):* Oriental, Red, or Asian ginseng is one of the most studied of herbs. Some of the established effects include antioxidant activity, improved immune function, improved cognition and memory, modification of vasomotor function, reduced platelet adhesion, an influence on ion channels, modulation of autonomic neurotransmitter release, improved lipid profiles, and improved glucose metabolism and glycemic control (Zhou, 2004; Kiefer, 2003; Kennedy, 2003a). Animal studies have shown that ginseng increases resistance to irradiation, temperature stress, hyperbaric stress, physical exercise, and viral and tumor load (Nocerino, 2000). The mechanism is still under investigation, but it is possible that ginsenosides may augment adrenocortical steroid production (Nocerino, 2000; Rai, 2003b; Kim, 2003).

AMERICAN GINSENG *(PANAX QUINQUEFOLIUS):* Although the energetic characteristics and traditional Chinese uses of American and Asian ginseng are different, the constituents and clinical studies suggest that they have similar broad uses as adaptogens. Few clinical trials have specifically addressed the effects of *P. quinquefolius* on stress.

SCHISANDRA *(SCHISANDRA CHINENSIS):* A clinical trial in athletes undergoing heavy exercise indicated that administration of Schisandra attenuated the rise in salivary nitric oxide that is usually seen after physical stress (Panossian, 1999b). Russian studies examining job-related stress suggested that Schisandra decreased illness, increased stamina, and prevented some stress-induced physiologic changes in people (Bone, 2003).

ASHWAGANDHA *(WITHANIA SOMNIFERA):* A variety of animal models of stress have shown an adaptogenic effect for this plant. In chronically stressed rats, ashwagandha administered at 25 to 50 mg/kg attenuated stress-related hyperglycemia, gastric ulcers, cognitive deficits, male sexual dysfunction, mental depression, and immune suppression (Bhattacharya, 2003). A withanolide-free extract also showed antistress effects in rats and mice (Singh, 2003a; Singh, 2001). Withania extract increased corticoid levels in stressed mice (Singh, 2000).

OTHER HERBS: Others include *Andrographis paniculata,* Gotu kola *(Centella asiatica),* and Licorice *(Glycyrrhiza glabra).*

Herbs with antistress activity

SIBERIAN GINSENG *(ELEUTHEROCOCCUS SENTICOSIS):* This plant is known to have protective effects on stress-induced disturbance of mental status. One study evaluated whether administration of Siberian ginseng (500 mg/kg) can affect concentrations of noradrenaline (NA), dopamine (DA), and their metabolites in the normal rat brain. Even a single oral administration of Siberian ginseng elevated NA and DA levels in the brain in a dose-dependent manner. Results suggested that Siberian ginseng may act by regulating NA and DA levels in specific brain regions related to stress response and Parkinson's disease (Fujikawa, 2002).

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* The antistress activity of an ethanolic extract was investigated on 14-day foot-shock stress (FSS)-induced behavior in albino rats. Gastric ulceration and adrenal gland and spleen weight were used as the stress indices. *Panax ginseng* (PG) was used as the standard adaptogenic agent for comparison. FSS induced marked gastric ulceration and a significant increase in adrenal gland weight with a concomitant decrease in spleen weight. Chronic stress also suppressed male sexual behavior and induced behavioral depression and cognitive dysfunction. All FSS-induced perturbations were attenuated dose dependently by Saint John's wort (100 and 200 mg/kg orally) and PG (100 mg/kg orally) (Vikas, 2001).

Antidepressants

Antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) are used in veterinary medicine for a variety of behavior problems, including anxiety-related behaviors such as house soiling and phobias, aggression, compulsive behaviors, and, recently, for chronic pain and "behavioral dermatoses." These uses are based on specific receptor pharmacology and not necessarily on the clinical effects noted with traditional herbal antidepressants such as Mugwort *(Artemisia vulgaris),* Milky oat *(Avena sativa),* and Damiana *(Turnera diffusa).*

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* This is a well-recognized and effective treatment for patients with mild to moderate depression. It has multiple constituents that may be active in the treatment of depression, including weak MAO-A and MAO-B inhibition; glutamate, GABA-A, and GABA-B affinity; downregulation of beta-adrenergic receptors and upregulation of 5-HT_2 receptors; and regulation of genes involved in the hypothalamic-pituitary-adrenal axis (Butterweck, 2003). The range of compounds at work include hypericin, hyperforin, and a number of flavonoids such as amentoflavone, quercetin, and a form of apigenin.

LAVENDER *(LAVANDULA OFFICINALIS):* Akhondzadeh (2003a) investigated the use of lavender in the treatment of patients with mild to moderate depression. In a 4-week, double-blind, randomized trial, 45 adults with depression received lavender tincture (1:5 in 50% alcohol, 60 drops/day, plus placebo tablet; imipramine alone; or lavender tincture plus imipramine). The combination of lavender and imipramine was more effective than either treatment alone. In cancer hospice patients, lavender administered by aromatherapy was compared with simple water humidification, and vital signs, depression, sense of well-being, pain, and anxiety were monitored. Lavender was superior to water humidification in pain and anxiety levels (Louis, 2002).

BACOPA *(BACOPA MONNIERI):* A standardized methanolic extract of Bacopa (bacoside A 38.0 ± 0.9) was investigated for potential antidepressant activity in rodent models of depression. The effect was compared with that of the standard antidepressant drug imipramine (15 mg/kg, intraperitoneally). The extract, when given at 20 and 40 mg/kg orally once daily for 5 days, was found to have significant antidepressant activity in models of depression that was comparable with that of imipramine (Sairam, 2002).

Analgesics

Before the advent of ether and subsequent improvements in anesthesia drugs, surgery and other painful procedures were accomplished under the influence of alcohol and toxic plants. These plants included datura *(Datura stramonium),* gelsemium *(Gelsemium sempervirens),* henbane *(Hyoscyamus niger),* poison hemlock *(Conium maculatum),* and opium poppy *(Papaver somniferum).* With the exception of gelsemium, most of the plants discussed in this section are less dramatic in their activity and can be used in formulas given over the long term.

CORYDALIS (*CORYDALIS YANHUSUO* AND OTHER SPECIES): This herb inhibits the reticular activating system (RAS) of the brain stem, and long-term use may result in tolerance and cross-tolerance with morphine (Huang, 2000). The herb was shown to reduce pain from inflammation in a rat model (Wei, 1999). A clinical trial in people administered pain via a cold-pressor test showed that corydalis had a significant ($P < .01$) dose-related analgesic effect (Yuan, 2004).

LAVENDER *(LAVANDULA OFFICINALIS):* A hydroalcoholic extract, polyphenolic fraction, and essential oil of lavender leaves were prepared and their analgesic effects and anti-inflammatory activities were studied in mice. Results of the study confirmed the traditional use of lavender for the treatment of patients with painful and inflammatory conditions (Hajhashemi, 2003).

WILD YAM *(DIOSCOREA VILLOSA):* Although research support has not been found for an analgesic or spasmolytic effect for this herb, traditional use centers primarily on abdominal pain and spasm. The US Dispensatory of 1918 claims that an indication for the pain of rheumatism was a Southern regional use. Interestingly the root of a species Dioscorea *(Dioscorea opposita)* has been used for the treatment of arthritis, muscular pain and urinary diseases in oriental medicine. A methanol extract of Dioscorea root down regulated the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase and reduced the level of reactive oxygen species in vitro (Kim, 2005b).

CALIFORNIA POPPY *(ESCHSCHOLZIA CALIFORNICA):* Rolland (1991, 2001) found that this extract had peripheral analgesic effects in laboratory animal studies. The US Dispensatory of 1918 describes it as "a powerful soporific and analgesic, which is free from the disadvantages of opium. . . . The narcotic power of the drug seems to be very weak, since . . . three drachms (5.3 g) were necessary to kill a rabbit . . . the alcoholic extract acts as a respiratory depressant and narcotic, affecting in toxic dose also the spinal cord . . . the extract [was used] in commencing doses of twelve grains (0.78 g) increasing to one hundred and eighty-five grains (12 g) a day . . ."

GELSEMIUM *(GELSEMIUM SEMPERVIRENS):* The 1918 US Dispensatory advocated this root mostly in "the treatment of neuralgias, especially those involving the facial nerves. The mode of its action in these cases is obscure, but there is considerable clinical evidence of its utility." It was also used for headache and toothache. This is a toxic herb that may cause extreme weakness, seizures, and respiratory arrest. It is not in popular use in veterinary herbal medicine, and should be used with care, as part of pain formulas, if at all.

JAMAICA DOGWOOD *(PISCIDIA PISCIPULA):* Ellingwood listed indications related to pain as gallstone colic, renal colic, intestinal colic, neuralgias, and as an anodyne for toothache and developing abscesses. No supporting studies can be found for an analgesic effect.

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* King's relates that *Hypericum* was used for the pain of spinal injuries, spinal irritation, and wounds. Multiple species of *Hypericum* have shown analgesic effects in laboratory animal studies, including *H. perforatum, H. brasiliense, H. cordatum,* and *H. empetrifolium* (Viana, 2003; Rieli, 2002; Kumar, 2001; Trovato, 2001). A human clinical trial using Saint John's wort for painful polyneuropathy showed no statistical significance from placebo, but a trend existed showing some pain relief for the extract—nine patients on Saint John's wort had complete, good, or moderate pain relief, and only two of those on placebo had the same benefit (Sindrup, 2001). No description of a possible analgesic mechanism was found.

OTHER HERBS: Anti-inflammatory herbs, such as Willow *(Salix alba),* Devil's claw *(Harpagophytum procumbens),* Boswellia *(Boswellia serrata),* Prickly ash *(Zanthoxylum* spp*),* Ginger *(Zingiber officinalis),* and others, are useful in controlling the pain of inflammation.

Anticonvulsants

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* Effects of different extracts of Saint John's wort on kindling epileptic discharges were analyzed in rabbits with chronically implanted electrodes in cortical structures and the hippocampus. Results showed that the effect depends on the constituents present; in particular, fractions and repression of epileptic activity correlated with polarity of plant constituents. Most polar constituents in the water fraction exerted the highest antiepileptic activity in 100% of animals tested. Substances present in the butanol fraction repressed the epileptic manifestations in 40% of animals with kindling epilepsy, whereas lipid-soluble constituents in the ether fraction potentiated epileptic activity (Ivetic, 2002).

SKULLCAP *(SCUTELLARIA LATERIFOLIA):* In rats given lithium and pilocarpine to induce status epilepticus, seizures resolved completely when skullcap was given in the water, but they returned when the herb was discontinued (Peredery, 2004). It contains the active constituents baicalin and baicalein, also found in Baical skullcap.

BAICAL SKULLCAP *(SCUTELLARIA BAICALENSIS):* Research suggests that the active component baicalein is a major contributor to the antiepileptic and neuronal protective effects of a traditional formula, and that the mechanism of its pharmacologic action is based on radical quenching and antioxidative effects (Hamada, 1993).

KAVA *(PIPER METHYSTICUM):* Studies described in the older literature have documented anticonvulsant effects for kavalactones in several experimental models (Gleitz, 1996a, b, c). The anticonvulsant properties of methysticin in vitro may arise from direct membrane action on the excitability of neurons, and in vitro assays have shown that methysticin, kavain, and the synthetics kavalactone and kavain appear to interact with voltage-dependent sodium channels, and that kavain also interacts with voltage-dependent calcium channels (Magura, 1997; Gleitz, 1996a,b,c; Schirrmacher, 1999). Substances that reduce extracellular glutamate concentrations are of interest for their potential as anticonvulsant agents. Reduction in veratridine-induced glutamate release following kavain administration has been reported both in vitro and in vivo in freely moving rats (Gleitz, 1996c; Ferger, 1998).

GELSEMIUM *(GELSEMIUM SEMPERVIRENS):* In rats given lithium and pilocarpine to induce status epilepticus, seizures resolved completely when gelsemium was given in the water but returned when the herb was discontinued (Peredery, 2004).

GASTRODIA *(GASTRODIA ELATA):* This Chinese herb is contained in many traditional formulas for seizures, often in combination with *Uncaria rhynchophylla*. In a study of rats with seizures induced by kainic acid, administration of Gastrodia extract 0.5 to 1 g/kg reduced lipid peroxidation in brain tissue, as well as seizure activity (Hsieh, 2001).

UNCARIA *(UNCARIA RHYNCHOPHYLLA):* In a study of rats with seizures induced by kainic acid, Uncaria 1 g/kg alone or Uncaria 1 g/kg plus Gastrodia 1 g/kg was administered to rats with induced epileptic seizures. Results showed that Uncaria alone reduced induced lipid peroxide levels in vitro. It was concluded that Uncaria has anticonvulsive and free radical scavenging activities, and effects appeared synergistic with those of Gastrodia (Hsieh, 1999).

BACOPA *(BACOPA MONNIERI):* This plant has been used for epilepsy in animals in traditional Indian medicine, although no supporting studies have been found.

CORYDALIS *(CORYDALIS YANHUSUO):* The influence of the constituent tetrahydropalmatine (THP), isolated from corydalis, was tested on the development of electrically kindled amygdala. Intraperitoneal injection of THP before application of the stimulus prevented development of the kindling process. The behavioral seizure score and motion responses that normally develop during electrical kindling were reduced to below initial values. Results suggest that THP may have antiepileptogenic and anticonvulsant activity (Lin, 2002). Administration of picrotoxin increases locomotion, elevation of turning, and inhibition of postural freezing in rats; it also increases amygdaloidal release of dopamine in anesthetized rats. All these activity measures induced by picrotoxin were suppressed following THP treatment. Results indicate that THP may act through inhibition of amygdaloid dopamine release to inhibit seizures (Chang, 2001).

OTHER HERBS: Chinese herbal combinations have been investigated more thoroughly and may be more effective than any single herb. Uncontrolled trials in humans suggest that the combination Sho saiko to and similar formulas (Xiao Chai Hu Tang, Minor Bupleurum formula) can help reduce seizure severity and frequency in people who are unresponsive to normal seizure medications. Combinations of the two herbs *Uncaria rhynchophylla* and *Gastrodia elata* have shown anticonvulsant activity in laboratory animals.

Nervine stimulants *(cognitive enhancers)*

GINKGO *(GINKGO BILOBA):* It is now clear that ginkgo is effective in the treatment of people with dementia and cognitive decline. A Cochrane meta-analysis showed some methodologic problems with earlier trials, but in general, ginkgo benefits cognition, activities of daily living, mood, and emotional function in people, with no difference from placebo in adverse effects (Birks, 2002).

LEMON BALM *(MELISSA OFFICINALIS):* This herb has been examined in two different forms for the treatment of patients with Alzheimer's disease. Akhondzadeh (2003b) administered 60 drops/day of an extract for 4 months to patients with mild to moderate Alzheimer's disease. The Melissa extract had a significantly better outcome for cognitive function than did placebo. In another human clinical trial, patients with Alzheimer's with severe dementia and agitation were treated with lemon balm oil via massage, and the placebo group was massaged with sunflower oil only. Agitation score was 30% improved in 60% of the Melissa group, but in only 14% of the placebo group. Quality of life improved significantly more in people receiving lemon balm than in those receiving placebo. It was concluded that lemon balm extract is of value in Alzheimer's disease and that it mitigates agitation (Akhondzadeh, 2003b).

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* A standardized 50% ethanolic extract of Saint John's wort was investigated in various experimental paradigms of learning and memory in rats. A dosage of 100 or 200 mg/kg was administered orally once daily for 3 days; piracetam (500 mg/kg intraperitoneally), was administered to rats as the standard drug control. Saint John's wort at both doses and piracetam facilitated acquisition and retention of active avoidance; the Saint John's wort effects were dose dependent. Results indicated a possible nootropic action of Saint John's wort that was qualitatively comparable with piracetam (Vikas, 2000). Another study investigated the effects of long-term Saint John's wort treatment on spatial learning and memory in rats. Saint John's wort standardized to 0.3% hypericin content was administered for 9 weeks in doses of 4.3 and 13 µg/kg, corresponding to therapeutic dosages in humans of 0.3 and 0.9 mg of total hypericins daily. Findings showed that the long-term administration of Saint John's wort can improve learning and spatial memory, with significant changes in the content of monoamines in several brain regions (Widy-Tyszkiewicz, 2002).

BACOPA *(BACOPA MONNIERI):* This herb has been shown to exert cognition-enhancing effects in animals. A human, double-blind, placebo-controlled trial found that *Bacopa monnieri* (300 mg; n = 18) or placebo (n = 20) had no acute effects on cognitive functioning in normal healthy subjects (Nathan, 2001). However, in a double-blind, randomized, placebo-controlled study in which various memory functions were tested and levels of anxiety measured in people, results showed a significant effect of Bacopa on a test for retention of new information. Follow-up tests showed that the rate of learning was unaffected, suggesting that Bacopa slows the rate at which people forget new information (Roodenrys, 2002).

KOREAN GINSENG *(PANAX GINSENG):* Studies have demonstrated that two ginsenosides—Rb(1) and Rg(1)—improve performance in a passive avoidance-learning paradigm and enhance cholinergic metabolism. One study examined the cellular neurotrophic and neuroprotective actions of these ginsenosides in two model systems. Results suggested that Rb(1) and Rg(1) have neurotrophic and selective neuroprotective actions that may contribute to the purported enhancement of cognitive function (Rudakewich, 2001).

Herbs with stimulant activity

ROSEMARY *(ROSMARINUS OFFICINALIS):* An increase in locomotor activity has been observed in mice following inhalation or oral administration of rosemary oil. The increase in activity paralleled a dose-related increase in serum 1,8-cineole level (Kovar, 1987).

COLA *(COLA NITIDA):* The xanthine constituents, caffeine and theobromine, are the active principles in cola. The pharmacologic properties of caffeine are well documented and include stimulation of the CNS, respiratory system, and skeletal muscle, as well as cardiac stimulation, coronary dilatation, smooth muscle relaxation, and diuresis (Leung, 1980).

ASIAN GINSENG *(PANAX GINSENG):* A double-blind, placebo-controlled clinical study assessed the effect of standardized ginseng (100 mg twice daily for 12 weeks) on psychomotor performance in 16 healthy individuals. Tests of psychomotor performance found favorable effects on attention, processing, integrated sensory motor function, and auditory reaction time. This study concluded that ginseng was superior to placebo in improving certain psychomotor functions in healthy subjects (D'Angelo, 1986).

DONG QUAI *(ANGELICA SINENSIS):* Hot aqueous extracts of dong quai stimulated smooth muscle contractions of the bladder, intestine, and uterus when administered intravenously to dogs (10 g/kg body weight) (Schmidt, 1924). Intravenous administration of an aqueous or 95% ethanol extract dong quai to cats, rats, and rabbits increased the strength of the contractions and the tone of uterine smooth muscles (Zhu, 1987).

NUX VOMICA SEED *(STRYCHNOS NUX VOMICA):* This spinal stimulant is the source of strychnine. Veterinarians are more familiar with the signs of overdose of strychnine than they are with its historical use as a spinal stimulant. Gresswell's *Veterinary Pharmacopeia, Materia Medica, and Therapeutics* (1887) describes the official preparation as the liquid extract that contains 15% alkaloids, or the tincture that contains 1 grain (65 mg) of alkaloids per fluid ounce. The dose for dogs was 0.5 to 2 grains (30-130 mg); for horses, 20 grains to 1 drachm (1.3-1.8 g). By 1949, Milks describes the official preparations as follows:

1. Fluid extract, containing 1.15% strychnine and 25% alkaloids. The dose of this form was 0.5 to 2 dram (1.8-7.1 mL) for horses, and 0.5 to 2 minims (0.03-0.12 mL) for dogs.
2. Extract, containing 7% to 7.5% strychnine. Horse dose was 7 to 15 grains (0.45-0.97 g), and dog dose was $^1/_8$ to $^1/_4$ grain (8.1-16.2 mg)
3. Tincture, containing 0.1% strychnine and 0.25% alkaloids. Horse dose was 3 dram to 2.5 oz (10.7-74 mL), and dog dose was 5 to 20 minims (0.3-1.2 mL).

The author (SW) has used Chinese formulas containing this herb with some success in the treatment of degenerative myelopathy.

Herbs with aphrodisiac activity

CLOVE *(SYZYGIUM AROMATICUM):* Spices can be considered sexual invigorators. Ethanol extracts of nutmeg and clove were found to stimulate the mounting behavior of normal male mice and to significantly increase their mating performance (Tajuddin, 2003).

PASSIONFLOWER *(PASSIFLORA INCARNATA):* The aphrodisiac properties of the methanol extract of Passionflower leaves were evaluated in mice by observing mounting behavior. The methanol extract exhibited significant aphrodisiac behavior in male mice at all doses (i.e., 75, 100, and 150 mg/kg). Among these, the highest level of activity was observed with the 100 mg/kg dose when the mountings were calculated about 95 minutes after the administration of the test extracts (Dhawan, 2003).

TRIBULUS *(TRIBULUS TERRESTRIS):* The puncturevine plant has long been considered an energizer and vitalizer in traditional medicine. Weight gain and improvement in sexual behavior parameters observed in rats, as well as the increase in intracavernous pressure, which confirms the proerectile aphrodisiac property, could be the result of an increase in androgen (Gauthaman, 2003). An experiment was carried out to define the stimulating effects of Tribestan on rams that were intended for breeding, as well as on rams that exhibited sexual impotence and deteriorated semen qualities. Treatment led to an extended period of sexual activity and improvement of semen production in rams over the service period. Results of Tribestan therapy with rams with reduced libido showed that the animals could recover with no morphologic changes in the structure of the testes and epididymides. The use of this preparation raised the testosterone level and normalized the sexual activity of rams affected by impotence (Dimitrov, 1987). Tribestan increased testosterone levels and accelerated sexual development in rams and male lambs, respectively (Georgiev, 1988). Libido and sexual reflexes were restored in boars with long-term sexual impotence (Zarkova, 1984).

Nervine tonics *(neurologic trophorestoratives)*

ELEUTHERO, SIBERIAN GINSENG *(ELEUTHEROCOCCUS SENTICOSIS):* This was found to reduce the pathologic effects of cerebral lesions in mice (Kaplan, 1965). A study conducted over several years examined the therapeutic value of Siberian ginseng in human brain injury. Most of the 124 patients were severely affected. The test group received Siberian ginseng extract $^1/_2$ hour before meals, and the control group received a placebo. Siberian ginseng administration resulted in a normalizing effect on brain activity and a higher functional level of recovery. Alleviation of neurodynamic disturbances in the vestibular apparatus and normalizing of effects on cerebral hemodynamics, cortical neurodynamics, unconditioned reflex vascular motor reactions, and leukocyte counts were found (Sandler, 1972).

BAICAL SKULLCAP *(SCUTELLARIA BAICALENSIS):* Clinical investigation of scutellarin involving 634 cases of cerebral thrombosis, cerebral embolism, and paralysis caused by stroke has been undertaken. An overall positive effect rate higher than 88% was reported following intramuscular, intravenous, or oral administration (Peigen, 1987).

KAVA *(PIPER METHYSTICUM):* A neuroprotective effect against ischemic brain damage in mice and rats has

been demonstrated for kava extract (WS-1490 containing 70% kavalactones) and the individual kavalactones methysticin and dihydromethysticin. Kava extract 150 mg/kg given orally 1 hour before experimentally induced ischemia, and methysticin and dihydromethysticin (both 10 and 30 mg/kg intraperitoneally 15 minutes before induction of ischemia) significantly reduced the size of the infarct area in mice brains. In rats, kava extract administered according to the same regimen as that used in mice significantly reduced infarct volume compared with control findings (Backhauss, 1992).

GINKGO *(GINKGO BILOBA):* Several studies have reported that treatment with standardized extract of ginkgo leaf (EGb 761) aids recovery of function following brain injury, as demonstrated by behavioral tests in rats who had undergone bilateral frontal lobotomy or septohippocampal deafferentation, and in rat models of cortical hemiplegia. It has been suggested that the effects of EGb 761 in the experimental animal models described previously may involve aspects of neuronal plasticity (e.g., neuronal regeneration) (DeFeudis, 1998). Ischemia-induced lipid peroxidation is one of the most important causes of tissue damage in spinal cord injury. In one study, the protective effects of *Ginkgo biloba,* thyroid-releasing hormone (TRH), and methylprednisolone on compression injury of the rat spinal cord were investigated. *Ginkgo biloba* treatments significantly decreased malondialdehyde levels, which suggests that methylprednisolone and *Ginkgo biloba* may provide protection against ischemic spinal cord injury through the antioxidant effect (Koc, 1995). In another study, when pretreatment with a ginkgo extract was given 7 days before induced ischemia, followed by reperfusion, treated rabbits had only a slight tremor in the hind limbs compared with completely paraplegic controls. This study indicated that the ginkgo extract can scavenge free radicals produced during ischemia/reperfusion and may reduce reperfusion damage (Mechirova, 2002).

AMERICAN GINSENG *(PANAX QUINQUEFOLIUS* [GINKGO *(GINKGO BILOBA)* EXTRACT AND SAINT JOHN'S WORT *(HYPERICUM PERFORATUM)* EXTRACT]): The effects of this combination on the survival and regeneration of transected axotomized retinal ganglion cells was studied in an optic nerve transection model in adult hamsters. Animals that had undergone surgery received daily oral administration of vehicle or herbal extracts, alone or in combination, for 7 and 21 days, respectively. Treatment with American ginseng, ginkgo extract, or Saint John's wort alone failed to offer neuroprotection to injured retinal ganglion cells. However, treatment with a mixture of American ginseng, ginkgo extract, or Saint John's wort significantly augmented retinal ganglion cells survival 7 days postaxotomy. Treatment with the combination also induced a significant increase in the number of regenerating RGCs 21 days after optic nerve transection. This study suggests that herbs can act as potential neuroprotective agents for damaged retinal ganglion cells and that the therapeutic value of herbal remedies may be maximized through the use of mixtures of appropriate herbs (Cheung, 2002).

WITHANIA *(WITHANIA SOMNIFERA):* Extensions of dendrites and axons in neurons may compensate for and repair damaged neuronal circuits in the brain. One study investigated the effects of activating neurite outgrowth and regenerating the neuronal network. A methanol extract of Ashwagandha significantly increased the percentage of cells with neurites in human neuroblastoma cells. The effects of the extract were dose and time dependent (Tohda, 2000).

Review of Specific Pain, Neurologic, and Behavioral Disorders

Anxiety

Anxiety is the root of many major complaints presented to veterinarians; it is also a leading reason for surrender of pets to shelters. Owner education about inappropriate interactions and behavior modification techniques is critical, but herbs may help the animal to focus on training and ignore distractions. All of the herbs in the "nervine relaxant" sedating, anxiolytic, antistress activity, and "antidepressant" sections should be considered.

The effects of supplementing tryptophan, vitamin E, or an herbal product with passionflower and valerian were investigated in terms of the effects on stress response in pigs during transport simulation. Pigs supplemented with tryptophan tended to spend more time lying down during the second hour of vibration. Vitamin E decreased peak heart rate, ventricular ectopic beats, and ST elevation. The herbal supplement caused smaller increases in heart variables (i.e., minimum heart rate, ventricular ectopic beats, ST elevation) during and after stress evocation compared with the control group. Tryptophan had a positive behavioral effect in this experiment, and vitamin E and the herbal supplement mediated an increase in some heart variables, suggesting sedative and antianxiety effects (Peeters, 2004).

Various combinations of kava, skullcap, valerian, lemon balm, Saint John's wort, Jamaica dogwood, and hops may be used. Formulas recommended by herbalists and marketed by herbal pharmacies contain variously skullcap, oat seed, hops, passionflower, valerian, California poppy, Eleuthero, chamomile, motherwort, and linden.

Because the mechanisms of action for most anxiolytic herbs are not well defined, it is recommended that herbs be used instead of anxiolytic drugs only if the owner gives informed consent. Herb–drug interactions in this area are not yet well defined.

Adaptogenic herbs may also be considered for chronically stressed animals.

A prescription for mild anxiety follows:

Chamomile	100% (carminative, bitter, spasmolytic, mild sedative, anxiolytic, cholagogue)

Chamomile tea can be added to food, 1 mL per kg once to twice daily.

A prescription for moderate (separation) anxiety is provided here:

Passionflower	20% (sedative, hypnotic, antispasmodic, anxiolytic)

Saint John's Wort	20% (antidepressant, nervine tonic, anti-inflammatory, anxiolytic)
Withania	40% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Chamomile	20% (carminative, bitter, spasmolytic, mild sedative, anxiolytic, cholagogue)

Give 1 mL per 5 kg.

An alternative prescription for moderate to severe anxiety is:

Kava kava	40%
Eleuthero	20%
Passionflower or California Poppy	40%

Give 1 ml per 5 kg BID-TID

A prescription for separation anxiety with stress-related gastrointestinal symptoms is given below:

Saint John's Wort	30% (antidepressant, nervine tonic, anti-inflammatory, anxiolytic)
Withania	40% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Chamomile	30% (carminative, bitter, spasmolytic, mild sedative, anxiolytic, cholagogue)

Administer 1 mL per 5 kg.

Cognitive dysfunction

Therapeutic Rationale

- Improve cognitive function and antioxidant status.

Ginkgo and lemon balm may be combined with other herbs appropriate to the patient in terms of concomitant signs and energetic presentation. Commercial formulas for Alzheimer's disease and other human cognitive disorders may contain gotu kola, rosemary schisandra, ginkgo, and lemon balm. A foundation formula for dogs may contain the following:

Lemon balm	50%
Gotu kola	25%
Bacopa	25%

An alternative prescription for cognitive disorder is as follows:

Ginkgo	40% (antioxidant, circulatory stimulant, cognition enhancer, neurorestorative)
Bacopa	20% (nervine tonic, spasmolytic, mild sedative, mental tonic, cognitive enhancer)
Withania	20% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Gotu kola	20% (adaptogen, alterative, nerve tonic, mild diuretic)

The recommended dose is 1 mL per 5 kg.

Degenerative myelopathy

Therapeutic Rationale: Because the cause of degenerative myelopathy (DM) is unknown, different therapeutic regimens have been suggested on the basis of the possibility of autoimmune disorder, vitamin E deficiency, vitamin B deficiency, or simple degenerative disorder.

- Maintain neurologic integrity and muscular function through exercise.
- In the absence of a known mechanism to be targeted with herbal therapy, formulas may be directed toward reducing inflammation, alleviating stress, and possibly stimulating spinal cord and muscle function.

A prescription for degenerative myleopathy is given here:

Prickly ash	40% (circulatory stimulant, carminative, diaphoretic, antirheumatic)
Capsicum	20% (circulatory stimulant, diaphoretic, digestive, carminative, metabolic stimulant)
Eleuthero	10% (adaptogen, nervine stimulant)
Panax ginseng	10% (adaptogen, anxiolytic, stimulant, tonic, immune stimulant, hepatoprotective, cardioprotective)
Schisandra	20% (hepatoprotective, nervine tonic, adaptogenic)

Another prescription for degenerative myelopathy follows:

Turmeric	20% (anti-inflammatory, antioxidant, antiplatelet, cholagogue, hepatoprotective, anticancer)
Bacopa	20% (nervine tonic, spasmolytic, mild sedative, mental tonic, cognitive enhancer)
Siberian ginseng	20% (adaptogenic, immune modulating, neurologic trophorestorative)
Ginkgo	20% (antioxidant, circulatory stimulant, cognition enhancer, neurotrophorestorative)
Bilberry	20% (vasoprotective, antiedema, antioxidant, anti-inflammatory)

NOTE: Nux vomica is available in tincture form in the U.S. and should be used only by experienced herbalists at very low doses. It is contained in some traditional Chinese veterinary herbal products.

Depression

Therapeutic Rationale

- Rule out physical disorders.

A prescription for mild depression is provided:

Saint John's Wort	30% (antidepressant, nervine tonic, vulnerary, anti-inflammatory)
Siberian ginseng	30% (adaptogenic, antistress, immune modulating, neurologic trophorestorative)
Bacopa	20% (nervine tonic, antidepressant, spasmolytic, mild sedative, mental tonic, cognitive enhancer)
Lavender	10% (carminative, spasmolytic, antidepressant, antirheumatic)

Oats *(Avena sativa)* can be given in the diet as porridge for use as a nourishing nervine.

Lavender is particularly indicated when disturbances in gastrointestinal function are apparent as well.

Epilepsy

See the general section on seizures later.

Facial paralysis

Therapeutic Rationale

- Identify treatable causes, which include otitis media or interna, hypothyroidism, neoplasia, encephalitis, polyneuropathy, and facial neuritis.

Although we would recommend primarily acupuncture and massage for this condition, an herbal adjunct might consist of the following.

A prescription for facial paralysis is provided:

Gelsemium	5% (analgesic, sedative, hypotensive)
Prickly ash or capsicum	25% (circulatory stimulant, carminative, diaphoretic, antirheumatic)
Ginkgo	25% (antioxidant, circulatory stimulant, cognition enhancer, neurotrophorestorative)
Ashwagandha	45% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)

Feline hyperesthesia syndrome

Therapeutic Rationale

- Control seizures.
- Reduce allergies, skin irritation and panniculitis.
- Rule out other musculoskeletal and central nervous system (CNS) disorders and abscessation of the tail head.

Hyperesthesia in cats is a sign, rather than a diagnosis. Underlying diseases that lead to the biting, licking, scratching, and even seizure activity are many, and any cause of pain or irritation should be ruled out. These include flea allergy, spinal or muscular pain (including a specific inclusion body myositis that has been identified in these cats), cystitis and dermatitis. True seizure or behavioral disorders are probably rare. Environmental stress can worsen the condition.

A formula for cats that have been treated for any skin disease after thorough orthopedic and chiropractic examination might include the following:

Saint John's Wort	50% (antidepressant, nervine tonic, anti-inflammatory, anxiolytic)
Valerian	10% (sedative, hypnotic, antispasmodic, carminative)
Bacopa or skullcap	20% (anxiolytic, nervine relaxant)
California poppy	20% (sedative, hypnotic, antispasmodic, analgesic)

Also, see the section on neuropathy, later.

Fly-biting seizures

See the general section on seizures later in the chapter.

Hyperactivity

Therapeutic Rationale

- Determine underlying cause.
- Counsel owner to provide high levels of exercise.
- Rule out owner lack of leadership.
- Rule out anxiety.
- Rule out possible dietary manifestation or hypersensitivity. Consider an elimination diet.
- Provide sedative and anxiolytic herbs.

A mild prescription for hyperactivity is given here:

Ashwagandha	40% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Motherwort	20% (sedative, antispasmodic, cardiac tonic)
Lemon balm	20% (carminative, spasmolytic, sedative)
Chamomile	20% (carminative, bitter, spasmolytic, mild sedative, anxiolytic, cholagogue)

Insomnia/Nocturnal restlessness

Therapeutic Rationale

- Rule out cognitive dysfunction, hyperthyroidism, hypertension and so forth.
- Provide sedating, anxiolytic, and relaxing herbs.

A prescription for insomnia or restlessness at night follows:

Ashwagandha	40% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Chamomile	20% (carminative, bitter, spasmolytic, mild sedative, anxiolytic, cholagogue)
Skullcap	20% (sedative, nervine relaxant)
Chaste tree	20% (enhances melatonin production)
Ginkgo	20% (antioxidant, circulatory stimulant, cognition enhancer, neurotrophorestorative)

Alternatively, valerian alone can be used.

Intervertebral disk disease *(cervical and thoracolumbar)*

Therapeutic Rationale

- Minimize spinal movement in acute stages.
- Reduce pain and inflammation.
- Maintain muscular strength throughout recovery.
- Give bladder care.
- Reduce pain.
- Reduce risk of trauma.

Formulas for this disorder should seek to relieve pain from spinal impingement, inflammation, and muscle spasm. A suggested foundation for formula building is provided here:

Corydalis	30% (analgesic, sedative, cardioprotective)
Kava kava or cramp bark	15%
Meadowsweet	20% (anti-inflammatory, possible diuretic)
Ashwagandha	10% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)
Prickly ash or capsicum	20% (circulatory stimulant, carminative, diaphoretic, antirheumatic)

Kirk (1948) indicated that nux vomica and belladonna are "two sovereign remedies" for lack of tone in the bladder.

Meningitis and encephalitis

Therapeutic Rationale

- Identify predisposing or associated injury, infection, or immune compromise.
- Control seizures.
- Improve circulation.

Cases of intractable meningitis (such as granulomatous meningitis, beagle meningitis, etc.) are frequently presented after other treatments have been ineffective.

A foundation formula in this case might be as follows:

Prickly ash or capsicum	20% (circulatory stimulant, carminative, diaphoretic, antirheumatic)
Kava kava or cramp bark	35%
Black cohosh	25% (relaxing nervine, sedative, antirheumatic)
California poppy or Jamaica dogwood	15%
Gelsemium	5% (analgesic, sedative, hypotensive)

Pain

Corydalis: Add to system-based formula, 20% to 50%.

Obsessive-compulsive disorder

Therapeutic Rationale

- Reduce stress.
- Provide adaptogens and anxiolytics.

A mild prescription for obsessive-compulsive disorder is provided:

Saint John's Wort	20%
Chaste tree	20%
Siberian ginseng	20%
Ashwagandha	40%

Peripheral neuropathy

Therapeutic Rationale

- Identify cause, if possible.
- Control immune-mediated damage, if present.
- Provide physical therapy.

A formula for oral use in animals that experience neuralgic pain might contain Saint John's Wort, corydalis, and prickly ash. If the animal can be prevented from licking the area, a local application of capsicum may be of benefit. For paralysis, the authors would prefer acupuncture and physical therapy, but herbal support with circulatory stimulants (such as prickly ash) may also be warranted.

Professional herbalists for humans include herbs such as Saint John's Wort, skullcap, oat seed, and Eleuthero. Peppermint oil may be used as a topical analgesic.

A prescription for neuralgia is offered:

Saint John's Wort	20%
Passionflower	20%
Ashwagandha	20%
Bacopa	20%
Lemon balm	20%

Nerve restorative and protective herbs should be used when nerve damage is suspected. Antioxidant status should be attended to as well.

A general foundation formula to build on for nerve damage is given here:

Ashwagandha	20%
Bacopa	20%
Gingko	20%
Bilberry	20%
Saint John's Wort	20%

Seizures, general

Therapeutic Rationale: The diagnosis of "epilepsy" is oversimplified in that a number of syndromes may cause recurrent seizures. The alternative therapies described in this section may help in a percentage of cases depending on the cause, but at this point, mechanisms are largely unknown and treatment must be provided on a trial-and-error basis.

The practitioner should first attempt to control seizures with conventional drugs because seizures usually become more frequent if untreated, and veterinary herbalists have not found consensus on the most useful herbal anticonvulsants.

Historical texts, both human and veterinary, seem to lament the fact that no cures have been found for this disease, and they point to bromide salts, amyl nitrate, and, later, phenobarbital. The herbs that are most often recommended include gelsemium, passionflower, verbena, and valerian. Kirk (1948) also recommends belladonna if bromide has had no effect on the condition in dogs.

A foundation formula for dogs that do not respond to dietary changes or administration of conventional drugs might consist of these ingredients:

Skullcap	45% (anticonvulsive, sedative)
Gelsemium	5% (analgesic, sedative, hypotensive)
Valerian	20% (sedative, hypnotic, antispasmodic, hypotensive)
Passionflower	30% (sedative, hypnotic, antispasmodic)

A prescription for epilepsy support (assuming conventional medicine is being given concurrently):

Bacopa	20% (nervine tonic, spasmolytic, mild sedative, mental tonic)
Milk thistle	40% (hepatotonic, hepatoprotective, antioxidant)
Baical skullcap	20% (anticonvulsive, anti-inflammatory, antiallergic, mild sedative, hypotensive, diuretic, bitter)
Ginkgo	20% (antioxidant, circulatory stimulant, cognitive enhancer)

Stress

Stress occurs commonly in domestic animals, but aside from behavior counseling and modification, it is not a focus for treatment. The effects of chronic stress in people are well documented.

Stress occurs in large animals such as horses and food animals during shipping and in feedlots. Small animals that have maladapted to their environments are also stressed—these might include cats in crowded environments, high-energy dogs not given enough exercise, and interdog/intercat aggression circumstances.

A study in horses examined changes in cortisol, white blood cell count, and lymphocyte subpopulations in horses following 24 hours of transport. These horses were given an adaptogenic combination proprietary supplement, consisting of eleuthero, schisandra, rhodiola, and Asian devil's club *(Echinopanax elatus),* 8 mL once daily, or placebo. No differences were observed between treatment and placebo groups. In the horses housed in stalls and

not exposed to transport stress, differences in lymphocyte subpopulation counts were noted, but no differences in cortisol, weight, white blood cell count, or lymphocyte responsiveness were reported. This supplement has documented effects in people, so it is possible that the supplement does not work in horses; that the level of stress intensity is different from that tested in humans, or that the dose was inadequate (Stull, 2004).

Stroke *(cerebrovascular accident)*

Therapeutic Rationale

- Improve circulation.
- Improve antioxidant status.
- Provide nerve restoratives.

A prescription to be given following stroke or suspected stroke is given:

Ginkgo	30% (antioxidant, circulatory stimulant, cognition enhancer, neurorestorative)
Lesser periwinkle *(Vinca minor)*	20% (circulatory stimulant [cerebral blood flow], increases cerebral oxygen uptake and glucose absorption, sedative, hemostatic)
Bacopa	20% (nervine tonic, spasmolytic, mild sedative, mental tonic, cognitive enhancer)
Withania	30% (tonic, adaptogen, nervine, sedative, anxiolytic, anti-inflammatory, antitumor)

Vestibular disease

Therapeutic Rationale

- Improve cerebral blood flow.
- Control nausea.

The recommended prescription is as follows:

Ginkgo	15% (antioxidant, circulatory stimulant, cognition enhancer, neurorestorative)
Lesser periwinkle *(Vinca minor)*	25% (circulatory stimulant [cerebral blood flow], increases cerebral oxygen uptake and glucose absorption, sedative, hemostatic)
Skullcap	15% (anticonvulsive, sedative)
Ginger	20%
Saint John's Wort	25% (antidepressant, nervine tonic, anti-inflammatory, anxiolytic)

HERBS FOR REPRODUCTIVE DISORDERS

General Considerations

Herbal medicine is commonly employed to assist men and women with reproductive disorders. It is curious that veterinary herbalists have much less experience in targeting herbs toward animal reproductive diseases, even though infertility and false pregnancy are common reasons for clients to seek herbal medicine treatment. Differences in female reproductive cycle types are likely one factor. In addition, our inability to evaluate sensations that go along with the physiologic processes of ovulation, gestation, and ejaculation, or clinical signs such as uterine bleeding or lack of libido in animals, undoubtedly contribute to this deficiency in herbal tools. This brief section attempts to pull together some clinical targets in human medicine and suggests possible strategies for the future in veterinary reproductive medicine.

Mechanisms of Interest

Emmenagogues

This traditional term refers to any plant that stimulates the menstrual process in women; it may apply to stimulation of menstrual bleeding or to normalization of the menstrual cycle in general. In veterinary medicine, emmenagogues may or may not normalize estrus cycles, but a few herbs with their potential mechanisms of action are given in the female endocrine modulators section that follows. Others include those listed here:

- Partridgeberry *(Mitchella repens)*
- Parsley *(Petroselinum crispum)*
- Rue *(Ruta graveolens)*
- Mugwort *(Artemisia vulgaris)*

Endocrine modulators

Female

Vitex (Chaste Tree Berry) *(Vitex agnus-castus):* This herb is dopaminergic. The berries of this plant are used primarily in women for complaints of premenstrual syndrome. Animal studies have shown that vitex inhibits prolactin and appears to selectively stimulate D_2-type dopamine receptors. A randomized, placebo-controlled trial in men showed no dose-dependent changes in serum prolactin, but studies in women with mastodynia showed that treatment with vitex reduced serum prolactin levels. Vitex has also been shown to reduce the symptoms of premenstrual syndrome and mastalgia in women (Schulz, 2001; Wuttke, 2003). Prolactin may inhibit estrus; vitex may be helpful in suppressing prolactin in animals and may have utility in the treatment of false heat in dogs. It should not be used in pregnant or lactating animals.

Black Cohosh *(Cimicifuga racemosa):* This plant is antiestrogenic. The root of the plant is used primarily in women for menopausal symptoms. Experiments have demonstrated that black cohosh contains compounds with antiestrogenic properties, and that the herb reduces levels of luteinizing hormone (which induces ovulation), with no changes in follicle-stimulating hormone. The triterpene glycosides also affect the hypothalamic-pituitary axis, potentially leading to a variety of secondary effects on the reproductive, nervous, and circulatory systems. Traditionally, black cohosh is considered a uterine tonic and nervine as well. To our knowledge, the herb is not recommended in historic veterinary texts for reproductive or hormonal disorders, and any clear indication for its use in animals is unknown.

Fennel *(Foeniculum vulgare):* Fennel extracts have been shown in mice to trigger a mating response, induce estrus, and increase the size of mammary glands, cervix, vagina, endometrium, and myometrium. On the other hand, an aqueous extract of the seed has been shown to reduce female fertility (Mills, 2000).

Szechuan Lovage Root *(Ligusticum wallichii):* This herb is a luteal phase normalizer that is traditionally prescribed for menstrual disorders caused by blood stasis.

Effects of ligusticum on the endocrine function of the ovary/uterus were studied in rats. Ligusticum had no influence on immature rats, except that it decreased prostaglandin E2 content in the ovary; in pseudopregnant rats, it inhibited the function of the corpus luteum, decreased the level of progesterone in the plasma, and reduced the hCG/luteinizing hormone receptor binding capacity of the ovary, compared with controls (Li, 1992).

DAN SHEN *(SALVIA MILTIORRHIZA):* This herb was investigated in terms of the endocrine function of the ovary and the uterus. In immature Wistar rats, it increased the level of estradiol in plasma, the weight of the uterus, and the ovarian prostaglandin F2 alpha content, but the ovarian prostaglandin E_2 content was reduced when compared with that in the control group. It stimulated ovulation in immature mice pretreated with PMSG. In pseudopregnant rats, it also inhibited the function of the corpus luteum, decreased the level of progesterone in the plasma, and reduced the hCG/luteinizing hormone receptor binding capacity of the ovary (Li, 1992).

OTHER HERBS: Herbs with estrogen-like activity include ladies' mantle *(Alchemilla vulgaris),* false unicorn root *(Chamaelirium luteum),* wild yam *(Dioscorea villosa),* fennel *(Foeniculum vulgare),* licorice *(Glycyrrhiza glabra),* white peony *(Paeonia lactiflora), Panax ginseng,* trillium *(Trillium erectum),* and vervain *(Verbena officinalis).*

Male

SAW PALMETTO *(SERENOA REPENS):* This herb may have numerous mechanisms of action, including an antiandrogenic action, an anti-inflammatory effect, and an antiproliferative influence attained through the inhibition of growth factors. It is effective in reducing symptoms in human benign prostatic hypertrophy (BPH) in men. The most intensively investigated form is the n-hexane lipidosterolic extract known as *Permixon* (Pierre Fabre Medicament, Boulogne, France) (Buck, 2004). It has been tested in dogs and was not effective in correcting measurements of BPH; however, these dogs were asymptomatic (Barsanti, 2000), so a true parallel to the demonstrated efficacy in human BPH has not yet been investigated.

NETTLE *(URTICA DIOICA):* This plant may be mildly effective in human males with BPH. Nettle is commonly used in combination with other herbs. Only the root is considered to have activity in BPH. Clinical observations of men after long-term treatment with an alcoholic extract of nettle root reported an improvement in bladder outlet obstruction symptoms and a decrease in postvoiding residual urine (Bruneton, 1995).

PYGEUM *(PYGEUM AFRICANUS):* This herb has been shown in clinical trials to reduce symptoms associated with BPH in men (Ishani, 2000). The mechanism by which it works is unknown, and pygeum use has not been popular for use in dogs to date.

PUMPKIN SEED *(CUCURBITA PEPO):* These contain sterols, similar to the herbs listed above, and have also been used for the treatment of BPH in men.

TRIBULUS *(TRIBULUS TERRISTIS):* In male rats, tribulus showed considerable stimulation of sperm production. Sperm cells were more viable, suggesting improved fertility (Zarkova, 1984). An experiment was carried out to define the stimulating effect of Tribestan, a proprietary extract on rams that were intended for breeding, as well as on rams that exhibited sexual impotence and deteriorated semen qualities. Treatment led to an extended period of sexual activity and to improved semen production in rams over the service period. Rams with reduced libido recovered by the seventh or eighth day with no morphologic changes in the structure of both testes and epididymides. The use of this preparation led to changes in the endocrine activity of the testis, raising the testosterone level and normalizing the sexual activity of rams affected with coital impotence (Dimitrov, 1987). Tribestan increased testosterone levels and accelerated sexual development in rams and male lambs, respectively (Georgiev, 1988). Libido and sexual reflexes were restored in boars with long-term sexual impotence (Zarkova, 1984).

Galactagogues

FENNEL *(FOENICULUM VULGARE)* OIL: This was shown to increase milk production and fat content in goats (Mills, 2000). Fennel has been used since at least the time of Dioscorides for this purpose.

GUAN MU TONG *(ARISTOLOCHIA FANGCHI* OR *A. MANSHURIENSIS):* This herb was administered in drinking water to lactating mice. A 5% solution suppressed lactation and was associated with decreased mammary RNA levels; a 0.05% solution improved lactation (Wu, 1995). This herb is carcinogenic with long-term use, and it has been removed from the market in some countries.

GOAT'S RUE *(GALEGA OFFICINALIS):* "In 1873, Gillet-Damitte, in a communication to the French Academy, stated that this plant when fed to cows would increase the secretion of milk from 35 to 50 per cent. Others have affirmed that goat's rue is a powerful galactagogue. The best preparation appears to be an aqueous extract prepared from the fresh plant" (Remington, 1918).

CHASTE TREE *(VITEX AGNUS-CASTUS):* This herb is used traditionally as a galactagogue, though no supporting evidence could be found; in fact, clinical trial evidence suggests that Vitex reduces serum prolactin levels (Wuttke, 2003), which would theoretically suppress milk production.

Uterine astringents

Astringents are used to suppress excessive bleeding—in women, they are used primarily for metrorrhagia (bleeding between periods), menorrhagia (heavy periods), or fibroids. Their use for this purpose is questionable in veterinary medicine.

- Ladies' mantle *(Alchemilla vulgaris)*
- Shepherd's purse *(Capsella bursa-pastoris)*
- Cranesbill *(Geranium maculatum)*

Uterine tonics

These plants are used traditionally to prepare the uterus for normal functions, including birth and involution, and may improve circulation or normalize hormonal influence on the uterus.

DONG QUAI *(ANGELICA SINENSIS):* Hot aqueous extracts of dong quai stimulated smooth muscle contractions of the bladder, intestine, and uterus when administered intravenously to dogs (10 g/kg body weight) (Schmidt, 1924). Intravenous administration of an aqueous or 95% ethanol extract of dong quai to cats, rats, and rabbits increased the strength of the contractions and improved the tone of uterine smooth muscle (Zhu, 1987). In vitro assays demonstrated that a decoction of dong quai stimulated the H1 receptor of the mouse uterus (Shi, 1995). It had varied actions on the uterus that were not related to estrogenic activity, and it promoted relaxation and uterine contractility and uterine hyperplasia (Belford-Courtney, 1994).

BLUE COHOSH *(CAULOPHYLLUM THALICTROIDES):* This plant was used by American natives to assist labor and delivery and is described in King's this way: "There is no doubt but that caulophyllum has a decided action upon the gravid uterus. During labor, it relieves *false pains* and coordinates muscular contractions, at the same time increasing their power. When used by delicate women, or those who experience prolonged and painful labors, for several weeks previous to confinement, it gives tone and vigor to all the parts engaged in the accouchement, facilitating its progress and relieving much suffering . . . Chronic corporeal or cervical endometritis, metritis, ovaritis, ovarialgia, uterine leucorrhoea, amenorrhoea, and dysmenorrhoea are conditions in which it has been most successfully employed." This herb has been associated with acute onset of labor and myocardial infarction in a woman, and a review by Paul Bergner notes that it was used in excess of traditional doses, and that it was not traditionally used alone (Bergner, 2001).

BLACK COHOSH *(ACTAEA RACEMOSA):* King's designates this plant as a remedy for "atony of the reproductive tract" and an "excellent *'partus praeparator.'"* No studies were found to support this use.

PARTRIDGEBERRY *(MITCHELLA REPENS):* This herb had similar uses as blue cohosh and black cohosh; it was taken a few weeks before birth to "tone" the uterus.

FALSE UNICORN ROOT *(CHAMAELIRIUM LUTEUM):* King's describes the value of false unicorn root in diseases of the reproductive organs of females. "Especially of the uterus, it is one of our most valuable agents, acting as a uterine tonic, and gradually removing abnormal conditions, while at the same time, it imparts tone and vigor to the reproductive organs. Hence, it is much used in leucorrhoea, amenorrhoea, dysmenorrhoea, and to remove the tendency to repeated and successive *miscarriages*. A particular phase removed by it is the irritability and despondency that often attends uterine troubles."

RASPBERRY *(RUBUS IDAEUS):* This plant is commonly used by breeders to ease parturition in dogs and cats. This use is somewhat mysterious, as it is not a traditional indication in the older literature. No studies can be found to support its use.

OTHER HERBS: Infusions of some medicinal plants were studied for their activity in enhancing uterine tone in in vitro experiments performed on isolated rabbit and guinea pig uterine smooth muscle. In concentrations of 1 to 2 mg crude herb per ml, the plants were ranked in descending order with regard to their tone-enhancing effects on the uterus: chamomile *(Matricaria chamomilla),* calendula *(Calendula officinalis),* cockscomb *(Celosia cristata),* plantain *(Plantago lanceolata),* comfrey *(Symphytum officinale),* shepherd's purse *(Capsella bursa-pastoris),* and Saint John's Wort *(Hypericum perforatum* L.*)*. No effect resulted from infusions of flaxseeds *(Linum usitatissimum* L.*)* and bearberry leaves *(Arctostaphylos uva ursi* L.*)* (Shipochliev, 1981).

Uterine relaxants

These may be useful in threatened miscarriage and false labor.

CRAMP BARK *(VIBURNUM OPULUS):* Cooks (1869) describes the bark as a "slowly acting relaxant, with gentle (mild) tonic properties that chiefly influences the nervous system. Because of its antispasmodic action, it is chiefly employed in hysteria, painful menstruation, neuralgia and rheumatism of the womb, and the uterine cramping incident to pregnancy (and is usually combined with *Mitchella*)."

OTHER HERBS: Others include *Ligusticum wallichii,* black haw *(Virburnum prunifolium),* and blue cohosh *(Caulophyllum thalictroides).*

Nervines and antispasmodics

Breeders frequently report signs of irritability, depression, and possibly pain in mares and bitches. Whatever the causes of the clinical signs, the herbs below have been used in women for the pain and emotional/behavioral symptoms of premenstrual syndrome and may have use if the breeder elects to experiment with them.

BLACK COHOSH *(ACTAEA RACEMOSA):* Most Eclectic uses of black cohosh as a nervine were associated with menstrual or menopausal disorders in women, and it is difficult to separate the antispasmodic and analgesic effects from any nervine effect in traditional herbal literature.

BLACK HAW *(VIBURNUM PRUNIFOLIUM)* AND CRAMP BARK *(VIBURNUM OPULUS):* Cramp bark and other *Viburnum* species have shown ability to reduce smooth muscle spasm in a number of in vitro studies (Cometa, 1998; Calle, 1999; Nicholson, 1972).

Anti-inflammatories *(female reproductive system)*

- Dong quai *(Angelica sinensis)*
- Wild yam *(Dioscorea villosa)*
- White peony *(Paeonia lactiflora)*

REVIEW OF SPECIFIC REPRODUCTIVE SYSTEM CONDITIONS

Abortion

Therapeutic rationale

- Determine infectious, toxic, or hormonal influences.

Antispasmodic herbs such as wild yam, black haw, and cramp bark and uterine relaxants have been suggested for impending miscarriage in women. For repeated miscarriage, false unicorn root can be incorporated into any

formula. Peterson (1905) described the action of caulophyllum in pregnancy by saying that it is used "to prolong gestation to the normal period. In labor, it is of value when the pains are feeble from atony of the uterus, patient weak, nervous."

Many, many herbs have been implicated as abortifacients. Although it is better to be safe than sorry, the reader should remember that many of the herbs discussed in the following section have only theoretical contraindications. With an abundance of caution, we have listed all herbs mentioned in our search of the literature. Types of herbs to be avoided include the following:

- Emmenagogues
- Herbs that may stimulate uterine contractions
- Herbs that are high in alkaloids (which may stimulate the uterus)
- Herbs that are high in volatile oils (which may stimulate or irritate the uterus)
- Herbs that affect hormonal function
- Harsh laxatives
- Strong diuretics

Specific Herbs to be Avoided in Pregnant Animals

Potentially toxic herbs should generally be avoided; however, some are used in low doses or during the last weeks of pregnancy (see individual monographs, where applicable, for more information) (Box 20-1).

Agalactia

Therapeutic Rationale

- Normalize hormonal control of milk production (prolactin and oxytocin).
- Evaluate for systemic illness, excessive epinephrine production (stress or pain induced), debility, or malnutrition.

Herbs with galactagogue activity are used in this condition. Fennel may be employed to increase milk production. Mouse studies suggest that the taste does cross into the milk.

Benign prostatic hyperplasia

Therapeutic Rationale

- Rule out infection.
- Normalize hormonal influences, if possible (although BPH in men and in dogs occurs through different processes).

In men, saw palmetto is well studied and apparently effective. The single trial that investigated saw palmetto in dogs reported a lack of effect for saw palmetto extract on prostatic weight, prostatic volume, prostatic histologic scores, prostatic ultrasonographs, and serum testosterone concentrations (Barsanti, 2000). Dogs included in this

BOX 20-1

Herbs and Poisonous Plants to Be Avoided During Pregnancy*

Achillea millefolium
Aconitum species
Acorus calamus
Adhatoda vasica
Aesculus hippocastanum
Agathosma betulina
Aloe vera (latex)
Ammi visnaga
Andrographis paniculata
Anemone pulsatilla
*Angelica sinensis***
Angelica archangelica
Anthemis nobilis
Apium graveolens
Arctostaphylos uva ursi
Aristolochia (all or any species)
Arnica (all or any species)
Artemisia species
Asarum canadense
Asclepias tuberosa
Atropa belladonna
Baptisia tinctoria
Berberis vulgaris
Borago officinalis
Brassica nigra
Brugmansia spp.
Brunfelsia uniflora
Calotropis procera, C. gigantea
Capsella bursa-pastoris
Cassia senna
Catha edulis
Caulophyllum thalictroides
Cephalis ipecacuanha
Chelidonium majus
Chenopodium ambrosioides
Cicuta virosa
Cimicifuga (Actea) racemosa
Cinchona spp
Cinnamomum species
Cnicus benedictus
Colchicum autumnale
Commiphora spp.
Convallaria majalis
Coptis teeta
Coronilla varia
Corydalis ambigua
Crocus sativus
Crotalaria (all or any species)
Croton (all or any species)
Cynoglossum officinale
Cystis scoparius
Daphne mezereum

BOX 20-1

Herbs and Poisonous Plants to Be Avoided During Pregnancy*—cont'd

Datura stramonium
Dauca carota (seed only)
Digitalis purpurea
Dryopteris fillix-mas
Duboisia myoporoides
Echium vulgare
Embelia ribes
Ephedra sinica
Erysimum cheiranthoides
Euonymus europaeus
Galanthus nivalis
Gelsemium sempervirens
Glycyrrhiza glabra
Gossypium herbaceum
Harpagophytum procumbens
Hedeoma pulegoides
Heliotropium (all or any species)
Helleborus (all or any species)
Hydrastis canadensis
Hyoscyamus niger
Hyssopus officinalis
Iris versicolor
Juniperus communis
Lantana camara
Larrea divaricata
Lathyrus sativus, other than the cooked seed
Leonurus cardiaca
Ligusticum chuanxiong
Ligusticum porterii
Lithospermum (any species)
*Lobelia inflata***
Lomatium dissectum
Lycopus species
Mahonia spp
Mandragora
*Marrubium nigrum***
Menispermum canadense
Momordica charantia
Myristica fragrans
Nerium oleander
Nicotiana tabacum
Opuntia cylindrica
Panax notoginseng
Panax pseudoginseng
Papaver somniferum
Paullinia cupana
Pausinystalia yohimbe
Peganum harmala
Petasites frigida
Petroselinum crispum root or seed
Peumus boldus
Phytolacca americana
Picrasma excelsa
Picrorrhiza kurroa
*Piper methysticum***
Piscidia erythrina
Podophyllum peltatum
Prunus africanum
Prunus serotina
Pteridium aquilinum
Pulsatilla vulgaris
Rauwolfia serpentina
Rhamnus cathartica
Rhamnus purshiana
Rheum palmatum
Ricinus communis
Robinia pseudoacacia, other than the leaf
Ruta graveolens
Salvia miltiorrhiza
Salvia officinalis
Sanguinaria canadensis
Santalum album
Schisandra chinensis, except in last 6 weeks to assist with birth
Schoenocaulon officinale (Sabadilla officinarum, Veratrum officinale)
Scopolia carniolica
Semecarpus anacardium (Anacardium orientale), other than the seed
Senecio aureus
Solanum (all or any species) except stems of *Solanum dulcamara* (Bittersweet) and potatoes
Sophora secundiflora
Spigelia marilandica
Strophanthus spp
Strychnos nux-vomica
Strychnos gaultheria
Strychnos ignatii (Ignatia amara)
Symphytum officinale
Tamus communis fruit and root
Tanacetum parthenium
Tanacetum vulgare
Teucrium (all or any species)
Thuja occidentalis
Thymus vulgaris
Toxicodendron radicans (Rhus toxicodendron)
Tribulus terrestris
Trigonella foenum-graecum
Trillium erectum
Tussilago farfara
Tylophora indica
Uncaria tomentosa
Urginea spp
Verbena hastate
Veronicastrum virginiana
Vinca rosea
Virola sebifera
Viscum album
*Vitex agnus-castus***
Xanthorrhiza simplicissima
*Zanthoxylum americanum***

*This list is compiled from multiple sources with an eye to conservatism
**These herbs may be used by experienced herbalists during pregnancy

study did not have the clinical signs of BPH (i.e., decreased urinary flow and residual urine volume) that often occur in men with BPH. Dogs did not appear to be randomly assigned to treatment, and mean prostatic volume in the control group was higher than that in the active treatment groups before treatment.

Crataeva may also be beneficial in animals with concurrent infection or bleeding from the penis, or when bladder tone may be compromised (see section on urinary tract herbs). Formulas for men are available over the counter and may contain saw palmetto, pygeum root, nettle root, and other herbs.

Herbalists tend to use formulas that contain saw palmetto berry, hydrangea, pygeum, sarsaparilla, white sage *(Salvia apiana),* collinsonia *(Collinsonia canadensis),* corn silk, and nettle root.

Infertility, female

Therapeutic Rationale

- Determine whether anatomic abnormalities prevent insemination.
- Identify potential ovarian or ovum dysfunction (due to toxins, systemic diseases, or congenital or hereditary problems).
- Identify potential hormonal imbalances that may prevent normal cycling, ovum production, maturation, implantation, and so forth.
- Determine whether uterine infection may be present.

Herbal treatment of female infertility should be attempted only after physical problems such as anatomic abnormalities and problems with the male have been ruled out. These may include hormone balancers such as vitex and tonics such as dong quai. Chinese medicine offers many formulas that may be appropriate; these may contain herbs such as white peony, rehmannia, ligusticum, cyperus, and others. It is good to remember that dogs are sensitive to estrogenic compounds and may exhibit bone marrow suppression when given high doses of pharmacologic estrogen compounds. How this relates to herbal estrogenic compounds is unknown.

Infertility, male

Therapeutic Rationale

- Determine whether anatomic abnormalities are present (e.g., testicular hypoplasia, persistent penile frenulum, hypospadia).
- Identify causes of low libido (e.g., behavioral problem, pain, neurologic disorder).
- Determine causes of abnormal or dysfunctional sperm.
- Determine whether genetic disorders are present (e.g., Klinefelter's syndrome, XX male syndrome).
- Identify infection, injury, or tumors that may cause testicular degeneration.

Ginsenosides from *Panax ginseng* may facilitate penile erection by directly inducing the vasodilation and relaxation of penile corpus cavernosum. These effects may be mediated by modification of nitric oxide release from endothelial cells and perivascular nerves. American ginseng *(P. quinquefolius)* has also been shown to enhance male copulatory behavior and lower prolactin levels in male rats (Murphy, 2002). Damiana may also be included in a formula for impotence.

Astragalus may improve sperm motility. In a study on how herbs influence human spermatozoal motility, *Astragalus,* as well as *Acanthopanax senticosus,* significantly enhanced percent viability, number of progressive motile spermatozoa, curvilinear velocity, average path velocity, and amplitude of lateral head displacement (as compared with other herbs in the study, which were ineffective) (Liu, 2004).

Mastitis

Therapeutic Rationale

- Make sure the environment is clean.
- Treat infection with appropriate antibiotics.
- Reduce inflammation to relieve pain.
- Protect infants from nursing abscessed or gangrenous teats.

Most herbalists recommend poultices or compresses, as well as systemic treatments. (See section on immune system and infections.) External applications of chamomile and calendula may have anti-inflammatory activity. Poke root is a stronger herb with a tradition of use in mastitis; King's says, "No other remedy equals phytolacca in acute mastitis." Safety for nursing infants is unknown, and they should not be allowed to nurse if this herb is in use.

Topical applications of Comfrey *(Symphytum offinale)* extract (in propylene glycol base with allantoin, ascorbic acid, and chlorophyll or carotene) to the teats of dairy cows and infusion of the extract into the udder cured acute mastitis after two applications (Noorlander, 1987). Chronically infected cows did not respond as well. Seven cows with teat ends that were ruptured and cracked received topical application of this extract, which healed the tissue. Similar success rates were observed in another herd—cows with chapped teats and skin lesions healed in less than 3 days, and the tissue became soft and smooth. A deep cut on the surface of one teat of one cow healed in less than 5 days after treatment was provided (Noorlander, 1987).

Tea leaves *(Camellia sinensis)* as a poultice were recommended by Sheldon (1880) in a treatise on treatment of mastitis in dairy cows.

Aloe *(Aloe vera)* for the treatment of cows with mastitis was described by Coats in 1985. Therapy was provided through injection of 20 to 60 mL of aloes (in gel or juice form) into the infected quarter at least once a day. It was claimed that aloe helps to drain the infection, has anti-inflammatory properties, and is a coagulant. It has a diuretic property also, which serves to soften the hardened udder.

Chamomile *(Matricaria recutita)* has a traditional use in external application for mastitis and mammary abscesses, as does cabbage, made into a poultice.

***PANAX GINSENG*:** Cows with subclinical mastitis caused by *Staphylococcus aureus* were subjected to subcutaneous injection with an extract from the root of *Panax ginseng* at a dose of 8 mg/kg body weight per day for 6 days. After the end of treatment, the numbers of *S. aureus*–infected quarters and milk and somatic cell count

tended to decrease in ginseng-treated cows, but not in the control group. Findings indicated that ginseng treatment may activate the innate immunity of cows and may contribute to the cow's recovery from mastitis (Hu, 2001).

KELP *(ASCOPHYLLUM NODOSUM):* This herb has been used to prevent mastitis (Vacca, 1954). In a 7-year experiment with twin cows, in which one was given kelp in its ration and the other was not, the incidence of mastitis was greatly reduced in the cows who received kelp. The original research is difficult to trace. Another study (Jensen, 1968) found the total milk yield to be around 6% higher in dairy cows fed 3% *Ascophyllum nodosum* in a fortified seaweed meal, over a 7-year period in Norway, than in controls. The test concluded that the fortified seaweed meal was superior to the standard mineral mixtures for milk production. In the seaweed group, the incidence of mastitis was markedly reduced (90% in the control group); the number of services needed per conception was decreased and the number of no returns was increased; and a marked increase was seen in the iodine content of milk. Trials at the Institute of Animal Husbandry at the University of Giessen, West Germany, affected an increase in number and "much greater" durability of live semen in bulls (Stephenson, 1974).

CALENDULA *(CALENDULA OFFICINALIS):* This herb is used in bioorganic farming as a mastitis salve (Jost, 1984).

PERSICARIA SENEGALENSE: This plant was studied through the use of in vitro and in vivo antimicrobial tests, with crude extracts and the leaf in different forms. The in vitro test showed that isolates of *Staphylococcus aureus, Candida albicans,* and *Corynebacterium bovis* from subclinical cases and an isolate of *Pseudomonas aeruginosa* from a clinical case of mastitis were all inhibited by the three crude extracts at an 820-µg concentration. A trial feeding of 1.5 kg of the cooked leaf per day for 5 days did not yield a significant cure rate, whereas a second trial in which 0.77 kg of leaf powder (equivalent to 3 kg of wet leaf) was fed per day for 5 days resulted in an apparent cure rate of 92.8% (52.8% actual); a 40% spontaneous cure rate was seen in the negative control group, in contrast to 80% (40% actual) in the positive control group that had been treated with an intramammary antibiotic preparation. The difference in cure rate between the negative control group and the experimental group given 0.77 kg leaf powder was significant ($P = .008$) (Abaineh, 2001).

HOUTTUYNIA CORDATA: An aqueous intramammary solution obtained from *Houttuynia* was made for the treatment of bovine clinical mastitis. A total of 104 acute and subacute mastitis cases were randomly assigned into two groups (with 52 cases in each group)—a treatment group and a control group (in which intramammary administration of 800,000 IU penicillin G in combination with 1 g streptomycin was conducted). No statistically significant difference was found between the treatment group and control groups in the treatment of acute and subacute mastitis. In addition, an inhibitory effect was seen on the growth of lactic streptococcus in the milk collected within 48 hours of intramammary treatment with penicillin G in combination with streptomycin. However, for the herbal preparation, a mild inhibitory effect on lactic streptococci was detected in the milk within 12 hours of treatment (Hu, 1997).

Metritis

Therapeutic Rationale

- Identify and treat infection.

Herbs such as blue cohosh, white dead nettle *(Lamium album),* and goldenseal have been recommended for women with endometritis. Echinacea and baptisia may be added for infection. Herbalists often recommend making these herbs into a vaginal suppository to be inserted at bedtime, whereas veterinarians may choose to use infusions. In small animals, however, vaginal douching or uterine infusions are not typically used, as an increase in inflammation usually results. The exception would be a case of vaginitis in which a large amount of pus has pooled (as with a foreign body).

A comfrey extract has also been used in the treatment of metritis of dairy cows. Treatment consisted of 90 mL of extract infused into the uterus every day for 3 days. No visible irritation to the mucous membrane or epithelial tissue was noted; however, a beneficial effect on the endometrium was observed (Noorlander, 1987).

Pseudocyesis (false pregnancy)

Therapeutic Rationale

- Lower prolactin levels.
- Evaluate for hormonal influences, such as hypothyroidism.

Chaste tree *(Vitex angus castus)* is the premier herb for consideration in lowering prolactin levels for these animals.

Pyometra

See the section on metritis. Surgery or luteolytic drugs are recommended for pyometra. As with any potentially life-threatening condition, open pyometra should be managed with extreme caution and diligent follow-up, if unproven alternative medical treatments are used. Herbal medicine is ideal for assisting in the recuperative stage following surgery or as a complementary approach, alongside antibiotics, in open pyometra. Uterine tonics and immune-supporting herbs should be used, as well as adaptogens.

Vaginitis

Therapeutic Rationale

- Address underlying causes (e.g., anatomic abnormalities, subclinical urinary incontinence, obesity-induced fat folds over vulva).
- Identify and suppress pathogenic bacteria.
- Reduce inflammation.

In addition to probiotics, quite a few herbs have been recommended for women with this problem, usually as a douche (see previous note) or sitz bath. These herbs include marshmallow, yerba mansa, black cohosh, myrrh, coptis, echinacea, gossypium, goldenseal, calendula, grindelia, and comfrey leaf.

A classic formula for vaginal discharge consisted of equal parts cranesbill *(Geranium maculatum),* bethroot

(Trillium erectum), marshmallow *(Althaea officinalis),* and agrimony *(Agrimonia eupatoria).*

The author (BF) has successfully treated a chronic case of lymphocytic plasmacytic vulvitis/vaginitis in a dog with Chinese formula Rehmannia 6.

HERBS FOR RESPIRATORY DISORDERS

Practitioners rely heavily on the traditional uses of respiratory herbs because these herbs have been less well researched than those used in other areas of herbal medicine. Similar to conventional medicine, symptomatic management is the mainstay of treatment, and a diagnosis assists herbalists in treating the underlying pathophysiology.

One of the first signs of respiratory disease is coughing, which in itself may be beneficial. Generally, coughs should be treated when they are unproductive, or when they keep the owner awake at night. Herbal treatment for respiratory disease may include tinctures, but steam inhalation and cough syrups are also useful. Herbs are commonly found in many cough syrups used in conventional medicine. Some of the actions we look for in treating respiratory disease include expectorants, which help remove excess mucus; demulcents, which reduce irritation;. antitussives, to prevent or reduce the severity of coughing; suppressants, which inhibit the coughing reflex; antimicrobials, to reduce infection; and, more recently, herbal antihistamines and immune modulators, to treat allergic respiratory disease.

Mechanisms of Interest

Antitussive herbs

Coughing is a complex reflex that originates in peripheral cough receptors, which are most concentrated in the epithelium of the upper and lower respiratory tracts but are also found in the external auditory meatus, tympanic membrane, esophagus, stomach, pericardium, and diaphragm. Vagal afferent nerves carry signals from irritants and mechanoreceptors to the central medullary cough center (or centers), and efferent signals reach bronchial smooth muscle through the vagal, phrenic, and spinal motor nerves. Stimulation at any point in this reflex arc may lead to a cough.

Antitussives work through central or peripheral means. Central-acting antitussives act on the central cough center. Conventional drugs with central antitussive activity include opioid agonists; however, few herbs with demonstrated opioid activity are also used as antitussives. One source (Mills, 2000) claims that cyanogenic glycosides have central antitussive activity—the premier herb in this case is wild cherry bark. Peripheral antitussives may have bronchodilator, expectorant, demulcent, or anti-inflammatory activity; these are discussed in their respective sections.

Swallowing itself helps to suppress coughing. In humans, cough lozenges include ingredients that work via several modes of action, but it should be noted that even the sugar in these lozenges may suppress cough by stimulating salivation and subsequent swallowing.

WILD CHERRY BARK *(PRUNUS SEROTINA):* Studies to support the antitussive activity of wild cherry bark could not be found. Wild cherry was often confused with *P. virginiana,* which is actually choke cherry, but for the reader's own information, it is useful to note that the Eclectic writers and the early US Dispensatory may have considered them synonymous. Ellingwood (1919) describes the indications as follows: "a common remedy in the treatment of chronic coughs, especially those accompanied with excessive expectoration . . . The syrup is used as a menstruum for the administration of other remedies in this disease. It is excellent also in reflex cough—the cough of nervous patients without apparent cause." The US Dispensatory (Remington, 1918) stated that hydrocyanic acid was believed to be the active principle, but wild cherry bark was not believed to be very effective. The dose recommended for people was 30 to 60 grains (1.9-3.8 g). Winslow states that the official products (fluid extract and syrup) were often used in cough mixtures for dogs, but that the official hydrocyanic acid was more reliable. Milks (1949) recommends doses of 2 mL of the fluid extract for dogs, or 4 mL of the syrup.

LICORICE *(GLYCYRRHIZA GLABRA):* Constituents may have some direct central effects on the cough reflex. Laboratory animal studies have suggested that the effect was comparable with that of codeine (Anderson, 1961), and that one component—liquiritin apioside—had antitussive effects that were dependent on both peripheral and central mechanisms (Kamei, 2003). The herb is considered both demulcent and expectorant and is used to decrease inflammation in the respiratory tract, and often as a stabilizing and flavoring base for troches or pills that included other antitussives.

BURDOCK *(ARCTIUM LAPPA):* A constituent (fructofuranan—a type of inulin), has been tested for antitussive activity in cats. It was found to be equally as active as some nonnarcotic, synthetic preparations used in clinical practice to treat patients with cough; in mitogenic and comitogenic tests, its biological response was comparable with that of the commercial zymosan immune modulator (Kardosova, 2003).

OTHER HERBS: Other antitussive herbs include the following:

- Neem *(Azadirachta indica)*
- Bupleurum *(Bupleurum falcatum)*
- Black cohosh *(Cimicifuga racemosa)*
- Pinellia *(Pinellia ternata)*
- Elecampane *(Inula helenium)*
- Thyme *(Thymus vulgaris)*
- Marshmallow *(Althaea officinalis)*
- Irish moss *(Chondrus crispus)*

Anti-inflammatory and antiallergic herbs

These herbs may stabilize mast cells, reduce leukotriene production, or have other effects that suppress acute allergic responses that lead to bronchoconstriction, inflammation, and mucous production.

PERILLA SEED *(PERILLA FRUTESCENS):* This is a traditional Oriental remedy for asthma. This treatment is frequently used in cats; they tolerate it well because of the neutral taste.

BOSWELLIA *(BOSWELLIA SERRATA):* In a controlled study, 40 human patients with asthma were treated with boswellia gum resin (300 mg three times daily for 6 weeks). In all, 70% of patients showed improvement in physical symptoms such as dyspnea, rhonchi, and frequency. Only 27% of control patients treated with lactose showed improvement (Gupta, 1998).

NETTLE LEAF *(URTICA DIOICA):* A double-blind, randomized trial examined the effects of freeze-dried nettle on 69 people with allergic rhinitis. Nettle was rated higher or slightly higher by physician assessment and patient diary entries, respectively (Mittman, 1990).

LICORICE ROOT *(GLYCYRRHIZA GLABRA):* King's (Felter, 1898) suggests that licorice is useful in "old bronchial affections." Because the herb inhibits 11-hydroxysteroid dehydrogenase, endogenous steroid levels may be elevated, which may also suppress allergic responses. Licorice is most often used as part of a formula because of concerns about mineralocorticoid-like adverse effects when it is used over the long term.

BUTTERBUR RHIZOME *(PETASITES HYBRIDUS):* Extracts of butterbur have been shown to bind the H1 histamine receptor (petasin), inhibit cyteinyl-leukotriene synthesis, and selectively inhibit cyclooxygenase (COX)-2 in vitro (Fiebich, 2005). The Asthma & Allergy Research Group at the University of Dundee has completed multiple human clinical trials undertaken to investigate the effects of butterbur extracts in allergic respiratory disease. Using the patented butterbur extract Petaforce® (50 mg twice daily), they compared the extract with placebo in patients challenged with adenosine monophosphate. In two randomized, double blind, crossover trials, butterbur effectively suppressed the signs of allergic rhinitis (Lee, 2004b; Lee, 2003); in another trial, it was ineffective (Gray, 2004). Tesalin® was used by another group and was compared with cetirizine in a double-blind, parallel-group trial. Tesalin contains the equivalent of 8 mg petasins per tablet. Similar improvements were noted in the two groups, and although butterbur use was not associated with adverse effects, the cetirizine group reported sedation as a common adverse effect (Schapowal, 2002). Petaforce® was also investigated for use in atopic asthmatic human patients who were already being treated with corticosteroid inhalers; it was found to be significantly beneficial as a complement to steroid use in a double-blind, crossover trial (Lee, 2004a). The proprietary product Petadolex® was administered to 80 asthmatic patients for 2 months in an open trial, and the number of asthmatic attacks, peak flow, and forced expiratory volume were measured. All symptoms improved during therapy, and more than 40% of patients were able to reduce their intake of other asthma medications (Danesch, 2004). Butterbur had no effect on skin test reactions to histamine (Jackson, 2004). Butterbur contains pyrrolizidine alkaloids and should not be used as crude herb or crude extract. The products mentioned here have been processed to remove the pyrrolizidine alkaloids, according to the manufacturers. Doses recommended for adult humans are as follows: Petaforce® (25-50 mg twice daily to three times daily), Petadolex® (25-75 mg twice daily to three times daily, maximum 150 mg/day), and Tesalin® (Ze 339; 1-2 tablets twice daily to three times daily).

GINKGO *(GINKGO BILOBA):* This plant was shown in one trial in asthmatic humans to improve forced expiratory volume significantly over placebo. A dose of 15 g of a concentrated extract was administered three times daily (Li, 1997). A protective effect is exerted by ginkgolides on platelet-activating factor (PAF)-induced bronchoconstriction and airway hyperactivity. Oral or intravenous injection of ginkgolide B antagonizes cardiovascular impairments and bronchoconstriction induced by PAF. Ginkgolide B does not appear to interfere with cyclooxygenase, but it does have an effect in an earlier step involving PAF receptors and phospholipase activation. Eosinophil infiltration occurs in asthma and in allergic reactions, the number of eosinophils increasing during late phase. Because PAF is a potent activator of eosinophil function, it has been argued that ginkgolide B may interfere with the late-phase response (Hosford, 1988). A randomized, double-blind, crossover study involved patients with atopic asthma who were challenged with a specific dust or pollen antigen. After 6.5 hours, participants were subjected to a provocation test with acetylcholine. Mixed ginkgolide standardized extract, 40 mg three times daily, or placebo was given during the 3 days before the test, and a final single dose of 120 mg of extract was given 2 hours before the challenge. Results suggested that ginkgolides were effective in both the early phase and the late phase of airway hyperactivity (Braquet, 1987).

TYLOPHORA *(TYLOPHORA INDICA/ASTHMATICA):* This traditional Ayurvedic herb is used for asthma. In vitro studies suggest that constituents from the plant are anti-inflammatory and may suppress mast cell activation. Clinical trial results, however, have been mixed. The human dose is 200 to 400 mg of dried leaf, or 1 to 2 mL of tincture, divided daily. Reported adverse effects include nausea, vomiting, and mouth soreness (Shivpuri, 1969; Shivpuri, 1972; Thiruvengadam, 1978; Gupta, 1979).

Expectorant herbs

Traditional practitioners from many cultures have noted a connection between the secretory functions of the respiratory and digestive tracts. A simple observation has been made that vomiting is preceded by salivation and nausea—but also by respiratory secretions. Ancient medical strategies to reduce phlegm in the respiratory tract concentrate on abnormalities in digestive function. This related reflex is not surprising when one considers the common embryologic origin of the bronchial and alimentary epithelium, as well as the shared vagal innervation. Herbs that cause expectoration do so by one of two mechanisms. Reflex expectorants irritate gastric mucosa, and some (like ipecac, *Cephaelis)* are used most often as emetics. Herbs that contain saponins (mullein, licorice, ivy, cowslip, senega snakeroot, and soap bark) probably stimulate the gastric mucosa. Mucolytic herbs increase the water content of respiratory mucus.

Stimulating expectorants

LOBELIA *(LOBELIA INFLATA):* This herb has not been investigated in controlled trials for its effects on the res-

piratory system. King's (Felter, 1898) describes the expectorant characteristics of the herb as follows: "It improves innervation and the circulation, and is one of the best remedies to employ in congestive conditions. It is frequently indicated in pleurisy and pleuropneumonia. . . . Acute pneumonia, with tendency to congestion, the breathing being oppressed, is quickly relieved by lobelia. Chronic pneumonia, bronchitis, and laryngitis are all conditions in which lobelia will be of great service . . . It is a remedy of great value in chronic catarrh, dry, hard, or barking coughs, colds, and all forms of irritation of the respiratory tract, with oppression. It relaxes the tissues, favors expectoration when a large quantity of mucus is secreted and there is want of power to remove it. The indications for this drug are . . . difficult respiration, oppression anywhere in the chest, with accumulation of the bronchial secretions, cough with loud mucous rates within the chest . . ." Milks (1949) lists the following doses: Horses—4 to 30 mL of fluid extract and 30 to 60 mL of tincture; dogs—0.03 to 1.3 mL of fluid extract and 0.2 to 2 mL of tincture.

BLOODROOT *(SANGUINARIA CANADENSIS):* This plant has not been scientifically investigated for possible usefulness in respiratory disease. King's (Felter, 1898) describes its use in this way: "Its action upon the pulmonary organs is somewhat similar to that of lobelia. It is important as a stimulating expectorant, to be used after active inflammation has been subdued . . . It restores the bronchial secretions when scanty, and checks them when profuse . . . when . . . the secretions are checked, it restores them, and removes the dry, harsh cough. It is useful in both acute and chronic bronchitis, laryngitis, sore throat, and acute or chronic nasal catarrh. It acts as a sedative to the irritable mucous surfaces, promotes expectoration, and stimulates their functions . . . Pharyngitis, with red and irritable mucous membranes, and burning, smarting, or tickling, is cured by it . . . In pneumonia, after the inflammatory stage has passed, it may be given in 1- or 2-drop doses, frequently repeated, or it may be combined with wild cherry, lycopus, or eucalyptus." Bloodroot does not make an appearance in the old veterinary pharmacopoeias. The human dose recommended by the US Dispensatory (1918) is 0.13 g. This herb is more safely used as part of a formula.

SQUILL *(URGINEA MARITIMA):* This herb was formerly used as a stimulating expectorant, but it contains cardiac glycosides and was said to be a stimulating irritant to the kidney. This plant has more powerful gastrointestinal adverse effects than digitalis. Winslow (1908) recommended it for ascites from heart disease but also said it was indicated in bronchitis with "scanty secretion, or when exudation is excessive, to improve the tone of the bronchial mucous membrane." Milks said that it was a powerful and commonly employed expectorant. The dose given in Milks is as follows: Horses—fluid extract 4 to 8 mL, tincture 15 to 30 mL, syrup 15 mL; dogs—0.06 to 0.3 mL, tincture 0.3 to 2 mL, and syrup 2 to 4 mL. No studies can be found to support its use. Considering the toxic cardiac and kidney effects, this herb should probably be avoided.

IVY LEAF *(HEDERA HELIX):* This herb contains saponins, which are thought to confer expectorant activity. A meta-analysis in 2003 examined five randomized, controlled trials that used ivy extract for the treatment of chronic bronchitis. Only one trial included a control, and three met the inclusion criteria. Analysis showed that ivy leaf extract improved respiratory function in children with bronchial asthma, but more trials were recommended (Hofmann, 2003). The preparation used in the placebo-controlled trial of children aged 4 to 12 years was a hydroethanolic extract, given at 35 mg/dose, equivalent to 210 mg of crude herb. The dose used for trials in adults was 60 mg of the extract, equivalent to 400 mg of crude herb.

MULLEIN *(VERBASCUM THAPSUS, V. DENSIFLORUM):* This is an expectorant and demulcent, but its primary action is thought to be as an expectorant because of its content of saponins (such as verbascosaponin). It is traditionally recommended for bronchitis, tracheitis, laryngitis, asthma, dry cough, and catarrh (1-4 mL three times daily to four times daily; dried herb $^1/_2$-$^3/_4$ teaspoon [3-4 g] three times daily).

PRIMULA ROOT *(PRIMULA VERIS, P. ELATIOR):* This is used occasionally as an expectorant, although this does not seem to be a primary traditional use for the plant. It contains saponins. The dose for adult humans is about 1 g of crude herb divided daily. The only scientific studies found on primula used a proprietary formula of thyme and primula, with beneficial results seen in people and horses (van den Hoven, 2003). See section on equine COPD.

SOAP BARK *(QUILLAJA SAPONARIA):* This herb contains saponins and is said to be similar in constituents and activity to senega (see next paragraph). No recent scientific studies have been found to support the use of soap bark. King's recommends $^1/_2$ to 1 oz of infusion for adult humans.

SENEGA SNAKEROOT *(POLYGALA SENEGA):* No recent scientific studies have been found to support the use of senega. King's describes the use of senega as follows: "Its expectorant properties render it very useful in chronic catarrh, . . . bronchorrhoea, chronic bronchitis, with profuse secretion, humoral asthma . . . In active inflammation, its use is contraindicated."

GRINDELIA (*GRINDELIA SQUARROSA* AND OTHER SPECIES): This plant contains saponins, as well as a volatile oil. No recent scientific studies have been found to support its use. King's recommends it as "especially efficient in asthma, giving prompt relief, and effecting cures in cases previously rebellious to medication. . It has likewise been found efficient in bronchial affections . . ." The dose for adult humans is as follows: fluid extract, from 15 minims to 1 fluid drachm (0.9-3.7 mL), repeated every 3 or 4 hours; [tincture], 5 to 40 drops.

LICORICE *(GLYCYRRHIZA GLABRA):* This plant contains a saponin (glycyrrhizin), but some authors believe it exerts expectorant activity primarily by other, unexplored, means. Veterinary doses vary, as most authors consider the herb harmless. See monograph on licorice for a discussion of whole versus deglycyrrhizinated DGL form.

Mucolytic expectorants

AROMATIC HERBS, SUCH AS CINNAMON, GINGER, FENNEL, ANISEED, CLOVE, SPRUCE NEEDLE, CAJEPUT, NIAOULI, AND TURPENTINE: Volatile oils have "bronchomucotropic" activity. They are well absorbed orally and are partially excreted through the lungs, acting on bronchial mucous glands as they pass through the bronchial tree. (Schulz, 2001). A typical terpene product called "Ozothin" was studied for its effects on the bronchial glands. In this study, the aromatic compound selectively stimulated serous glands while depressing the function of mucous glands, resulting in a net liquefaction of bronchial secretions (Lorenz, 1985).

PUNGENT HERBS, SUCH AS HORSERADISH, GARLIC, MUSTARD, AND CAYENNE: These may increase blood flow to the lower respiratory tract, stimulated by an increase in blood flow to the upper gastrointestinal mucosa, which occurs after these spicy herbs are ingested. Horseradish and mustard contain sulphoraphanes that may interact with sulfide linkages in mucus as well.

Demulcent herbs

The pharynx, larynx, and trachea contain mechanoreceptors that are sensitive to irritation; the demulcent herbs coat irritated pharyngeal tissue on a short-term basis. Some herbalists speculate that the systemic effect on the lower respiratory tract is mediated via the effect of mucilage on the gastrointestinal tract.

MARSHMALLOW *(ALTHAEA OFFICINALIS):* Intragastric administration to cats of an extract of marshmallow root, or the polysaccharide fraction, demonstrated significant antitussive activity, depressing the cough that resulted from irritation of laryngopharyngeal and tracheobronchial mucosa. The isolated polysaccharide, administered at 50 mg/kg, was as effective as marshmallow syrup administered at 1 g/kg and was more effective than the whole extract, administered at 100 mg/kg (Nosal'ova, 1992).

SLIPPERY ELM *(ULMUS FULVA):* This demulcent was thought to have expectorant qualities as well by traditional practitioners. King's says that, "for mucous inflammations of the lungs . . . used freely in the form of a mucilaginous drink (1 ounce of the powdered bark to 1 pint of water), it is highly beneficial, as well as in diarrhoea, dysentery, coughs, pleurisy, strangury, and sore throat, in all of which it tends powerfully to allay the inflammation."

ENGLISH PLANTAIN *(PLANTAGO MAJOR):* Two observational studies have suggested that plantain has mild antitussive activity, with miminal adverse effects (Matev, 1982; Kraft, 1997a).

ICELAND MOSS *(CETRARIA ISLANDICA):* This lichen contains unique depsidones (lichenic acids), although the polysaccharides are considered most important in its demulcent effects. Results of a randomized trial suggested that Iceland moss can prevent dryness and inflammation of the oral cavity in patients who had undergone surgery of the nasal septum who were forced to undergo prolonged mouth breathing. Emollient effects were found with the daily use of 0.48 mg Iceland moss lozenges (Kempe, 1997). The human dose is 4 to 6 g/day of cut herb powdered or made into an infusion, 4 to 6 mL of the fluid extract (1:1), or 20 to 30 mL of the tincture (1:5).

IRISH MOSS *(CHONDRUS CRISPUS):* This herb, also called carrageen, is a common ingredient in cough mixtures available in most drug stores. Cook (1869) describes its use as follows: "for its demulcent influence in bronchial and pulmonary irritation, diarrhea and dysentery, and irritability of the kidneys and bladder. It is most available in recent colds and coughs, where it may be used freely in warm decoction. Its mucilaginous, demulcent properties are used traditionally to reduce coughing."

COLTSFOOT *(TUSSILAGO FARFARA):* This plant contains 6% to 10% mucilage and inulin, but some specimens also contain pyrrolizidine alkaloids. King's recommended the plant as "useful in coughs, asthma, whooping-cough, laryngitis, pharyngitis, bronchitis, and other pulmonary affections . . ." A sesquiterpene, tussilagone, was shown to produce a pressor effect in anesthetized dogs (0.02-0.3 mg/kg), cats (0.02-0.5 mg/kg), and rats (0.4-4 mg/kg) when administered intravenously (Li, 1988). Tussilagone also stimulated respiration in anesthetized animals. The herb is approved by Commission E for acute catarrhal or inflammatory conditions of the respiratory tract; it is noted that although coltsfoot should not be used on a long-term basis because of its possible pyrrolizidine content, it is safe for acute use. The human dose is 2 to 4 mL of the tincture (1:5), or 1 to 2 tsp of the dried flower and leaf (dry or in infusion), three times daily.

COMFREY *(SYMPHYTUM OFFICINALE):* This demulcent herb has traditionally been used for coughing and bronchial irritation. Unfortunately, internal use of the herb has been associated with at least four human deaths, and in laboratory animal studies, it is carcinogenic. It is banned in Australia and Europe. It consistently contains pyrrolizidine alkaloids, and recent studies point to an additional quinoid toxin. Commission E recommends it for external use only; however, some traditional herbalists still use it for **short** periods.

MULLEIN *(VERBASCUM THASPUS):* This plant contains only 3% mucilage, and although it is usually listed as a demulcent antitussive, most of its action is probably expectorant, which is caused by saponins.

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* According to King's, the "only property worth mentioning is its emolliency. It has been used to allay irritation of the throat and breathing passages. Respiratory irritation is thought to be relieved by its internal use."

Spasmolytic herbs

Bronchodilating herbs may suppress cough simply by relaxing bronchoconstriction, which is thought to stimulate some types of cough receptors. Bronchodilating herbs such as ephedra also tend to dry mucosal secretions.

Mechanisms by which bronchial tone is mediated include the following:

1. Parasympathetic system maintains mild bronchoconstriction.
2. Sympathetic system causes constriction via α_1 receptors, and dilation via β_2 receptors.

3. Vasoactive peptides mediate bronchodilation through nonadrenergic, noncholinergic neuroendocrine mechanisms.

LOBELIA *(LOBELIA INFLATA):* King's says this about the herb: "It is for its antispasmodic effects that it is given in asthmatic paroxysms, spasmodic croup, and whooping-cough. . . . It has come to be the first of remedies for spasmodic asthma." Lobeline is a nicotinic acid receptor agonist (mimics actions of acetylcholine at nicotinic sites) similar to but weaker than nicotine. Experimentally, it stimulates respiration and induces coughing. However, some trials suggest that lobeline may improve lung function, possibly by suppressing bronchial constriction and thinning mucus (Pocta, 1970). Lobelia is a low-dose herb.

EPHEDRA *(EPHEDRA SINICA):* This plant contains sympathomimetic alkaloids (ephedrine, pseudoephedrine, and others) that have bronchodilatory, decongestant, and cardiac stimulant effects. The herb is not now commercially available in many countries, although US Food and Drug Administration (FDA) language leaves the door open for professional herbalists to use it, and current civil cases in the United States (as of 2005) may make it available again to consumers in low doses. The herb was used most commonly in the context of traditional Chinese formulas.

GRINDELIA *(GRINDELIA CAMPORUM, G. ROBUSTA, G. HIRSUTA, G. HUMILIS, G. SQUARROSA):* The volatile oil and resin from these herbs have slight antispasmodic activity. Supporting data could not be found, but King's describes the use of grindelia as "especially efficient in *asthma,* giving prompt relief, and effecting cures in cases previously rebellious to medication. . . . It has likewise been found efficient in bronchial affections . . ."

YERBA SANTA *(ERIODICTYON CALIFORNICUM):* This herb is described in Ellingwood (1919) this way: "It is of value in chronic bronchitis, chronic pneumonitis and in phthisis pulmonalis, in allaying the cough which seems to increase the patient's feebleness and advance the development of the disease. It is an excellent remedy combined with Grindelia robusta. It acts well in all forms of cough where there is dryness of the mucous membranes, in conjunction with other directly indicated remedies. It is prepared in the form of a syrup . . ."

HYSSOP *(HYSSOPUS OFFICINALIS):* This is traditionally used as a mild antispasmodic and expectorant, because of its volatile oil content. It is not well studied.

RED ROOT *(CEANOTHUS AMERICANUS):* This is stated in King's to be antispasmodic and expectorant, and to be of value in chronic bronchitis, asthma, whooping cough, and other "pulmonary affections."

THYME *(THYMUS VULGARIS):* This herb contains volatile oils and flavonoids that suppress bronchospasm and are mucolytic; the herb also has antibacterial activity (Bisset, 1994; Van Den Broucke, 1983; Muller-Limmroth, 1980). It was not used much by the Eclectic medical doctors, but Lloyd's *History of the Vegetable Drugs of the U.S.P.* (1911) states that it was used in veterinary medicine as oil of origanum or oil of thyme.

CHUAN XIONG *(LIGUSTICUM WALLICHII):* This plant was shown in one human clinical trial to improve forced expiratory volume when compared with placebo treatment. A parallel study in guinea pigs suggested that the mechanism of action involved tracheal smooth muscle relaxation and suppression of thromboxane B2. The dose used was 10 mL three times daily, presumably of the decoction (Shao, 1994).

Anticatarrhal herbs

Catarrh is inflammation (and usually subsequent discharge from) mucous membranes, especially in the respiratory tract. Catarrh is a feature of allergic rhinitis and sinusitis, and is also a feature of infections, such as viral upper respiratory infections.

PLEURISY ROOT *(ASCLEPIAS TUBEROSA):* This was considered in King's to be one of the best anticatarrhal herbs for the respiratory tract—primarily the upper respiratory tract. It is not a well-studied herb and it contains cardiac glycosides, so high doses should be avoided.

EYEBRIGHT *(EUPHRASIA OFFICINALIS):* This plant has been used for acute, watery rhinitis. It is not well studied.

GOLDENSEAL *(HYDRASTIS CANADENSIS):* This plant has not been studied for catarrhal respiratory disorders. King's describes its use in this way: "For that disagreeable state accompanying nasal and pharyngeal catarrh, in which the mucus forms in gelatinous masses and drops into the throat, hydrastis is probably without an equal. It should be applied locally and also administered internally."

ELDER FLOWER *(SAMBUCUS NIGRA):* This is considered a diaphoretic; it has been suggested in a human clinical trial to hasten recovery from influenza.

OTHER HERBS: Other anticatarrhals, especially for the lower respiratory tract: Bryony, Polygala, Sage, Mullein.

Other anticatarrhals, especially for the upper respiratory tract include: garlic, Indian barberry, eyebright, elder flower, and goldenrod.

Decongestant herbs

Drug decongestants are sympathomimetics or H1 blockers. Ephedra is the only herb of assistance in this category.

Diaphoretic herbs

These herbs cause sweating, sometimes because of inherent qualities in the herb, and sometimes because they were administered as hot teas. Traditionally, these herbs were administered to help the body release "toxins" through the skin by stimulating sweating; they were thought to lower fevers. It is also possible that some of them raise body temperature slightly and transiently, hastening resolution of viral or bacterial infection. The relevance of diaphoretic herb therapy in small animals without the ability to sweat is unknown. Horses and other species that sweat may benefit from their use. The best known diaphoretic herbs are yarrow, elder flower, ginger, cayenne, garlic, boneset, lemon balm, peppermint, linden, and hyssop.

Pectorals

This is an old term that included herbs used in the treatment of diseases of the chest, more often respiratory

remedies. The term is too vague to be of much modern use.

Other herbs that have been used for respiratory conditions include astragalus root *(Astragalus membranaceus),* black cohosh, ground ivy *(Glechoma),* lomatium *(Lomatium dissectum),* osha *(Ligusticum porteri),* stillingia *(Stillingia sylvatica),* thyme *(Thymus vulgaris),* usnea *(Usnea barbata), Picrorrhiza kurroa, Solanum xanthocarpum/trilobatum,* Boswellia *(Boswellia serrata),* and sundew *(Drosera rotundifolia).*

Review of Specific Respiratory Conditions

Allergic bronchitis *(feline asthma, canine chronic bronchitis)*

Therapeutic Rationale

- Manage underlying disorders, including lung parasites and infection.
- Manage immune reactivity and inflammation.
- Control bronchoconstriction.
- Loosen airway mucus.

Formulas for allergic bronchitis should include expectorants (mucolytic and stimulating), antispasmodics, antiallergics, immune-modulating herbs, demulcents, and perhaps antimicrobials and adaptogens.

A prescription for allergic bronchitis follows:

Elecampane, mullein, or ivy	25% (stimulating expectorants)
Fennel or ginger	25% (mucolytic expectorants)
Lobelia for acute exacerbation, khella *(Ammi visnaga)* for long-term use	15% (antispasmodics)
Iceland moss or marshmallow	20% (demulcents)
Pyrrolizidine alkaloid (PA)–ree butterbur or licorice	15% (antiallergics)

Human herbalists have recommended various recipes for the treatment of asthma. These may include Reishi, ephedra, anise, *Euphorbia pilufera,* Ginkgo leaf, Khella, Lobelia, grindelia, wild cherry, motherwort and Licorice. Chinese formulas for asthma may include coltsfoot flower, ephedra, licorice, and apricot seed.

Weiss (1988) provides formulas that contain Primula tincture, Ephedra tincture, Anise tincture, and thyme syrup or fluid extract.

For cats that become stressed by administration, marshmallow glycetracts mixed with food or perilla seeds added to food may be used.

Equine chronic obstructive pulmonary disease or heaves

Therapeutic Rationale

- Manage underlying disorders, including lung parasites and infection.
- Manage immune reactivity and inflammation.
- Control bronchoconstriction.
- Loosen airway mucus.

Herbs listed in the allergic bronchitis section (earlier) may also be used for horses with heaves.

Bronchipret®, with extracts of *Thymus vulgaris* and *Primula veris,* is a proprietary remedy for the treatment of human bronchitis. The formula was tested in five warmblood horses with confirmed recurrent airway obstruction by van den Hoven and associates (2003). The horses were administered 2400 mg of Thyme extract and 900 mg of Primula root extract twice daily. Lung compliance, pulmonary pressure, and airway resistance were all significantly improved after 1 month of treatment, but the severity of clinical signs and arterial oxygen partial pressure did not improve.

Titus (1865) recommended that horses be fed no hay, and that 1 tablespoonful of ginger be added to each meal. He thought the best fodder for heavy horses was "good, bright cornstalks." In addition, doses of the following were given:

Tincture of aromatic sulphur acid 1 drachm
1 pint of water

To be followed by an alterative formula, which consisted of these ingredients:

Powdered ginger	2 oz
Powdered gentian	2 oz
Salt	3 oz
Cream of tartar	2 oz
Powdered licorice	2 oz
Powdered elecampane	1 oz
Powdered caraway seed	2 oz
Powdered balm of gilead buds	2 oz

This powder, 1 oz, was given twice daily in food.

Another "cure for heaves" given by Titus was:

Sumach bobs (the flowering head of sumac)	3 pounds
Ginger	1 pound
Mustard seed	1 pound
Rosin (pine resin)	1 pound
Air-slaked lime	1 pound
Cream of tartar	6 oz

This was mixed and divided into 30 doses, given once daily in the morning.

Titus gives a recipe for a strong expectorant powder that contains 2 oz powdered ipecac, 2 oz powdered lobelia, 2 oz powdered bloodroot, and 4 oz powdered licorice.

For a cough in horses, Titus recommended cutting the "boughs of cedar or white pine" finely, and adding it to the grain.

Titus prepared two recipes for cough balsams for horses—one of which contained the active ingredient paregoric. The one containing only herbs is provided here:

Cough balsam No. 1 (the ingredients below are mixed and the dose is $^1/_2$ oz)

Molasses	1 pint
Tincture lobelia	4 oz
Essence peppermint	1 oz
Essence anise	1 oz

More modern approaches to the treatment of heaves may be found in Chapter 21, Herbal medicine in equine practice.

Feline viral upper respiratory disease *(especially herpesvirus)*

Therapeutic Rationale

- Provide nutritional and fluid support.
- Control secondary bacterial infections.

Formulas for viral upper respiratory infection may include antiviral herbs, antibacterial herbs, expectorants, and immune support.

A prescription for viral respiratory disease follows:

Echinacea (immune stimulant, possibly antimicrobial)	50%
Ginger or fennel (mucolytic expectorant)	25%
Goldenseal (anticatarrhal)	25%

In vitro, quite a number of herbs have been shown to have antiviral activity, at least against herpesvirus. Lemon balm has been the subject of more investigations than many other herbs and may be worth including.

Human herbalists may recommend any of the following for "the common cold": Yarrow, Garlic or Onion, Horseradish, Mustard, Cayenne, Boneset, Chamomile, Peppermint, Elder, and Linden.

Another strategy for chronic cat flu is to provide concentrated mushroom extracts, which can be given in small doses mixed with food. The author's cat (SW) loves fresh mushrooms.

Rhinitis/sinusitis

Therapeutic Rationale

- Depends on cause, which may be infectious, neoplastic, allergic, or traumatic, or may be related to a foreign body.

For allergic rhinitis/sinusitis, a typical formula might contain these ingredients:

- Nettle or butterbur (antiallergic)
- Goldenseal, Pleurisy root, Ephedra, or Euphrasia (anticatarrhal)

One prescription for idiopathic sinusitis/rhinitis is provided:

Echinacea	20% (immune enhancing, anti-inflammatory, antibacterial, antiviral, vulnerary)
Nettle	20% (astringent, circulatory stimulant, nutritive, hemostatic)
Eyebright	20% (anticatarrhal, astringent, anti-inflammatory)
Elder flowers	20% (anticatarrhal, diaphoretic)
Marshmallow	20% (demulcent, vulnerary)

Pneumonia; lower respiratory infection

Therapeutic Rationale

- Address cause of infection through culture and sensitivity testing.
- Move airway mucus.
- Provide immune support.

Although antibiotics are necessary for life-threatening infection, herbs may provide support that is particularly helpful for chronic cases. A basic recipe on which to build would include:

Echinacea (immune stimulating, antimicrobial)	35%
Astragalus (immune stimulating)	15%
Fennel or thyme (mucolytic expectorant)	25%
Garlic or elecampane (stimulating expectorant)	25%

Historical recipes for large animals featured stimulating expectorants prominently, along with demulcents. Titus gives a recipe for an expectorant powder that contains 2 oz powdered ipecac, 2 oz powdered lobelia, 2 oz powdered bloodroot, and 4 oz powdered licorice.

For cough in cattle, Titus recommended the following recipe, mixed and divided into 6 parts, with 1 part being administered every 6 hours in linseed tea, or as a ball in syrup:

Powdered elecampane	2 oz
Powdered licorice root	2 oz
Powdered anise seed	2 oz
Powdered honey	4 oz

For cough in sheep, Titus recommended the following, mixed and given as 1 gill every 6 hours:

Lobelia *root*	1 drachm
Licorice root	4 drachm
Bloodroot	2 drachm
Mandrake root	2 drachm
Boiling water	1 quart

After this formula began to "work on the bowels," he recommended administering a teaspoonful of the following combination three times daily:

Powdered licorice root	2 oz
Powdered ipecac	2 drachm

For pneumonia in swine, the recipe was as follows:

Lobelia herb	4 oz
Licorice	2 oz
Boiling water	4 quarts

The tea was administered 1 gill at a time, every 15 to 20 minutes, until symptoms abated; then, the following mixture was administered:

Mandrake root	1 oz
Cream of tartar	2 oz

This was to be divided into 6 doses and given every 6 hours until signs improved.

HERBS FOR URINARY TRACT CONDITIONS

General Considerations

In the urinary system, the emphasis is on supporting the normal functioning of the kidneys and bladder, which is to excrete metabolic wastes in urine. It is no surprise that traditional herbal medicine "diuretics" played an important role in the treatment of urinary tract disorders. However, the term *diuretic* in herbal medicine is not the same as that in conventional medicine; it can be used in a number of other ways. Traditionally, herbs were given as a decoction or infusion for urinary conditions, and the additional water consumption would have produced an observable diuresis. Hence, many herbs were classified as diuretics, whether they had genuine diuretic action or not. The "flushing" of the bladder naturally assisted in

the treatment of cystitis. This strategy can also be employed in treating animals. Simply encouraging animals to drink more water or broth may accomplish the same end. Nonetheless, in many traditional herbal writings, diuretics were herbs that were considered to enhance excretion of waste through the kidneys (perhaps better classed as "diuretic depuratives"); they included herbs like Dandelion leaf *(Taraxacum officinale),* Cleavers *(Gallium aparine),* Burdock *(Arctium lappa),* Red clover *(Trifolium pretense),* Heartsease *(Viola tricolor),* and Celery *(Apium graveolens)*. Improving elimination through other systems of the body with the use of these alteratives and diuretics was another important strategy that aided one of the most important elimination systems—the urinary tract.

Mechanisms of Interest

Diuretics

Although diuretics might not be the most important agents needed in the treatment of urinary tract disorders, many of the herbs outlined in the following section have diuretic activity that might be useful. Herbal diuretics may also be useful in cases of edema or fluid retention and tissue congestion, and in their role as gentle "blood cleaners," when an excess of metabolic waste is being filtered through the kidneys.

In Europe, phytotherapists have proposed the term *Aquaretic* to describe those herbs that create actual diuresis. It is suggested that these herbs act directly on the glomerulus to increase water excretion, but their impact on electrolytes is neutral (Werk, 1994). In other words, aquaretics work by promoting the formation of urine. Diuretic activity may also be due to the mineral (electrolyte) content of herbs. In decoctions of herbs traditionally regarded as diuretics, the ratio of potassium to sodium was found to be higher compared with other herbs (Szentmihályi, 1998).

Herbs with diuretic or aquaretic activity are discussed here.

NETTLE *(URTICA DIOICA):* In an open, uncontrolled study, 32 patients with myocardial or chronic venous insufficiency were treated with 15 mL of nettle juice three times daily for 2 weeks (ESCP, 1999). A significant increase in daily volume of urine was observed throughout the study, and it has been proposed that the diuretic activity of aqueous extracts of nettle may be attributed to the high potassium content (Szentmihályi, 1998).

PARSLEY *(PETROSELINUM CRISPUM):* Edema and dropsy have been treated with parsley traditionally in Europe. Galen said, "It provoketh the urine mightily." In France, it was used to treat kidney stones. One experimental study provides evidence for the advocated diuretic effect. Rats offered an aqueous parsley seed extract to drink eliminated a significantly larger volume of urine per 24 hours as compared with when they were drinking water. The mechanism of action of parsley seems to be mediated through an inhibition of the Na^+-K^+ pump that would lead to a reduction in Na^+ and K^+ reabsorption, leading thus to an osmotic water flow into the lumen, and diuresis (Kreydiyyeh, 2002).

CORN SILK *(ZEA MAYS):* This herb is stated to possess diuretic and stone-reducing properties. It has been used for cystitis, urethritis, nocturnal enuresis, prostatitis, and, specifically, acute or chronic inflammation of the urinary system (Wren, 1988). The diuretic action confirmed in animals may be due to the high concentration of potassium (2.7%) (Bradley, 1992). Maizenic acid is also claimed to be active; it acts as a cardiac tonic, thus stimulating diuretic action (Willard, 1991). However, no influence of corn silk was recorded for 12- and 24-hour urine output, or sodium excretion, in people tested under standardized conditions in a placebo-controlled, double-blind, crossover model (Doan, 1992).

BUCHU *(AGATHOSMA BETULINA):* This is stated to possess urinary antiseptic and diuretic properties. It has been used for cystitis, urethritis, prostatitis, and, specifically, acute catarrhal cystitis (Wren, 1988).

CELERY *(APIUM GRAVEOLENS):* This herb is stated to possess mild diuretic and urinary antiseptic properties. It has been used for urinary tract inflammation (Wren, 1988).

COUCH GRASS *(AGROPYRON REPENS):* This plant is stated to possess diuretic properties. It has been used for cystitis, urethritis, prostatitis, benign prostatic hypertrophy, renal calculus, lithuria, and, specifically, cystitis with irritation or inflammation of the urinary tract (Wren, 1988). It contains mannitol as a constituent, which is an osmotic diuretic that in small quantities may confer a mild diuretic effect.

LAVENDER *(LAVANDULA OFFICINALIS):* The aqueous extract of lavender was compared with acetazolamide. It accelerated elimination of fluid and, at the peak of diuretic response, urinary osmolarity was significantly less than controls; sodium excretion was moderate compared with a synthetic diuretic acetazolamide. The stability of aldosterone and the absence of correlation with plasma sodium concentrations, coupled with the observed clearance of free water, show that the increase in diuresis is of tubular origin (Elhajili, 2001).

DANDELION *(TARAXACUM OFFICINALIS):* A diuretic effect in rats and mice was documented in early studies for dandelion extracts, following oral administration (Rácz-Kotilla, 1974). Herb extracts were found to produce greater diuresis than root extracts; a dose of 50 mL (equivalent to 2 g dried herb/kg body weight) produced an effect comparable with that of furosemide, at 80 mg/kg. By contrast, no significant increases in urine volume or sodium excretion were observed in mice following oral administration of leaf or root extracts, or of purified fractions (Hook, 1993). Similarly, oral and intravenous administration of an ethanolic extract of dandelion root failed to produce a diuretic effect in laboratory animals (Tita, 1993).

JUNIPER *(JUNIPERUS COMMUNIS):* According to some sources, juniper increases urine volume without loss of electrolytes such as potassium (Blumenthal, 2000). The diuretic activity of juniper berries is attributed to the volatile oil terpinen-4-ol and to hydrophilic constituents that are reported to increase the glomerular filtration rate (Tyler, 1993). Terpenin-4-ol is also stated to be an irritant to the kidneys, although in a later review by the same

author, no such statement was made, and the oil was stated to represent no hazards (Tisserand, 1995).

BEARBERRY *(ARCTOSTAPHYLOS UVA URSI):* An aqueous extract was tested for diuretic activity in rats; pharmacologic evaluation revealed that it led to an increase in urine flow (Beaux, 1999).

TRIBULUS *(TRIBULUS TERRESTRIS):* In rats, the aqueous extract of *T. terrestris,* in an oral dose of 5 g/kg, elicited a positive diuresis, which was slightly greater than that of furosemide. Na^+, K^+, and Cl^- concentrations in the urine had also increased greatly (Al Ali, 2003).

OTHER HERBS: A total of 23 herbs traditionally used as diuretics were examined for their effects on horse kidney (Na^+ + K^+)–adenosine triphosphatase (ATPase). Among these Atractylodes *(Atractylodes lanceae* and *A. japonica), Plantago asiatica herb and seed,* and Alisma *(Alisma orientalis)* were shown to have strong inhibitory effects on kidney (Na^+ + K^+)-ATPase activity (Satoh, 1991).

Anti-inflammatory herbs

KAVA *(PIPER METHYSTICUM):* Traditional uses listed for kava rhizome in standard herbal and pharmaceutical reference texts include cystitis, urethritis, infection or inflammation of the genitourinary tract, and rheumatism (British Herbal Medicine Association, 2003).

Antilithics

Antilithic herbs are used to dissolve urinary stones and reduce their formation; they may also help a patient to expel stones. Possible mechanisms of action are discussed in the following paragraphs.

Seven plants with suspected application to prevent and treat kidney stone formation were studied. Changes in urolithiasis risk factors (i.e., citraturia, calciuria, phosphaturia, pH, and diuresis) were evaluated. The herb infusions were believed by the author to cause change primarily due to disinfectant action and because of saponin content. Some solvent action was postulated due to alkalinizing capacity of some of these infusions (Grases, 1994). These include Vervain *(Verbena officinalis),* Lithospermum *(Lithospermum officinale),* Dandelion *(Taraxacum officinale),* Horsetail *(Equisetum arvense),* Bearberry *(Arctostaphylos uva ursi),* Burdock *(Arctium lappa),* and Tufted catchfly *(Silene saxifraga).*

CORN SILK *(ZEA MAYS):* In rats, corn silk was investigated in terms of risk factors for kidney stones; however, an extract did not influence citraturia, calciuria, or urinary pH (Grases, 1994).

FENUGREEK SEEDS *(TRIGONELLA FOENUM-GRAECUM):* Another study investigated the effect of fenugreek seed on experimentally induced kidney stones. Oxalate urolithiasis in male rats was produced by 3% glycolic acid in the diet. Daily treatment with fenugreek significantly decreased the quantity of calcium oxalate deposited in the kidneys. These results supported the similar use of fenugreek in Saudi folk medicine (Ahsan, 1989).

COUCH GRASS *(AGROPYRON REPENS):* This plant did not appear to have any effect on the main urolithiasis risk factors in calcium oxalate urolithiais in rats (Grases, 1995).

STONEROOT *(COLLINSONIA CANADENSIS):* This is stated to possess antilithic, litholytic, mild diaphoretic, and diuretic properties. Traditionally, it has been used for renal calculus, lithuria, and, specifically, urinary calculus (British Herbal Pharmacopoeia, 1983; Wren, 1988).

GRAVELROOT *(EUPATORIUM PURPUREUM):* This herb is stated to possess antilithic, diuretic, antiinflammatory and antirheumatic properties. Traditionally, it has been used for urinary calculus, cystitis, dysuria, urethritis, prostatitis, rheumatism, gout, and, specifically, renal or vesicular calculi (British Herbal Pharmacopoeia, 1983; Wren, 1988, Habtemariam 2001).

HYDRANGEA *(HYDRANGEA ARBORESCENS):* This is stated to possess diuretic and antilithic properties. Traditionally, it has been used for cystitis, urethritis, urinary calculi, prostatitis, enlarged prostate gland, and, specifically, urinary calculi with gravel and cystitis (British Herbal Pharmacopoeia, 1983; Wren, 1988).

CRANBERRY *(VACCINIUM MACROCARPON):* In a study undertaken to investigate the potential influence of cranberry juice on urinary biochemical and physicochemical risk factors associated with the formation of calcium oxalate kidney stones, the ingestion of cranberry juice significantly altered three key urinary risk factors. Oxalate and phosphate excretion decreased, and citrate excretion increased. In addition, a decrease was noted in the relative supersaturation of calcium oxalate, which tended to be significantly lower than that induced by water alone. It was concluded that cranberry juice has antilithogenic properties (McHarg, 2003). However, cranberry juice has a moderately high concentration of oxalate, a common component of kidney stones in humans. In five healthy volunteers, urinary oxalate levels in volunteers significantly increased by an average of 43.4% while they were receiving cranberry tablets. The excretion of potential lithogenic ions calcium, phosphate, and sodium also increased. However, inhibitors of stone formation—magnesium and potassium—rose as well (Terris, 2001).

CRATAEVA *(CRATAEVA NURVALA):* This herb significantly inhibited bladder stone formation in an experimental model in rats. The bladders of treated animals showed less edema, ulceration, and cellular infiltration when compared with those of controls (Deshpande, 1982). A crude extract at 100 mg/kg given orally to rats significantly reduced stone formation (81%) (Prabhakar, 1997). The effects of oral administration of *Crataeva nurvala* bark decoction on calcium oxalate lithiasis have been studied in rats. Crataeva reduced the oxalate-synthesizing liver enzyme, glycolate oxidase, which is produced by the feeding of glycolic acid; this caused a regulatory action on endogenous oxalate synthesis. Increased deposition of stone-forming constituents in the kidneys of calculogenic rats was lowered with decoction administration. Increased urinary excretion of the crystalline constituents, along with lowered magnesium excretion, in stone-forming rats was partially reversed by decoction treatment (Varalakshmi, 1990). Among 46 human patients with calcium oxalate stones that used 50

mL decoction twice daily for between 1 and 47 weeks, 28 passed the stone and 18 experienced symptomatic relief. This is thought to be due to the tonic contractile action of the drug on smooth muscle (Deshpande, 1982). Stem bark decoction was used in patients with calcium oxalate stones. After 12 weeks, a significant reduction in pain and dysuria was observed, along with some reduction in the size of stones (Singh, 1991).

TRIBULUS *(TRIBULUS TERRESTRIS):* An ethanolic extract of tribulus fruits showed significant dose-dependent protection against induced uroliths in rats. It protected against deposition of calculogenic material around a glass bead, and it also protected leukocytosis and elevation in serum urea levels (Anand, 1994). In addition to its diuretic activity, *T. terrestris* evoked contractile activity on guinea pig ileum. The diuretic and contractile effects of *T. terrestris* suggest that it may have the potential to propel urinary stones (Al Ali, 2003).

Bladder tonics

Bladder tonics are used to improve the tone of the bladder smooth muscle and are ideal for neurologic conditions of the bladder. They can also be used for more efficient voiding of urine in cystitis, when residual urine increases the risk of bacterial infection, so they may be useful with recurrent cystitis. The most useful tonic is Crataeva.

CRATAEVA *(CRATAEVA NURVALA):* In human studies, 50 mL decoction given twice daily for 3 months significantly improved incontinence, pain, and retention in prostatic hypertrophy with hypotonic bladder (Deshpande, 1982). After 4 weeks of treatment, 68% had symptomatic relief of chronic urinary tract infection, and 17% were devoid of microorganisms and neutrophils (Deshpande, 1982). Water extract of the stem bark improved smooth muscle tone (intestine and ureters) of guinea pigs, dogs, and humans, as well as skeletal muscle, in vitro (Das, 1974). After oral treatment with Crataeva for 40 days, a significant increase in bladder tone was noted in dogs (Deshpande, 1982).

Renal protective agents/kidney tonics

Traditionally, kidney tonics (in Western herbal medicine) have been used in conjunction with diuretic depuratives to improve kidney function; they may also provide a protective effect.

ASTRAGALUS *(ASTRAGALUS MEMBRANACEUS):* Proteinuria is regarded as a marker for significant renal injury and as a contributor to renal pathology. Astragalus can increase albumin level in plasma, decrease the output of urinary protein, and increase muscle protein. These actions may help prevent glomerular sclerosis (Zhou, 1999). Oral doses improve renal function in rats with experimental nephritis, and large doses are traditionally used in the treatment of chronic nephritis (Chang, 1987). A total of 30 human patients with chronic glomerulonephritis were enrolled in an open study. After injection of 40 mg/day for 3 weeks, proteinuria dropped dramatically—by more than half (Shi, 2002). Two other studies in 106 patients with chronic glomerulonephritis and in animal models that included immune complex nephritis have also demonstrated the ability of Astragalus to significantly reduce proteinuria (Peng, 2005). Thus, the effects of Astragalus on reduction of proteinuria may have benefit in slowing the progression of renal disease. In another study, serum creatinine was significantly reduced and creatinine clearance increased in patients treated with 32 g of Astragalus per day, compared with controls, in whom no significant change was observed (Zhao, 2000).

CHAMOMILE *(MATRICARIA RECUTITA):* This volatile oil has been documented to reduce the serum concentration of urea in rabbits with experimentally induced uremic conditions (Grochulski, 1972).

EVENING PRIMROSE *(OENOTHERA BIENNIS):* Prostaglandins of the E series are believed to be important in maintaining adequate renal blood flow. Administration of Evening primrose to animals has been reported to prevent or attenuate renal damage. Effects of orally administered *Oenothera biennis* on chronic renal failure were studied in partially nephrectomized rats. Compared with control groups, the group treated with Oenothera showed that urine protein excretion was reduced, serum cholesterol was decreased, levels of PGE_1 and PGE_2 were increased in renal cortex and medulla, 6-keto PGF_1-alpha was increased in cortex, and thromboxane 2 production was increased at only 4 weeks after nephrectomy. Glomerular lesions were more severe in the control group (Bi, 1992). A single, placebo-controlled trial involving human patients postrenal transplantation demonstrated a better graft survival rate for the group receiving evening primrose oil (45 patients) compared with the placebo group (44 patients) (Horrobin, 1990).

CORDYCEPS *(CORDYCEPS SINENSIS):* Cordyceps is regarded in Traditional Chinese Medicine as a premier "kidney tonic" that may prevent gentamicin-induced nephrotoxicity in animals. Cordyceps ameliorated deterioration of tubule metabolism and ion transport (Tian, 1991a), promoted DNA synthesis of kidney cells, lessened urinary β-N-acetylglucosaminidase and lysozyme levels, and delayed proteinuria (Tian, 1991b, 1991c). A comparative clinical study of Cordyceps (3-5 g/day) was conducted in 51 patients with chronic renal failure. In all, 28 received Cordyceps and showed a significant increase in renal function and T-lymphocyte subsets, including the T helper cell ratio, compared with the control group (Guan, 1992).

LICORICE *(GLYCYRRHIZA GLABRA):* This herb and two constituents—glycyrrhizin and 3-glycyrrhetinic monodesmoside—significantly suppressed lactate dehydrogenase leakage and malondialdehyde release from renal cells subjected to hypoxia–reoxygenation, whereas glycyrrhetinic acid had no effect. However, in rats subjected to ischemia–reperfusion, activities of endogenous antioxidant enzymes, including catalase and glutathione peroxidase, showed recovery, whereas levels of urea nitrogen and creatinine in serum were reduced by oral administration of glycyrrhizin (2.5 or 10 mg/kg daily) for 30 days before ischemia–reperfusion. Results indicated that licorice may be promising for amelioration of hypoxia–reoxygenation injury and for improvement of renal function in that it acts directly or indirectly as an

antioxidant and an oxygen radical scavenging agent (Yokozawa, 2000).

ASTRAGALUS *(ASTRAGALUS MONGHOLICUS)* AND DONG QUAI *(ANGELICA SINENSIS):* These plants have been used in China to treat patients with nephrotic syndrome. Rats with chronic induced nephrosis were treated with astragalus and dong quai or enalapril and were compared with control rats. Astragalus and dong quai significantly reduced deterioration of renal function and histologic damage. This combination of herbs slowed the progression of renal fibrosis and the deterioration of renal function with effects comparable to enalapril (Wang, 2004). The primary cause of anemia of chronic renal failure (CRF) is insufficient production of erythropoietin by diseased kidneys. *Angelica sinensis* improved red blood cell parameters in a person who was nonresponsive to erythropoietin administration (Bradley, 1999).

NETTLE SEED *(URTICA DIOICA):* This was first suggested by North American herbalist David Winston for the treatment of renal disease. Treasure (2003) reported two cases of humans with persistently elevated serum creatinine that required them to undergo chronic dialysis. A hydroethanolic (1:5) tincture of nettle seed (5 mL given three times daily) led to reductions in serum creatinine in both patients. In one patient, discontinuing the nettle seed was associated with a subsequent rise in creatinine, and when the herb was started again, the creatinine fell once more.

PERILLA LEAVES *(PERILLA FRUTESCENS):* A decoction of perilla leaves had suppressive effects on the progression of glomerulonephritis in an animal model of spontaneous immunoglobulin (Ig)A nephropathy. The active constituent rosmarinic acid was identified as causing the in vitro antiproliferative effects of perilla decoction (Makino, 2001).

TRIPTERYGIUM WILFORDII: This plant reduced proteinuria, and remission was gained, in 83% of human patients with nephritic syndrome at 2 mg/kg/day for at least 4 weeks (Peng, 2005).

CHUAN XIONG *(LIGUSTICUM WALLICHII):* This herb has been evaluated in many clinical studies for its effects in reducing serum creatinine, increasing creatinine clearance, and reducing proteinuria. Studies on the phenolic constituent sodium ferulate suggest that it corrects abnormal endothelial gene expression, and that the reduction in proteinuria or improvement in renal functional deterioration associated with the correction of an endothelial disorder (Peng, 2005).

Spasmolytics

Many spasmolytic herbs have been discovered. Some that should be considered for urinary disorders, such as the pain of interstitial cystitis or passing a kidney stone, are discussed here.

CRAMP BARK *(VIBURNUM OPULUS):* According to King's (Felter, 1898), this herb has been used for spasmodic contraction of the bladder, as well as for spasmodic stricture.

PUMPKIN SEED *(CUCURBITA PEPO):* The expressed oil of pumpkin seeds, in doses of 6 to 12 drops given several times a day, is said to be an efficient diuretic that provides relief in "scalding of urine, spasmodic affections of the urinary passages" (Felter, 1898).

OTHER HERBS: A combination of uva ursi, hops, and peppermint has been used to treat patients with compulsive strangury, enuresis, and painful micturition. Of 915 patients treated for 6 weeks, success was reported in about 70% (Lenau, 1984).

Urinary tract demulcents

The mucopolysaccharide layer produced by the transitional cells that coat the bladder plays an important role as a defense mechanism of the lower urinary tract. Traditionally, demulcents have been thought to soothe the mucous membrane lining of the urinary tract; therefore, they have been used in inflammatory conditions such as cystitis. It is probable that some of these herbs may work to improve the integrity of this layer through their influence on the mucous membrane, but a paucity of data supports this. For example, carbenoxolone, derived from licorice, was shown to provide a protective effect in laboratory-induced lower urinary tract infection in the rabbit model; in the same way, it is used to treat peptic ulcers in people (Mooreville, 1983).

MARSHMALLOW *(ALTHAEA OFFICINALIS):* Mucilage content ranges from 10% to 20%, and this herb may work through a reflex effect.

COUCH GRASS *(AGROPYRON REPENS):* This plant contains both triticum 3% to 8%—a polysaccharide related to inulin—and 8% to 10% mucilage.

CORN SILK *(ZEA MAYS):* This plant contains allantoin, which is a vulnerary.

LICORICE *(GLYCYRRHIZA GLABRA):* This herb may provide reflex demulcency.

Urinary antiseptics/antimicrobials

These herbs produce metabolites that are excreted in urine, and they exert their antiseptic effects there. Compared with antibiotics, this effect is expected to be mild; however, these agents may have a role in chronic or recurrent urinary tract infection. Herbs with antiseptic activity include the following.

CRANBERRY *(VACCINIUM MACROCARPA):* Cranberry juice and crushed cranberries have a long history of use in the treatment and prevention of urinary tract infection (Kingwatanakul, 1996). Initially, it was thought that the antibacterial effect of cranberry juice was a result of its ability to acidify urine and, therefore, to inhibit bacterial growth. However, recent work has focused on the effects of cranberry in inhibiting bacterial adherence and on the effects of antiadhesion agents in cranberry juice. Bacterial adherence to mucosal surfaces is considered to be an important step in the development of urinary tract infection (Reid, 1987). It is facilitated by fimbriae on the bacterial cell wall, which produce adhesins that attach to specific receptors on uroepithelial cells (Beachey, 1981). Proanthocyanidins extracted from cranberries have been shown to inhibit the adherence of P-fimbriated *Escherichia coli* to uroepithelial cell surfaces, suggesting that proanthocyanidins may be important for the stated effects of cranberry in urinary tract infection (Howell,

1998). Cranberry juice cocktail provided antiadherence activity directed toward gram-negative rods, including *Klebsiella, Enterobacter, Pseudomonas,* and *Proteus* species (Schmidt, 1988). In a review of two randomized controlled trials, it was found that cranberry (as juice or capsule) significantly reduced the incidence of urinary tract infection in women. Evidence supports the use of cranberry to prevent urinary tract infection in some populations, but none to support its use as a treatment (Griffiths, 2003).

BUCHU *(AGATHOSMA BETULINA):* In 1821, it was introduced from Africa into Great Britain as an official medicine for treating cystitis, urethritis, nephritis, and catarrh of the bladder (Grieve, 1931). Urinary tract antiseptic actions of buchu are thought to be due to the volatile oils. The primary volatile oil component thought to have antibacterial action is the monoterpene disophenol. However, one test tube study of buchu oil found no significant antibacterial effect (Didry, 1982). Very low activity was observed against *Escherichia coli, Saccharomyces cerevisiae,* and *Staphylococcus aureus,* suggesting little potential for use as an antimicrobial agent (Lis-Balchin, 2001).

UVA URSI *(ARCTOSTAPHYLOS UVA URSI):* Uva ursi is stated to possess diuretic, antiseptic, and astringent properties. Traditionally, it has been used for cystitis, urethritis, dysuria, pyelitis, lithuria, and, specifically, acute catarrhal cystitis with dysuria and highly acidic urine (British Herbal Pharmacopoeia, 1983; Wren, 1988). The antiseptic and diuretic properties claimed for uva ursi can be attributed to its hydroquinone derivatives, especially the constituent arbutin. Arbutin is absorbed intact from the gastrointestinal tract and during renal excretion is hydrolyzed to yield the active principle, hydroquinone, which exerts antiseptic and astringent actions on the urinary mucous membranes (Matsuda, 1992b). In a double-blind, placebo-controlled, randomized clinical trial, 57 women with more than three episodes of cystitis in the previous year received herbal extract or placebo. The herbal medicine consisted of bearberry and dandelion root and leaf. Treatment for 1 month significantly reduced the recurrence of cystitis during the 1-year follow-up, with no cystitis in the treated group and 23% recurrence in the placebo group. No adverse effects were reported (Larsson, 1993). It should be noted that alkaline urine is necessary for arbutin to work. Urinary acidifiers inhibit the conversion of arbutin to an active hydroquinone, making uva ursi less effective (De Smet, 1993).

COUCH GRASS *(AGROPYRON REPENS):* Broad antibiotic activity has been documented for agropyrene and its oxidation products (Leung, 1980).

GOLDENROD *(SOLIDAGO VIRGAUREA):* Fresh Solidago tincture was evaluated in a double-blind, placebo-controlled trial of patients with urinary tract infection. A significant rise (30%) in the amount of secreted urine was observed after a single dose of 100 drops (4-5 mL). A subsequent open trial showed that 70% of patients experienced improvement in symptoms such as dysuria, frequency, and tenesmus (Bruhwiler, 1992).

SAW PALMETTO *(SERENOA REPENS):* This herb is stated to possess diuretic, urinary antiseptic, endocrinologic, and anabolic properties. Traditionally, it has been used for chronic or subacute cystitis, catarrh of the genitourinary tract, testicular atrophy, sex hormone disorders, and, specifically, prostatic enlargement (British Herbal Pharmacopoeia, 1983; Wren, 1988).

Urinary tract astringents

PLANTAIN *(PLANTAGO MAJOR):* This plant is stated to possess diuretic and antihemorrhagic properties. Traditionally, it has been used for cystitis with hematuria and for hemorrhoids with bleeding and irritation (British Herbal Pharmacopoeia, 1983; Wren, 1988).

HORSETAIL *(EQUISETUM ARVENSE):* This has traditionally been used for gravel ulcerations in the urinary tract and for kidney affectations generally. It can be used for irrigation therapy for bacterial and inflammatory diseases of the lower urinary tract and renal gravel (American Botanical Council, 1998). Its hemostyptic effect may be due to silicic acid or flavonoids.

Alkalinizing agents

Cranberry juice has the ability to lower urinary pH (Jackson, 1997). In patients with urostomy, peristomal skin problems are common and may stem from alkaline urine. In a study on patients with human urostomy, drinking cranberry juice did not appear to acidify the urine, as expected; however, improvements were seen in the skin conditions of study participants, suggesting that drinking cranberry juice does positively affect the incidence of skin complications among these patients (Tsukada, 1994).

Review of Specific Urinary Tract Conditions

Cystitis

Therapeutic Rationale

- Evaluate for predisposing causes, such as infection, environmental and food allergies, impaired immune function, and chronic constipation.
- Encourage diuresis by providing broths and soups.
- Provide a source of glycosaminoglycans.

Prescription 1 for cystitis: For recurrent cystitis, rotate between prescriptions. Use alcohol or glycetract tinctures for best results; alternatively, use teas.

Crataeva	20% (antilithic, bladder tonic, anti-inflammatory)
Licorice	20% (anti-inflammatory, adaptogen, antispasmodic, taste improver, demulcent)
Corn silk	20% (diuretic, demulcent, antilithic)
Marshmallow	20% (demulcent, vulnerary, diuretic)
Horsetail	20% (genitourinary astringent, antihemorrhagic)

Prescription 2 for cystitis: Use alcohol or glycetract tinctures for best results; alternatively, use teas.

Goldenrod	20% (anti-inflammatory, antiseptic, diuretic, carminative)
Buchu	20% (diuretic, antiseptic)
Uva ursi	20% (urinary antiseptic, astringent)
Corn silk	20% (diuretic, demulcent, antilithic)
Bilberry	20% (antioxidant, astringent, anti-inflammatory)

Bladder stones—urolithiasis

Therapeutic Rationale

- Enhance diuresis.
- Reduce mucosal inflammation.
- Reduce smooth muscle spasm.
- Control infection, where appropriate.
- Initiate stone dissolution, if possible.
- Restore mucosal polysaccharide layer.
- Avoid using high doses of vitamin C, where appropriate.

A prescription for bladder stones is given here:

Use alcohol or glycetract tinctures for best results; alternatively, use teas.

Crataeva	20% (antilithic, bladder tonic, anti-inflammatory)
Hydrangea	20% (diuretic, antilithic, antihyperprostatic)
Marshmallow	20% (demulcent, vulnerary, diuretic)
Gravelroot	20% (antilithic, diuretic)
Licorice	20% (anti-inflammatory, adaptogen. laxative, taste improver)

Incontinence

Therapeutic Rationale

- Improve sphincter tone.
- Improve bladder tone.
- Reduce odor.
- Prevent infection from residual urine.

Cranberry will help reduce odor of urine; use capsules or powder and add to food.

A prescription for incontinence support follows:

Crataeva	40% (antilithic, bladder tonic, anti-inflammatory)
Uva ursi	20% (urinary antiseptic, astringent)
Marshmallow	20% (demulcent, vulnerary, diuretic)
Add Chaste tree	20% for females (or Saw palmetto 20% for males).

Alternate uva ursi with couch grass or bilberry or horsetail over time.

Interstitial cystitis and feline lower urinary tract disease

Therapeutic Rationale

- Reduce inflammation.
- Reduce pain.
- Relieve stress.
- Improve integrity of bladder wall.
- Reduce risk of uroliths.
- Consider a source of glycosaminoglycans.

Consider Horsetail for irrigation therapy for FLUTD as a tea or diluted tincture, for its astringent, antihemorrhagic, anti-inflammatory, and diuretic properties.

A prescription for feline cystitis is provided:

Crataeva	20% (antilithic, bladder tonic, anti-inflammatory)
Marshmallow	40% (demulcent, vulnerary, diuretic)
Saint John's Wort	20% (antidepressant, nervine tonic, vulnerary, anti-inflammatory)
Horsetail	20% (genitourinary astringent, antihemorrhagic)

Another prescription for interstitial cystitis is:

Kava kava	40% (anxiolytic, anti-inflammatory)
Saint John's Wort	30% (anxiolytic, analgesic)
Marshmallow	30% (demulcent)

A traditional Kampo formula, Choreito, has been investigated in the treatment of lower urinary tract disease in cats. Choreito (Zhu Ling San) has been shown to decrease struvite crystalluria and hematuria in cats (Buffington, 1994, 1997a, 1997b).

Kidney disease

Kidney fibrosis is a common sequel of chronic kidney disease. Standard treatment includes dietary phosphorus restriction, maintenance of proper hydration, blood pressure control, use of angiotensin-converting enzyme inhibitors and aspirin for proteinuria, and so forth. Evidence suggests that there is value in using herbal medicine, including nephroprotective herbs. Many Chinese herbs have been investigated, including Astragalus, Angelica, Ligusticum, Tripolide, and Rhubarb, and some have been shown to slow the progression of chronic kidney disease. On the other hand, some herbs can be nephrotoxic or hazardous to patients with renal disease, so caution is required (Peng, 2005).

A prescription for chronic renal disease is given here:

Marshmallow	20% (demulcent, vulnerary, diuretic)
Rehmannia	20% (anti-inflammatory, antihemorrhagic, antipyretic)
Astragalus	40% (immune modulating, tonic, hypotensive, renal protective)
Siberian ginseng	20% (adaptogenic, immune modulating)

A second prescription is provided:

Rehmannia	25% (anti-inflammatory, antihemorrhagic, antipyretic)
Cordyceps	25% (nephroprotective, immune modulating)
Astragalus	25% (immune modulating, tonic, hypotensive, renal protective)
Nettle seed	25% (reduces creatinine)

Many herbalists use the traditional Chinese formula (Jin Gui Shen Qi Wan or Ba Wei Wan) (Rehmannia, 8) to successfully slow the progression of chronic kidney disease.

HERBS FOR TOPICAL USE

This section presents well-known and less-recognized herbs that are used topically to enhance wound healing, reduce inflammation, and shrink or cause necrosis of tumors. Information on traditional uses comes from the popular herb literature, most of it (and wherever quotes are found below) from *King's American Dispensatory,* 1898 version, by Felter and Lloyd. Scientific literature searches were done on Medline, Google, and the websites of the Southwest School of Botanical Medicine and HealthNotes online. Search terms were generally of two types: (1) the word "herbal" plus the mechanism of action, and (2) the individual herb name, sometimes narrowed with the descriptor "topical" or "topically."

Definitions (from Merriam-Webster Online and Traditional Sources)

Fomentation
The application of hot, moist substances to the body to ease pain, or (as a noun) the material so applied.

Plaster
A medicated or protective dressing that consists of a cloth or plastic film spread with a medicated substance.

Poultice
A soft, usually heated medicated mass spread on cloth and applied to cutaneous lesions.

Compress
A folded cloth or pad applied so as to press upon a body part.

Ointment
A salve or unguent for application to the skin.

Salve
An unctuous adhesive substance for application to wounds or sores.

Cataplasm
Synonymous with plaster or poultice.

Anodyne
An agent that relieves pain via topical application.

Astringent
A substance that contracts and firms tissues and organs; a styptic; an agent that decreases secretions.

Counterirritant
A substance that is externally applied to relieve deep-seated pain by way of causing hyperemia or local irritation.

Demulcent
A substance that soothes, protects, and restores mucous membranes and relieves irritation of inflamed or abraded surfaces, usually through mucilage content.

Embrocation
A liquid or wash applied to a diseased or painful part, usually by rubbing; liniment.

Escharotic
A caustic or corrosive that is capable of producing a slough or eschar (scab).

Hemostatic
A substance that stops the flow of blood.

Rubefacient
Something that reddens the skin by causing capillary dilation from external application.

Scrofula
Tuberculosis or other swellings of the lymph nodes, especially of the neck

Styptic
Something that contracts or binds to prevent bleeding; it stops blood flow by constricting blood vessels.

Vesicant
A substance that causes blistering.

Vulnerary
An agent that aids in wound and skin healing.

TYPES OF TOPICAL APPLICATIONS USED IN VETERINARY PATIENTS

Herbs may be applied to the eyes in the form of infusions, usually water infusions. Stomatitis may be treated with the use of infusions or decoctions (well filtered) administered from a spray bottle. Prescribers should remember that many herbs taste bad, and animals may not accept treatment unless the herb is diluted with a sweet liquid such as juice. Ear treatments may consist of water or oil infusions or decoctions applied as ear drops. Tinctures are usually diluted with an active or inactive vehicle to prevent alcohol from causing pain in inflamed or ulcerated ear canals. Wounds may be best managed with wet or wet-dry dressings, with the use of infusions or decoctions of the herb. Oil infusions or ointments may provide a protective coating for open wounds, chronic ulcers, and so forth.

Cautions

Many of the herbs listed are toxic (e.g., Chinaberry, Henbane, Hellebore, Mayapple) or caustic (e.g., Bloodroot, Chelidonium), if ingested. Readers should refer to individual herb monographs for further information on toxicity.

Mechanisms of Interest

Ectoparasiticidal herbs

Fleas: Fleas are a constant problem in warm climates. Commercial flea sprays and powders are available, mostly based on Neem and various aromatic herbs (e.g., cedar, rosemary). These have not been evaluated critically, to our knowledge.

Flies: Herbal sprays are available to horsekeepers; they generally contain combinations of aromatic herbs and Neem. These must be applied frequently if they are to be effective, especially if the horses sweat a lot. These have not been evaluated critically, to our knowledge.

PYRETHRUM *(TANACETUM CINERARIIFOLIUM* OR *CHRYSANTHEMUM CINERARIIFOLIUM):* This agent is the source of pyrethrins used in commercial natural flea products.

CHASTE TREE *(VITEX ANGUS-CASTUS):* A study suggests that a CO_2 extract of the seeds of the Mediterranean plant Vitex agnus castus (monk's pepper) can be used as a spray to repel especially Ixodes ricinus and Rhipicephalus sanguineus ticks from animals and humans for at least 6 hours. In addition mosquitoes, biting flies and fleas were also repelled for about 6 hours (Mehlhorn 2005).

LOUSEWORT *(DELPHINIUM STAPHISAGRIA LINN):* A traditional flea remedy, found in veterinary school notes from the early 1900s, was based on Stavesacre or Lousewort seed. Instructions were given as follows: "Crush 1 oz Stavesacre seed well, and boil for 2 hours in 20 to 30 oz of water, making up the original quantity used, and use as a wash."

NEEM *(AZADIRACHTA INDICA):* This herb may be potentially useful for managing flea and tick infestation in dogs and cats. Azadirachtin and other constituents in various parts of this tree possess more than one mode of action against insects. These include antifeedancy, growth regulation, fecundity suppression and sterilization, oviposition repellency or attractancy, changes in biological fitness, and blockage of the development of vector-borne pathogens. Some of these activities have been studied in mosquitoes, flies, cockroaches, fleas, lice, and other parasites of veterinary importance (Mulla, 1999). In a study in which topical Neem extract was used on both dogs and cats, 1000 to 2400 ppm azadirachtin reduced fleas on Greyhounds and cats by 53% to 93% in a dose-dependent manner for 19 days (Guerrini, 1998). Clinical experience suggests that Neem spray should be applied every few days.

FLEABANE *(ERIGERON CANADENSE):* This herb has been used for many centuries (Aristotle mentions it). The traditional recommendation is to repel fleas by burning the herb, but some sources recommend rubbing the herb on clothing (or the fur for animals) or applying extracts topically. No data are available to support the use of fleabane for fleas.

LABRADOR TEA *(LEDUM GLANDULOSUM* OR *LEDUM LATIFOLIUM):* King's claims that the plant was strewn among clothes to prevent moth damage, and that a strong decoction used externally was effective against lice and other insects.

AZEDARACH *(MELIA AZEDARACH):* The "pulp" of this tree has been used in traditional medicine for destroying human ectoparasites. Azedarach extracts were shown to kill *Boophilus microplus* tick larvae (Borges, 2003). Sixteen of 17 species of parasitic insects consumed significantly less food when treated with an extract of the fruit (Carpinella, 2003). Poisoning caused by eating the berries has been reported in a number of mammalian species.

CHAULMOOGRA, GYNOCARDIA *(GYNOCARDIA ODORATA):* This herb had a reputation among the Eclectics for destroying lice and scabies mites.

PARSLEY *(PETROSELINUM SATIVUM):* When an ointment was prepared with the use of seeds and leaves, or when the seeds and leaves were powdered, this was said to be effective in destroying "vermin."

IVY *(HEDERA HELIX):* This was said to kill "vermin in the hair, which, it is stated, is stained black by the application."

PERU BALSAM TREE *(MYROXYLON PEREIRAE):* This was used for the treatment of scabies. It was administered as the balsam, 40 drops over the whole body (of a human) for 2 days. It has been known to lead to contact hypersensitivity.

WHITE HELLEBORE *(VERATRUM ALBUM):* This was used as a decoction or ointment to kill lice and scabies; however, the plant is highly toxic and teratogenic and should be avoided because animals often lick topical applications.

Astringent herbs

TEA *(CAMELLIA SINENSIS):* This has been used for burns and excoriations. In veterinary medicine, a particularly useful application is for moist dermatitis and traumatic dermatitis, or "hot spots." Tea catechins, when applied percutaneously in the ears of mice and given orally, inhibited signs of oxazolone-induced type IV allergy (Suzuki, 2000). The saponins also reduce allergy mediator release in in vitro studies (Akagi, 1997). The tannins are astringent and may coagulate serum proteins in oozing lesions.

WITCH HAZEL *(HAMAMELIS VIRGINIANA):* Witch hazel bark contains catechins and has barrier-stabilizing, antimicrobial, and anti-inflammatory activities (Gloor, 2002; Hughes-Formella, 2002; Erdelmeier, 1996; Duwiejua, 1994). The Eclectics used it in poultice form for painful swellings, tumors, and external inflammation. It was also popular, in decoction form, for treating mouth inflammation and ulcers. Typical over-the-counter witch hazel products are preserved with alcohol and may cause irritation.

GERANIUM, CRANESBILL *(GERANIUM MACULATUM):* This herb has a variety of uses because of its astringency, including ulcers. It may also be used for hot spots and excoriations.

GNAPHALIUM, WHITE BALSAM *(GNAPHALIUM POLYCEPHALUM):* This was used in fomentation form for bruises, tumors, and other focal cutaneous problems.

HEUCHERA, ALUM ROOT *(HEUCHERA AMERICANA):* This is considered a very strong astringent and was used for all kinds of mucosal hemorrhage (e.g., epistaxis, wounds, nonhealing ulcers).

MOUNTAIN ASH FRUIT, SORBUS FRUIT *(PYRUS AUCUPARIA, SORBUS AUCUPARIA):* These were used primarily in poultice form.

BLACK OR WHITE ASH TREE BARK *(FRAXINUS SAMBUCIFOLIA, FRAXINUS AMERICANA):* This was used in plaster form and was considered tonic as well as astringent.

STATICE, MARSH ROSEMARY *(STATICE CAROLINIANA):* This was used as a gargle or mouthwash for sore throat and mouth ulcers, and as a decoction for eye inflammation. The powdered root was applied directly to nonhealing ulcers or was mixed into an ointment.

NETTLE, STINGING NETTLE *(URTICA DIOICA):* This powdered leaf or infusion can be used as a styptic for bleeding surfaces such as abrasions or hot spots.

Antibacterial herbs

ECHINACEA *(ECHINACEA PURPUREA, E. ANGUSTIFOLIA):* One of the most important traditional uses for this plant was as a wash or dressing for snake and spider bites,

or "other envenomations that lead to necrosis; crush injuries leading to necrosis and infection. . . . [Think of Echinacea for] swelling when extensive, tense, and of a purplish-red hue. . . ." Echinacoside and the polyacetylene constituents have antibacterial activity, and the polyacetylenes have antifungal activity (Bisset, 1994); however, Echinacea demonstrated a propensity for increasing bacterial resistance in vitro by greatly increasing the minimum inhibitory concentration of ampicillin against *E. coli* (Ward, 2002). Nonetheless, it is potentially indicated when given as simultaneous oral medication and topical dressing for serious and infected wounds, snake and brown recluse spider bites, and cat abscesses. An interesting ancillary effect is that Echinacea acts as a mild anodyne.

TEA TREE *(MELALEUCA ALTERNIFOLIA):* This herb was used by the Eclectics as mild anodyne for neuralgic pain, but also for various cutaneous problems and to relieve the pain of toothache. Tea tree oil has shown activity in vitro against Malassezia yeast (Weseler 2002; Hammer 2000), and Staphylococcus aureus (including resistant strains)(Halcon 2004), in addition to other skin pathogens. In a clinical case series of dogs treated with a 10% preparation of tea tree for dermatitis, the authors suggested that tea tree oil was effective in reducing the signs of dermatitis (Fitzi 2002). Tea tree has potential as a diluted wound dressing, and in diluted form for other infections such as otitis. Undiluted tea tree oil is highly toxic to cats and potentially toxic to small dogs as well. This author (SW) uses 10% as the highest concentration, but adverse events may still occur.

BASIL *(OCIMUM GRATISSIMUM):* This agent is not used traditionally as a topical antimicrobial, but it has potential. In one trial, Ocimum gratissimum oil was found to be equivalent to conventional treatments for acne (Ernst, 2003). Thyme *(Thymus vulgaris)* and various species of Sage (*Salvia* species, especially *S. apiana*) are also used as antibacterial herbs.

Demulcent herbs

QUINCE SEED *(CYDONIA VULGARIS):* This herb was used by the Eclectics as a mucilage to soothe oral lesions such as aphthous ulcers and excoriations, as well as for conjunctivitis.

OKRA *(HIBISCUS ESCULENTUS):* Seed pods and leaves both contain mucilage and can be used as wound dressing in the form of a cataplasm.

PSYLLIUM *(PLANTAGO MAJOR):* This seed contains large amounts of mucilage; one study showed that the capillary action that draws water away from wounds inhibits bacterial growth (Westerhof, 2001). This herb has been used since the time of Gerard, who wrote, "The seed stamped, and boyled in water to the forme of a plaister, and applied, taketh away all swelling of the joynts, especially if you boyle the same with vinegar and oyle of Roses, and apply it as aforesaid . . . unto any burning heate . . . or any hot and violent impostume [abscess], asswageth the same. . . ."

MULLEIN *(VERBASCUM THAPSUS):* These leaves have been used as a fomentation for inflamed hemorrhoids and ulcers.

FENUGREEK *(TRIGONELLA FOENUM-GRAECUM):* This herb, prepared as a poultice or decoction (1 oz of seeds in 1 pint of water) of the seeds, has been used on inflamed mucous membranes, for instance, for throat, rectal, and vaginal irritation.

Hemostatic herbs

YUNNAN PAI YAO: This proprietary Chinese formula is said to be composed of *Panax notoginseng,* San Yu Cao *(Ajuga patantha), Dioscorea opposita,* Chuan Shan Long *(Dioscorea nipponica),* Lao Guan Cao *(Erodium stephanianum), Alpinia officinarum,* Bai Niu Dan, and *Dryobalanops aromatica* (or *Blumea balsamifera*) (package label, 2005). Alternatively, some formulas contain *(Panax pseudoginseng or Radix notoginseng),* and variously Chinese yam *(Dioscorea opposita),* yam rhizome *(Dioscorea hypolglauca),* sweet geranium *(Erodium stephanianum),* and galangal rhizome *(Alpinia officinarum)* (Polesuk 1973). It is used orally and locally to stop bleeding. Studies show decreased bleeding times in an animal model and possible effects on blood platelets (Ogle, 1977; Ogle, 1976).

NETTLE, STINGING NETTLES *(URTICA DIOICA):* This is traditionally used as a styptic for bleeding.

ZONAL GERANIUM *(PELARGONIUM ZONALE):* This species forms the basis for decorative pot geraniums. The juice has been applied to staunch bleeding, and one study in a rat model confirmed its efficacy (Paez, 2003).

RHATANY, KRAMERIA *(KRAMERIA TRIANDRA):* This herb contains tannins and is high in proanthocyanidins. It has been used in epistaxis, bleeding from tooth extraction sites, wounds, anal fissures, and bleeding gums. One traditional preparation used tinctures of rhatany and myrrh mixed with chalk. Contact hypersensitivity has been reported with this herb.

MATICA *(PIPER ANGUSTIFOLIUM):* This leaf has been used to stop hemorrhage from wounds and leech bites.

Escharotic herbs

CHELIDONIUM *(CHELIDONIUM MAJUS):* A patented extract, Ukrain, has documented cytostatic and cytotoxic effects against a number of cancer cell lines and has immunemodulatory activity as well. Preclinical studies in humans with cancer have been promising (Ernst 2005; Uglyanitsa 2000). This herb was used traditionally as a caustic to remove warts and stimulate healing of indolent ulcers and ringworm. It was also used on the cornea for removal of opacities. It is said to cause inflammation and vesication when applied to normal skin. Contact dermatitis and hepatotoxicity after oral ingestion have been reported.

BLOODROOT *(SANGUINARIA CANADENSIS):* This herb is part of the most popular escharotic salves (or black salves) available today, which also include zinc chloride and perhaps other herbs such as galangal root. Clinical experience among multiple veterinarians has been good for small cutaneous tumors. Tumor removal was not an indication for this plant in Eclectic medicine. An extract, sanguinarine, initiates apoptosis in certain tumor cells (Ahmad, 2000). In a clinical series, escharotic ointments that contained bloodroot were effective in removing tumors locally but did not prevent metastasis (McDaniel,

2002). Animals must be prevented from licking the salve. Long-term use of sanguinarine in toothpaste in humans is suspected to be a cause of leukoplakia. Long-term oral ingestion of sanguinarine has led to "epidemic dropsy."

PRICKLY POPPY *(ARGEMONE MEXICANA):* This herb was used topically for warts, chancres, and ulcers. It contains sanguinarine, which may in part account for an escharotic-like effect. Oral ingestion causes "epidemic dropsy," a generalized vasculitis that may lead to respiratory impairment, renal tubular necrosis, generalized edema, and death.

Herbs for warts, corns

In small animal practice, clients complain that their dogs develop warts, which are usually sebaceous gland adenomas or other benign tumors. One experimental treatment that is being explored by herbalists at the time of this writing is black salve (see the section on tumors, later).

DROSERA *(DROSERA ROTUNDIFOLIA):* This has been used for corns and warts; however, the plant is highly endangered in the wild and should not be used.

HAWKWEED *(HIERACIUM VENOSUM):* Fresh juice from the leaves has been recommended to remove warts.

MOSSY STONECROP (*SEDUM* SPP): This is said to be a topical vesicant if the leaves are pounded and applied fresh to warts, corns, and other small growths.

CASHEW NUT RIND JUICE *(ANACARDIUM OCCIDENTALE):* This herb is an irritant in the poison ivy family; it has been used to stimulate indolent ulcers, as well as to remove warts and corns.

NETTLE, STINGING NETTLES *(URTICA DIOICA):* In King's, this herb is said to make warts disappear with no pain, if they are rubbed with fresh nettle juice 3 to 4 times daily for 10 to 12 days.

THUJA *(THUJA OCCIDENTALIS):* This herb is popular today for removal of warts and similar growths, such as sebaceous adenomas. It can be used in ointment or tincture form (although the tincture may be more effective). King's claimed that it was effective on most warts, except for rapidly growing venereal warts.

MAYAPPLE *(PODOPHYLLUM PELTATUM)* (GREEN OR DRIED ROOT): This was said to cause irritation and suppuration when applied continuously to warts. Podophyllin, an extract of *Podophyllum peltatum,* is effective in the treatment of human warts (Miller, 1996; White, 1997).

Counterirritants

Capsaicin is a modern example of a counterirritant, which can be used to relieve deep-seated local painful conditions, such as arthritis and shingles. Counterirritants relieve pain locally, possibly via substance P–mediated mechanisms.

MUSTARD *(SINAPISA ALBA, S. NIGRA):* Applied topically, this herb causes inflammation, stinging pain, scaling, and, if left long enough, ulceration. The goal was to cause reddening of the skin, but not vesication or ulceration. "Sinapisms" were applied to the abdomen and spine to relieve discomfort or signs of gastrointestinal inflammation, such as vomiting, pain, or even constipation; on the chest for painful chest disorders such as pleurisy; or on the head for headaches. It was also applied to other areas as a rubefacient to relieve local pain caused by joint inflammation. It was applied as a plaster using equal parts wheat or rye flour and lukewarm water with $^{1}/_{12}$ to 2 drops of mustard oil dissolved in a mucilaginous herb, or as a liniment composed of 1 part oil in 16 parts alcohol or 10 parts carrier oil.

AMMONIAC *(DOREMA AMMONIACUM):* This is a similar irritant and was formerly used for buboes, joint tumors, enlarged glands, and "other indolent swellings."

OTHER HERBS: Various species of *Clematis* contain triterpenoid saponins. One, *C. hirsutissima,* is a known blistering agent and was used by Native Americans as a "horse stimulant."

Herbs for Eyes

Herbs can be used in infusion form in the eyes, but irritating forms such as alcohol extracts must be avoided. Sterility is a concern, and if teas are made fresh, they must be cooled while covered, and made fresh every day.

EUPHRASIA *(EUPHRASIA OFFICINALIS):* This herb is used for conditions that produce serous or mucoid discharges of the eye. An uncontrolled case series that used *Euphrasia rostkoviana* for catarrhal conjunctivitis resulted in resolution or improvement in 98.5% of treated patients (Stoss, 2000). It is most often used for allergic or irritant conjunctivitis.

GOLDENSEAL *(HYDRASTIS CANADENSIS):* This is a fairly common prescription for conjunctival inflammation, superficial corneal ulcers, and blepharitis.

DUSTY MILLER, SILVER RAGWORT *(SENECIO MARITIMA):* This has been used, especially as a topical homeopathic preparation, for cataracts, on the basis of early laboratory animal studies. The herb is irritating and must be used in very diluted form.

RED ROSE *(ROSA GALLICA):* This was used as a poultice, sometimes in infusion form with the pith of sassafras, for acute conjunctivitis.

PRICKLY POPPY *(ARGEMONE MEXICANA):* This herb is an irritant that was formerly used for corneal opacities and some forms of chronic conjunctivitis.

LOOSESTRIFE, LYTHRUM *(LYTHRUM SALICARIA):* This herb has been used for chronic conjunctivitis and keratitis, as well as for corneal ulcers.

BLACK HAW *(VIBURNUM PRUNIFOLIUM):* This was used for "various ophthalmic disorders."

OTHER HERBS: Sunflower (Helianthus annuus), Galbanum (Ferula galbaniflua), Tall Ambrosia, Great Ragweed (Ambrosia trifida), Wild Cherry Bark (Prunus serotina), and Chamomile (Matricaria recutita) were also used for conjunctivitis (called "ophthalmia" in older texts). The pith mucilage of Pitcher plant *(Sarracenia purpurea)* was also used—2 drachms to 1 pint of water.

Herbs for Ears

GOLDENSEAL *(HYDRASTIS CANADENSIS):* This was said to be specifically indicated for purulent otitis media,

both acute and chronic, otitis externa, and "irritation due to inspissated cerumen." King's recommended about 10 drops of a 1:1 up to a 1:8 solution dropped into the ear, or it could be mixed with a preparation of witch hazel. Berberine has antibacterial activity against *Staphylococcus* and other bacteria, and topical use is most likely to repeat the success demonstrated in in vitro studies.

PRIVET LEAVES *(LIGUSTRUM VULGARE):* Infusion was said to be indicated for ulcerated ears.

WITCH HAZEL *(HAMAMELIS VIRGINICA):* This herb was often used with glycerin, or with an equal measure of goldenseal, for otitis externa.

MULLEIN *(VERBASCUM THAPSUS):* Flowers infused in oil were used primarily for deafness, to normalize cerumen production, and for some possible benefit to an inflamed tympanic membrane.

Base formula for yeast or bacterial otitis (not to be used in place of the appropriate antibiotic for bacterial infections):

Aloe vera gel	40%-50%
Goldenseal	30%-40%
Thyme or white sage (as an antibacterial)	10%-15%
Tea tree (dogs only)	5%-10%

Herbs for Stomatitis

It is important to note that human patients can be instructed to use herbs as a gargle or mouthwash without swallowing the herbs. If these herbs are used in animals, it may be advisable to use a lower dose in the form of a spray. If an herb is nontoxic or is not contraindicated for concurrent medical disorders, herbs may be mixed in liquefied food (such as baby food) for increased contact time with the oral mucosa. Most of the herbs below (except for the astringents) are strongly bitter, and creative flavoring should be attempted to gain the animal's cooperation for more than one treatment!

BAPTISIA *(BAPTISIA TINCTORIA):* This herb is specifically indicated for severe, painful oral ulceration.

MYRRH *(COMMIPHORA MYRRHA):* This has been used for oral ulcerations, pharyngitis, and dental caries. Extracts of myrrh have antibacterial and analgesic activities (Dolara, 2000).

BLOODROOT *(SANGUINARIA CANADENSIS):* Multiple studies suggest efficacy against gingivitis/periodontal disease and plaque build-up; however, the possibility exists that sanguinarine-containing products are associated with a preneoplastic lesion known as leukoplakia. This is a strong plant, and animals should be prevented from ingesting it chronically.

GOLDENSEAL *(HYDRASTIS CANADENSIS):* This herb was thought by the Eclectics to be indicated specifically for subacute or chronic stomatitis. Berberine and two other extracts of goldenseal root showed antibacterial activity against oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum* (Hwang, 2003). Other plants containing berberine that have been recommended for stomatitis are Goldthread *(Coptis trifolia)* and Barberry *(Berberis vulgaris)*.

OTHER HERBS: Agrimony (Agrimonia eupatoria), Heuchera, Alum Root (Heuchera americana), and Cranesbill (Geranium maculatum) have been used as astringent gargles for mouth and throat ulceration.

Other herbs that have been used for mouth and throat ulceration or inflammation include Amaranth, Tall ambrosia or Great ragweed *(Ambrosia trifida),* Red root or New Jersey tea *(Ceanothus americanus),* Persimmon, Diospyros *(Diospyros virginiana),* Epilobium or Willow herb *(Epilobium angustifolium, E. palustre),* Rockbrake or Common brake *(Pteris atropurpurea,* other species*),* Gnaphalium or White balsam *(Gnaphalium polycephalum),* Twinleaf or Jeffersonia *(Jeffersonia diphylla),* Privet leaves *(Ligustrum vulgare),* Statice or Marsh rosemary *(Statice caroliniana),* Bellwort *(Uvularia perfoliata),* Blue whortleberry *(Vaccinium frondosum),* Pokeweed *(Phytolacca decandra, P. dodecandra, P. americana),* Kino *(Pterocarpus marsupium),* Helenium or Frostwort *(Helianthemum canadense),* Oak gall *(Quercus lusitanica),* and Bayberry *(Myrica cerifera)*.

Antipruritics

BLACK OR GREEN TEA *(CAMELLIA SINENSIS):* Tea catechins, when applied percutaneously in the ears of mice and given orally, inhibited signs of oxazolone-induced type IV allergy (Suzuki, 2000). The saponins also reduce allergy mediator release in in vitro studies (Akagi, 1997). The tannins are astringent and may coagulate serum proteins in oozing lesions, such as in acute traumatic dermatitis or hot spots.

GELSEMIUM *(GELSEMIUM SEMPERVIRENS):* This herb appears to act as an anodyne, which is possibly the reason for traditional use for focal pruritus. This is a potentially toxic herb, and animals should not be allowed to lick any topical preparation of gelsemium.

CAYENNE *(CAPSICUM FRUTESCENS):* An extract of capsicum, capsaicin is well accepted as a topical analgesic in human medicine. In a trial of capsaicin to suppress pruritus in dogs, owners found it to be effective; investigators did not (Marsella, 2002).

Anodyne

CAYENNE *(CAPSICUM FRUTESCENS):* This herb was formerly used more as a counterirritant than as an anodyne. The isolated constituent capsaicin has been well investigated as an anodyne and is in commercial trade as Capsaizin. If the animal can be prevented from licking the area, it should be effective for local pain of osteoarthritis or neuritis. The taste itself may act as a deterrent to licking!

NETTLE, STINGING NETTLES *(URTICA DIOICA):* In a controlled trial that examined "base of thumb pain" in humans, fresh nettle leaf applied to the area was significantly more effective in reducing pain than was placebo (Randall, 2000).

ECHINACEA ROOT *(ECHINACEA ANGUSTIFOLIA):* This herb has mild anodyne properties.

CONIUM, POISON HEMLOCK *(CICUTA MACULATA):* This extract, combined with petrolatum, was traditionally used as a poultice for painful tumors, ulcers, neuralgia, and so forth. This is a highly toxic herb and should not be used at all.

JIMSON WEED (ALSO KNOWN AS THORNAPPLE OR STRAMONIUM) *(DATURA STRAMONIUM)*, BELLADONNA *(ATROPA BELLADONNA)*, HENBANE *(HYOSCYAMUS NIGER):* These are other very poisonous plants that should be used only by experienced herbalists, if at all. They were used in ointment form or as fomentations for many local painful disorders such as painful ulcers, tumors, orchitis, and mastitis, but they should not be used in animals because they will lick the applications.

CHELONE *(CHELONE GLABRA):* This herb was used as an ointment for painful ulcers, tumors, mastitis, and hemorrhoids.

MIMULUS, MONKEY FLOWER *(MIMULUS PILOSUS):* This was used by bruising the leaves or as a hot infusion, as a cataplasm.

CYNOGLOSSUM *(CYNOGLOSSUM OFFICINALE):* This herb was particularly used for bruising or chapping, and an interesting indication was for "excoriation of the feet from much traveling."

OTHER HERBS: Lavender (Lavandula vera, L. officinalis, L. angustifolia), Meadow Lily (Lilium candidum) Flowers, Horsemint (Monarda punctata), and Spearmint (Mentha viridis) were used occasionally in fomentation or oil form for local pain. The plants are high in essential oils. Some Lily spp are toxic to cats.

Herbs for Snakebite

Many plants in many cultures have been identified as beneficial in the treatment of snake bites. Mors and colleagues (2000) reviewed these plants and tested some of the plant constituents in a murine snakebite model. The mice were given 100 mg/kg of a specific phytochemical orally 1 hour before subcutaneous injection with the venom of the jararaca snake *(Bothrops jararaca).* The capacity for these phytochemicals to prevent death from envenomation was expressed as percentage of surviving animals in each group. Beta-sitosterol administration resulted in 70% protection; this is a common plant sterol contained in Yarrow *(Achillea millefolium),* Calendula *(Calendula officinalis), Cynanchum paniculatum, Eclipta prostrata, Ocimum basilicum,* Saw palmetto (*Serenoa repens),* Dandelion *(Taraxacum officinale),* and many other herbs. Hydroxybenzoic acids and their methyl esters gave up to 83% protection. Plants that contain these acids include Bistort *(Polygonum bistorta),* Gentian *(Gentiana lutea),* and *Perilla ternata.* Coumarins gave 40% protection, and many flavonoids provided 40% to 80% survival. Secondary metabolites of plants appear to interact with snake venom proteins, either by blocking receptors, chelating enzymes, or inhibiting enzymes in other ways.

This review contains an extensive listing of plants with ethnobotanical data for use in snakebites. Some of the better known plants include *Acacia catechu, Achyranthes aspera, Agrimonia eupatoria, Allium cepa, Arctium lappa, Argemone mexicana, Belamcanda chinensis, Brunfelsia grandiflora, Buddleia brasiliensis, Chenopodium ambrosioides, Cimicifuga racemosa, Coffea arabica, Curcuma longa, Daphne mezereum, Echinacea anugustifolia, Foeniculum vulgare, Gymnema sylvestre, Impatiens balsamina, Impatiens capensis, Morus alba, Nerium oleander, Perilla frutescens, Phyllanthus amarus, Pinellia ternata, Plantago major, Pinus sylvestris, Polygala senega, Ruta graveolens, Strychnos nux-vomica, Thymus vulgaris, and Verbascum thapsus* (Mors, 2000).

LIATRIS SPECIES: Roots were bruised and applied directly to the bite, while the root was also decocted and mixed with milk to be administered orally.

ECHINACEA *(E. ANGUSTIFOLIA):* This herb was used by Native Americans for bites, and this was a primary indication for its use for many years.

LION'S FOOT, NABALUS *(NABALUS ALBUS):* This was used as the root decoction.

BELLWORT *(UVULARIA PERFOLIATA):* This herb was boiled in milk to be administered orally, and the root was applied as a poultice simultaneously.

Herb for Anal Fistula

SWEET GUM *(LIQUIDAMBAR STYRACIFOLIUM):* Resin was melted with equal parts of lard or tallow; this was used as an ointment for anal fistula in people.

Poison Ivy, Poison Oak Herbal Treatment

LOBELIA *(LOBELIA INFLATA):* This herb was used in infusion form on wet cloths that were applied frequently to affected areas.

PUSSY WILLOW, BLACK WILLOW *(SALIX NIGRA):* This was said to be very effective for this condition and was prepared by simmering powdered bark in cream.

JEWELWEED *(IMPATIENS BALSAMIFERA):* This well-known traditional remedy was used for poison ivy, and teachers often point out that it grows near poison ivy. One study demonstrated that an extract of jewelweed was ineffective in the treatment of poison ivy contact dermatitis (Long, 1997)

GRINDELIA *(GRINDELIA SQUARROSA)*, DIERVILLA, BUSH HONEYSUCKLE *(DIERVILLA TRIFIDA):* These were also used for poison ivy.

Vulnerary Herbs

Many, many herbs have been used to enhance wound healing. The list that follows was derived from the complete list of herbs in *King's American Dispensatory.* Clearly, some are more effective than others, but the large list below is provided because herbalists often find that they must use the herbs they have if the "best" choice is not available.

ALOE *(ALOE VERA):* This herb has been shown to enhance healing in surgically induced wounds in dogs (Swaim, 1992). Aloe also may have anti-inflammatory

and angiogenic properties, and it contains a glycoprotein that stimulates cell proliferation and migration (Vazquez, 1996; Moon, 1999; Choi, 2001).

PLANTAIN *(PLANTAGO LANCEOLATA, P. MAJOR):* The leaves contain constituents with antibacterial, antihistamine, neutrophil-chemotactic, antifungal, analgesic, and anti-inflammatory properties (Samuelsen, 2000). They have been used for all types of skin lesions and wounds since at least the time of Dioscorides and are favorite choices of herbalists worldwide because they grow nearly everywhere.

CALENDULA *(CALENDULA OFFICINALIS):* The petals for the basis for one of the most popular vulnerary herbs in trade. The herb may enhance epithelialization of wounds and may have mild anti-inflammatory properties (Klouchek-Popova, 1982). It was strongly recommended by the Eclectics and used for "cancerous and other ulcers . . . lacerated wounds . . . [enhances] wound healing by replacement or first intention. . . . It is to be made into a saturated tincture with whiskey diluted with one-third its quantity of water; lint is saturated with this, applied to the parts, and renewed as often as it becomes dry . . . to wash abscess cavities, to prevent cicatrization from burns and scalds, in eczematous and ulcerative skin diseases, vaginitis (wash or tampon) . . . calendula has received strong endorsement . . . applied diluted to inflamed conjunctival and aural tissues, and to traumatic injuries of the eye and ear."

GOTU KOLA *(CENTELLA ASIATICA):* This has been used for ulcers, chronic eczema, and other cutaneous disorders. Gotu kola is well documented to enhance wound healing. Mechanisms may include increase of extracellular matrix, angiogenesis, and various growth factors (Maquart, 1999; Coldren, 2003).

CHELIDONIUM *(CHELIDONIUM MAJUS):* This herb contains, among other alkaloids, berberine, which is antibacterial. The Eclectics found it a powerful vulnerary, recommending "an alcoholic tincture of the root (3 ounces to 1 pint) will be found an unrivaled external application to prevent or subdue traumatic inflammations." Contact dermatitis has been reported. As stated above, the herb can be toxic and animals should be prevented from licking it, if used.

ARNICA, LEOPARDS BANE *(ARNICA MONTANA):* This herb is in popular use, both as the herb and as the homeopathic remedy. It was used to prevent and treat local inflammation and bruising, and also as a dressing for cuts, lacerations, and bruises. In vitro studies show that Arnica inhibits activation of NF-kappa B and NF-AT, which leads to release of cytokines and inflammatory mediators (Klaas, 2002). Arnica may have mild antibacterial activity (Iauk, 2003), although other studies show no effect. Arnica is a contact allergen that may cause dermatologic reactions in some patients with repeated use (Reider, 2001). It is toxic, and animals should be prevented from licking it.

CHAMOMILE *(MATRICARIA RECUTITA):* This herb has many traditional uses, including as treatment for ruptured abscesses. Few studies have been done, but one showed very mild anti-inflammatory activity in a trial of treatment for atopic eczema (Patzelt-Wenczler, 2000). Chamomile is a contact sensitizer in susceptible patients.

GOLDENSEAL *(HYDRASTIS CANADENSIS):* This treatment was particularly indicated in Eclectic medicine for "eczematous manifestations around the outlets of the body . . ."

SAINT JOHN'S WORT *(HYPERICUM PERFORATUM):* This is used in oil or ointment form for painful ulcers, tumors, and bruises. An extract reduced T-cell proliferation in healing wounds (and the authors concluded that this was possible support for traditional wound healing use) (Schempp, 2000). Another specis, *H. patulum,* may enhance wound contraction and epithelialization (Mukherjee, 2000). Oral and topical use may lead to skin photosensitization.

BAY LAUREL, SWEET BAY *(LAURUS NOBILIS):* This is the bay leaf used in cooking. The leaves have been used in powder or decoction form for "insect bites and stings, scalp eruptions." Contact hypersensitivity has been reported.

ROAST OR BOILED FIGS *(FICUS CARICA):* These have been used for infected ulcers, boils, and so forth. No medicinal principles from figs have been specifically investigated; however, the sugar may be active. Sugar and honey have been used as an antibacterial and vulnerary agent for burns and ulcers (Tanne, 1988; Okeniyi, 2005; Dunford, 2005). Figs were used as a poultice when the dried fruit was added to milk.

LOBELIA *(LOBELIA INFLATA):* This herb was considered useful for a wide variety of disorders, including "herpes, lichen, eczema, nettlerash, . . . sprains, bruises, rheumatic pains, erysipelas, and erysipelous inflammations, tetter, and other forms of cutaneous diseases."

FIGWORT *(SCROPHULARIA NODOSA):* Three compounds in this plant stimulate human fibroblast activity in vitro (Stevenson, 2002). It has been used for hemorrhoids, ringworm, vesicular eruptions, painful swellings, and so forth.

OTHER HERBS: Herbs used for indolent cutaneous ulcers, felons, or slow-healing abscesses or wounds include False sarsaparilla, small spikenard *(Aralia nudicaulis),* Copaiba *(Copaiba langsdorffii),* Daphne or Mezereum *(Daphne mezereum),* cataplasm of bruised Cyclamin *(Cyclamen hederifolium)* tubers, Wild carrot *(Daucus carota),* Epiphegus *(Epiphegus virginiana),* Galbanum *(Ferula galbaniflua),* Grindelia *(Grindelia robusta),* Ivy *(Hedera helix),* Bayberry *(Myrica cerifera),* Virginia stonecrop *(Penthorum sedoides),* Poke root *(Phytolacca americana),* Bearsfoot, Polymnia *(Polymnia uvedalia),* Potentilla, Tormentil *(Potentilla tormentilla),* Black alder bark and berries *(Prinus verticillatus),* Wild cherry bark *(Prunus serotina),* Yellow dock *(Rumex crispus),* Sorrel *(Rumex acetosa),* White willow *(Salix alba),* Pussy willow, Black willow *(Salix nigra),* Mossy stonecrop *(Sedum),* Chickweed *(Stellaria media),* Thuja *(Thuja occidentalis),* Red clover *(Trifolium pretense),* Blue whortleberry *(Vaccinium frondosum),* Mullein *(Verbascum thapsus),* Cramp bark, highbush cranberry *(Viburnum opulus),* and Black Haw *(Viburnum prunifolium).* A few of these plants are irritants to stimulate healing, and the reader is advised to understand them well before using them.

Useful Web Sites
King's American Dispensatory
www.ibiblio.org/herbmed/eclectic/kings/main.html
Botanical Dermatology Database
bodd.cf.ac.uk/
Paula Begoun's Cosmetic Dictionary
www.cosmeticscop.com/learn/dictionary.asp?TYPE=MAIN

Herbs cited in traditional literature for "various cutaneous affections" include Canada thistle root *(Cirsium arvense),* Stoneroot *(Collinsonia canadensis)* as a poultice, Cynoglossum *(Cynoglossum officinale),* Helenium, Frostwort *(Helianthemum canadense),* Elecampane *(Inula helenium),* Ox-eye daisy *(Chrysanthemum leucanthemum),* Loosestrife, Lythrum *(Lythrum salicaria),* Smartweed or Water pepper *(Polygonum hydropiper),* Peru balsam tree *(Myroxylon pereirae),* Jack-in-the-Pulpit *(Arisaema triphyllum),* and Bellwort *(Uvularia perfoliata).*

Herbs used for external inflammation, excoriations, and burns include Fringe tree bark *(Chionanthus virginicus),* False bittersweet *(Celastrus scandens),* American larch *(Larix americana),* Meadow lily *(Lilium candidum),* Bugleweed *(Lycopus virginicus),* Catnip *(Nepeta cataria),* and Passionflower *(Passiflora incarnata).*

Herbs used for bruising and ecchymoses include the powdered flowers of Lily of the Valley *(Convallaria majalis),* the bruised leaves of Navelwort, Cotyledon *(Cotyledon umbilicus),* Hyssop *(Hyssopus officinalis)* leaves, and Pearly everlasting *(Antennaria margaritacea).*

Herbs used for various chronic eruptions such as psoriasis, eczema, ringworm, leprosy, and ulcers include Cleavers *(Gallium aparine),* Chaulmoogra, Gynocardia *(Hydnocarpus kurzii),* Ivy *(Hedera helix),* Jewelweed *(Impatiens pallida)* juice, Mountain laurel, Kalmia *(Kalmia latifolia)* leaves, Labrador tea *(Ledum latifolium),* Sweet gum *(Liquidambar styraciflua),* Kamala, Rottlera *(Mallotus phillipiensis, Echinus philippinensis, Rottlera tinctoria, Croton philippensis),* Azedarach or Chinaberry tree *(Melia azedarach),* Myrtle *(Myrtus communis),* and Nettle *(Urtica dioica).*

References

Abaineh D, Sintayehu A. Treatment trial of subclinical mastitis with the herb *Persicaria senegalense* (Polygonaceae). Trop Anim Health Prod 2001;33:511-519.

Abells Sutton G, Haik R. Efficacy of garlic as an anthelmintic in donkeys. Israel Journal Veterinary medicine Vol 54 (1), 1999.

Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med 2001;161:813-824.

ACP Australian College Phytotherapy. Course Notes, Module 4, Gastrointestinal System, 1999.

Ademola IO, Fagbemi BO, Idowu SO Anthelmintic activity of extracts of *Spondias mombin* against gastrointestinal nematodes of sheep: studies in vitro and in vivo. Trop Anim Health Prod 2005;37:223-235.

Adzet T, Camarasa J, Laguna JC. Action of an artichoke extract against CCl4-induced heptotoxicity in rats. Acta Pharm Jugosl 1987;37:183-187.

Ageel AM, Mossa JS, al-Yahya MA, al-Said MS, Tariq M. Experimental studies on antirheumatic crude drugs used in Saudi traditional medicine. Drugs Exp Clin Res 1989;15:369-372.

Ahmad N, Gupta S, Husain MM, Heiskanen KM, Mukhtar H. Differential antiproliferative and apoptotic response of sanguinarine for cancer cells versus normal cells. Clin Cancer Res 2000;6:1524-1528.

Ahsan SK, Tariq M, Ageel AM, al-Yahya MA, Shah AH. Effect of Trigonella foenum-graecum and Ammi majus on calcium oxalate urolithiasis in rats. J Ethnopharmacol 1989 Oct; 26(3):249-254.

Ajay M, Gilani AU, Mustafa MR. Effects of flavonoids on vascular smooth muscle of the isolated rat thoracic aorta. Life Sci 2003;74:603-612.

Akagi M, Fukuishi N, Kan T, Sagesaka YM, Akagi R. Anti-allergic effect of tea-leaf saponin (TLS) from tea leaves (*Camellia sinensis* var. sinensis). Biol Pharm Bull 1997;20:565-567.

Akhani SP, Vishwakarma SL, Goyal RK. Anti-diabetic activity of Zingiber officinale in streptozotocin-induced type I diabetic rats. J Pharm Pharmacol. 2004 Jan;56(1):101-105.

Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 2001a;26:363-367.

Akhondzadeh S, Kashani L, Mobaseri M, Hosseini SH, Nikzad S, Khani M. Passionflower in the treatment of opiate withdrawal: a double-blind randomized controlled trial. J Clin Pharm Ther 2001b;26:369-373.

Akhondzadeh S, Kashani L, Fotouhi A, et al. Comparison of *Lavendula angustifolia* Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 2003a;27:123-127.

Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial. J Neurol Neurosurg Psychiatry 2003b;74:863-866.

Al-Ali M, Wahbi S, Twaij H, Al-Badr A. *Tribulus terrestris:* preliminary study of its diuretic and contractile effects and comparison with *Zea mays*. J Ethnopharmacol 2003;85:257-260.

Al-Qarawi AA, Abdel-Rahman HA, Ali BH, El Mougy SA. Liquorice (Glycyrrhiza glabra) and the adrenal-kidney-pituitary axis in rats. Food Chem Toxicol. 2002 Oct;40(10): 1525-1527

al-Zuhair H, el-Sayeh B, Ameen HA, al-Shoora H. Pharmacological studies of cardamom oil in animals. Pharmacol Res 1996; 34:79-82.

Alarcon-Aguilara FJ, Roman-Ramos R, Perez-Gutierrez S, Aguilar-Contreras A, Contreras-Weber CC, Flores-Saenz JL. Study of the anti-hyperglycemic effect of plants used as antidiabetics. J Ethnopharmacol 1998;61:101-110.

Alacrìn De La Lastra C, Martin MJ, Marhuenda E: Gastric Anti-Ulcer Activity Of Silymarin, A Lipoxygenase Inhibitor, In Rats. J Pharm Pharmacol 1992;44:929-931.

Alarcon de la Lastra AC, Martin MJ, Motilva V, Jimenez M, La Casa C, Lopez A. Gastroprotection induced by silymarin, the hepatoprotective principle of Silybum marianum in ischemia-reperfusion mucosal injury: role of neutrophils. Planta Med. 1995 Apr;61(2):116-119.

Albert-Puleo M. Fennel and anise as estrogenic agents. J Ethnopharmacol 1980;2:337-344.

Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel *(Foeniculum vulgare)* seed oil emulsion in infantile colic: a randomized, placebo-controlled study. Altern Ther Health Med 2003;9:58-61.

Ali M, Thomson M. Consumption of a garlic clove a day could be beneficial in preventing thrombosis. Prostaglandins Leukot Essent Fatty Acids 1995;53:211-212.

Allen FM. Blueberry leaf extract: physiologic and clinical properties in relation to carbohydrate metabolism. JAMA 1927;89: 1577-1581.

Amellal M, Bronner C, Briancon F, et al. Inhibition of mast cell histamine release by flavonoids and bioflavonoids. Planta Medica 1985;51:16-20.

Ammon HP, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumine and boswellic acids. J Ethnopharmacol 1993;38:113-119.

Amri H, Drieu K, Papadopoulos V. Transcriptional suppression of the adrenal cortical peripheral-type benzodiazepine receptor gene and inhibition of steroid synthesis by ginkgolide B. Biochem Pharmacol 2003;65:717-729.

Anand R, Patnaik G, Kulshreshtha D. Activity of certain fractions of *Tribulus terrestris* fruits against experimentally induced urolithiasis in rats. Indian J Exp Biol 1994;32:548-552.

Anderson J, Smith W. The antitussive activity of glycyrrhetinic acid and its derivatives. J Pharm Pharmacol 1961;13:396-404.

Anderson PM, Meyers DE, Hasz DE, et al. In vitro and in vivo cytotoxicity of an anti-osteosarcoma immunotoxin containing pokeweed antiviral protein. Cancer Res 1995;55:1321-1327.

Archana R, Namasivayan A. Antistressor effect of *Withania somnifera*. J Ethnopharmacol 1999;64:91-93.

Armanini D, Karbowiak I, Funder JW. Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors. Clin Endocrinol 1983;19:609-612.

Armanini D, Strasser T, Weber PC. Binding of agonists and antagonists to mineralocorticoid receptors in human peripheral mononuclear leucocytes. J Hypertens 1985;3(3):S157-159.

Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods Hum Nutr. 2002 Winter;57(1):41-52.

Arzneimitteforschung 1996;46:389-394.

Atal CK, Sharma ML, Kaul A, Khajuria A. Immunomodulating agents of plant origin. I: Preliminary screening. J Ethnopharmacol 1986;18:133-141.

Auf'mkolk M, Kohrle J, Gumbinger H, et al. Antihormonal effects of plant extracts: iodothyronine deiodinase of rat liver is inhibited by extracts and secondary metabolites of plants. Horm Metab Res 1984a;16:188-192.

Auf'mkolk M, Ingbar JC, Amir SM, et al. Inhibition by certain plant extracts of the binding and adenylate cyclase stimulatory effect of bovine thyrotropin in human thyroid membranes. Endocrinology 1984b;115:527-534.

Austin S, Dale EB, DeKadt S. Long-term follow-up of cancer patients using Contreras, Hoxsey and Gerson therapies. Journal of Naturopathic Medicine 1994;5(1):74-76.

Awad R, Arnason JT, Trudeau V, et al. Phytochemical and biological analysis of skullcap *(Scutellaria lateriflora* L.*):* a medicinal plant with anxiolytic properties. Phytomedicine 2003;10: 640-649.

Aydin S, Beis R, Ozturk Y, Baser KH. Nepetalactone: a new opioid analgesic from *Nepeta caesarea* Boiss. J Pharm Pharmacol 1998;50:813-817.

Baba K, Abe S, Mizuno D. Antitumor activity of hot water extract of dandelion, *Taraxacum officinale*—correlation between antitumor activity and timing of administration. Yagugaku Zasshi 1981;101:538-543.

Babu TD, Kuttan G, Padikkala J. Cytotoxic and anti-tumour properties of certain taxa of Umbelliferae with special reference to *Centella asiatica* (L.) Urban. J Ethnopharmacol 1995;48:53-57.

Backhauss C, Krieglstein J. Extract of kava *(Piper methysticum)* and its methysticin constituents protect brain tissue against ischemic damage in rodents. Eur J Pharmacol 1992;215:265-269.

Balasenthil S, Arivazhagan S, Ramachandran CR, Ramachandran V, Nagini S. Chemopreventive potential of neem *(Azadirachta indica)* on 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinogenesis. J Ethnopharmacol 1999;67:189-195.

Balasenthil S, Ramachandran CR, Nagini S. Prevention of 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis by garlic. Fitoterapia 2001;72:524-531.

Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. J Clin Psychiatry 2002;63:553-558.

Baltina LA. Chemical modification of glycyrrhizic acid as a route to new bioactive compounds for medicine [Review]. Curr Med Chem 2003;10:155-171.

Baluchnejadmojarad T, Roghani M. Endothelium-dependent and -independent effect of aqueous extract of garlic on vascular reactivity on diabetic rats. Fitoterapia 2003;74:630-637.

Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutr J 2002;1:4.

Barsanti JA, Finco DR, Mahaffey MM, et al. Effects of an extract of *Serenoa repens* on dogs with hyperplasia of the prostate gland. Am J Vet Res 2000;61:880-885.

Basch EM, Ulbricht CE. *Natural Standard Herb and Supplement Handbook: The Clinical Bottom Line*. St. Louis, Mo: Elsevier-Mosby; 2005.

Basit N, et al. In vitro effect of extracts of *Euphorbia hirta* Linn. on *Entamoeba histolytica*. Riv Parasitol 1977;38:259-262.

Baumann G, Felix S, Sattelberger U, Klein G. Cardiovascular effects of forskolin (HL 362) in patients with idiopathic congestive cardiomyopathy—a comparative study with dobutamine and sodium nitroprusside. J Cardiovasc Pharmacol 1990;16:93-100.

Beachey EH. Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacteria to mucosal surface. J Infect Dis 1981;143:325-345.

Beaubrun G, Gray GE. A review of herbal medicines for psychiatric disorders. Psychiatr Serv. 2000 Sep;51(9):1130-1134.

Beaux D, Fleurentin J, Mortier F. Effect of extracts of *Orthosiphon stamineus* Benth., *Hieracium pilosella* L., *Sambucus nigra* L. and *Arctostaphylos uva-ursi* (L.) Spreng. in rats. Phytother Res 1999;13:222-225.

Beech J, Donaldson MT, Lindborg S. Comparison of *Vitex agnus castus* extract and pergolide in treatment of equine Cushing's syndrome. Proc AAEP 2002;48:177.

Beesley A, Hardcastle J, Hardcastle PT, Taylor CJ. Influence of peppermint oil on absorptive and secretory processes in rat small intestine. Gut 1996;39:214-219.

Beijamini V, Andreatini R. Effects of *Hypericum perforatum* and paroxetine in the mouse defense test battery. Pharmacol Biochem Behav 2003a;74:1015-1024.

Beijamini V, Andreatini R. Effects of *Hypericum perforatum* and paroxetine on rat performance in the elevated T-maze. Pharmacol Res 2003b;48:199-207.

Belford-Courtney R. Comparison of Chinese and Western uses of *Angelica sinensis*. Austral J Med Herbalism 1994;5:4,87-91.

Ben-Arye E, Goldin E, Wengrower D, Stamper A, Kohn R, Berry E. Wheat grass juice in the treatment of active distal ulcerative colitis: a randomized double-blind placebo-controlled trial. Scand J Gastroenterol 2002;37:444-449.

Bensoussan A; Talley NJ; Hing M; Menzies R; Guo A; Ngu M, 1998. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 11;280(18):1585-1589.

Bergner P. Immune treatment outcomes at Mexican cancer clinics: Hoxsey treatment may help some late stage cancer. Med Herbalism 1995;6:10.

Bergner P. Cardiotoxic effects of Blue Cohosh on a fetus. Available at: http://medherb.com/Materia_Medica/Caulophyllum_-_Cardiotoxic_effects_of_Blue_Cohosh_on_a_fetus.htm. Accessed June 13, 2005.

Bermejo Benito P, Abad Martinez MJ, Silvan Sen MJ. In vivo and in vitro antiinflammatory activity of saikosaponins. Life Sci 1998;63:1147-1156.

Bezakova L, Misik V, Malekova L, Svajdlenka E, Kostalova D. Lipoxygenase inhibition and antioxidant properties of bisbenzylisoqunoline alkaloids isolated from *Mahonia aquifolium*. Pharmazie 1996;51:758-761.

Bharani A, Ganguly A, Bhargava KD. Salutary effect of *Terminalia arjuna* in patients with severe refractory heart failure. Int J Cardiol 1995;49:191-199.

Bhatia N, Zhao J, Wolf DM, Agarwal R. Inhibition of human carcinoma cell growth and DNA synthesis by silibinin, an active constituent of milk thistle: comparison with silymarin. Cancer Lett 1999;147:77-84.

Bhattacharya SK, Mitra SK. Anxiolytic activity of *Panax ginseng* roots: an experimental study. J Ethnopharmacol 1991;34:87-92.

Bhattacharya SK, Satyan KS, Ghosal S. Antioxidant activity of glycowithanolides from *Withania somnifera*. Indian J Exp Biol 1997;35:236-239.

Bhattacharya SK, Ghosal S. Anxiolytic activity of a standardized extract of *Bacopa monniera:* an experimental study. Phytomedicine 1998;5:77-82.

Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Anxiolytic-antidepressant activity of *Withania somnifera* glycowithanolides: an experimental study. Phytomedicine 2000;7:463-469.

Bhattacharya SK, Muruganandam AV. Adaptogenic activity of *Withania somnifera:* an experimental study using a rat model of chronic stress. Pharmacol Biochem Behav 2003;75:547-555.

Bhuvaneswari V, Velmurugan B, Nagini S. Dose-response effect of tomato paste on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. J Exp Clin Cancer Res 2004a;23:241-249.

Bhuvaneswari V, Rao KS, Nagini S. Altered expression of anti and proapoptotic proteins during chemoprevention of hamster buccal pouch carcinogenesis by tomato and garlic combination. Clin Chim Acta 2004b;350:65-72.

Bi ZQ, Bo YH, Duan JH. [Treatment of chronic renal failure with *Oenothera beinnis* L. in rats with subtotal nephrectomy.] Zhonghua Nei Ke Za Zhi 1992;31:7-10,59.

Bianchini F, Vainio H. Wine and resveratrol: mechanisms of cancer prevention? Eur J Cancer Prev 2003;12:417-425.

Birks J, Grimley EV, Van Dongen M. *Ginkgo biloba* for cognitive impairment and dementia. Cochrane Database Syst Rev 2002;4:CD003120.

Bisset NG, ed. *Herbal Drugs and Phytopharmaceuticals* (Wichtl M, ed. [German edition]). Stuttgart: Medpharm; 1994.

Bliddal H, Rosetzsky A, Schlichting P, et al. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage 2000;8:9-12.

Block JR, Evans S. A review of recent results addressing the potential interactions of antioxidants with cancer drug therapy. JAMA 2001;4:11-19.

Blumenthal M, Busse WR, Goldberg A etal, eds. *The Complete German Commission E Monographs*. Austin, Tex: American Botanical Council; 1998.

Blumenthal M Busse WR, Goldberg A etal eds. *Herbal Medicine. Expanded Commission E Monographs*. Austin, Tex: American Botanical Council; 2000.

Bochorakova H, Paulova H, Slanina J, et al. Main flavonoids in the root of *Scutellaria baicalensis* cultivated in Europe and their comparative antiradical properties. Phytother Res 2003;17:640-644.

Boik J. *Cancer and Natural Medicine: A Textbook of Basic Science and Clinical Research*. Princeton, Minn: Oregon Medical Press; 1996.

Boik J. *Natural Compounds in Cancer Therapy*. Princeton, Minn: Oregon Medical Press; 2001.

Bomser J, Madhavi DL, Singletary K, Smith MA. In vitro anticancer activity of fruit extracts from *Vaccinium* species. Planta Med 1996;62:212-216.

Bond R, Lloyd DH. A double blind comparison of olive oil and a combination of evening primrose oil and fish oil in the management of canine atopy. Vet Rec. 1992;131(24):558-60.

Bond R, Lloyd DH. Combined treatment with concentrated essential fatty acids and prednisolone in the management of canine atopy. Vet Rec. 1994;134(2):30-32.

Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs—Monographs for the Western Herbal Practitioner.* Warwick, Queensland, Australia: Phytotherapy Press; 1996:94.

Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs—Monographs for the Western Herbal Practitioner.* Warwick, Queensland, Australia: Phytotherapy Press; 1997.

Bone K. Echinacea: when should it be used? Alt Med Rev 1997;2:451-458.

Bone K. Echinacea: useful for autoimmune disease? Eur J Herbal Med 1997-1998;3:13-17.

Bone K. Automimmune disease. Townsend Lett 1999;193:94-98.

Bone K. *A Clinical Guide to Blending Liquid Herbs*. St. Louis, Mo: Churchill Livingstone; 2003:197.

Bone K. Phytotherapy for autoimmune disease. Townsend Lett 2004;250.

Bonnett B, Poland C. Preliminary results of a randomized, double blind, multicenter, controlled clinical trial of two herbal therapies, acetylsalicylic acid and placebo for osteoarthritic dogs. Proceedings of the American Holistic Veterinary Medical Association. Burlington, Vt: AHVMA; 1996:143-147.

Borges LM, Ferri PH, Silva WJ, Silva WC, Silva JG. In vitro efficacy of extracts of *Melia azedarach* against the tick *Boophilus microplus*. Med Vet Entomol 2003;17:228-231.

Bradley PR, ed. *British Herbal Compendium,* vol 1. Bournemouth: British Herbal Medicine Association; 1992.

Bradley RR, Cunniff PJ, Pereira BJ, Jaber BL. Hematopoietic effect of *Radix angelicae sinensis* in a hemodialysis patient. Am J Kidney Dis 1999;34:349-354.

Braquet P. The ginkgolides: potent platelet-activating factor antagonists isolated from *Ginkgo biloba* L.: chemistry, pharmacology and clinical applications. Drugs Future 1987;12:643-699.

Braun JM, Ko HL, Schierholz JM, Beuth J. Standardized mistletoe extract augments immune response and down-regulates local and metastatic tumor growth in murine models. Anticancer Res 2002;22:4187-4190.

Braun L, Lester S, Kuzma AB, Hosie SC. Gastric dilatation-volvulus in the dog with histological evidence of preexisting inflammatory bowel disease: a retrospective study of 23 cases. J Am Anim Hosp Assoc 1996;32:287-290.

Brinker FJ. *Herb Contraindications and Drug Interactions*. Oregon: Eclectic Institute; 1997:104-106.

British Herbal Medicine Association. *A Guide to Traditional Herbal Medicines*. Bournemouth: British Herbal Medicine Association Publishing, 2003.

British Herbal Pharmacopoeia. Keighley: British Herbal Medicine Association; 1983.

Brousseau M, Miller SC. Enhancement of natural killer cells and increased survival of aging mice fed daily Echinacea root extract from youth. Biogerontology 2005;6:157-163.

Bruhwiler K, Frater-Sroder M, Kalbermatten R, et al. Golden Rod effective for urinary tract inflammation. International Congress on Phytotherapy; Munich, Germany; September 1992.

Bruneton J. *Pharmacognosy, Phytochemistry, Medicinal Plants*. Paris, France: Lavoisier Publishing; 1995:604.

Buck AC. Is there a scientific basis for the therapeutic effects of *Serenoa repens* in benign prostatic hyperplasia? Mechanisms of action. J Urol 2004;172:1792-1799.

Buffington CA, Blaisdell JL, Komatsu Y, Kawase K. Effects of choreito consumption on struvite crystal growth in urine of cats. Am J Vet Res 1994;55:972-975.

Buffington CA, Blaisdell JL, Komatsu Y, Kawase K. Effects of choreito and takushya consumption on in vitro and in vivo struvite solubility in cat urine. Am J Vet Res 1997a;58: 150-152.

Buffington CA, Blaisdell JL, Kawase K, Komatsu Y. Effects of choreito consumption on urine variables of healthy cats fed a magnesium-supplemented commercial diet. Am J Vet Res 1997b;58:146-149.

Burger AM, Mengs U, Schuler JB, Fiebig HH. Anticancer activity of an aqueous mistletoe extract (AME) in syngeneic murine tumor models. Anticancer Res 2001;21:1965-1968.

Busquets S, Carbo N, Almendro V, Quiles MT, Lopez-Soriano FJ, Argiles JM.Curcumin, a natural product present in turmeric, decreases tumor growth but does not behave as an anti-cachectic compound in a rat model. Cancer Lett. 2001 Jun 10;167(1):33-38.

Butterweck V. Mechanism of action of St John's wort in depression: what is known? CNS Drugs. 2003;17(8):539-562.

Calle J, Toscano M, Pinzon R, Baquero J, Bautista E. Antinociceptive and uterine relaxant activities of *Viburnum toronis* alive (Caprifoliaceae). J Ethnopharmacol 1999;66:71-73.

Cao J, Xu Y, Chen J, Klaunig JE. Chemopreventive effects of green and black tea on pulmonary and hepatic carcinogenesis. Fundam Appl Toxicol 1996;29:244-250.

Caron ME, White CM. Evaluation of the antihyperlipidemic properties of dietary supplements. Pharmacotherapy 2001;21: 481-487.

Carpinella MC, Defago MT, Valladares G, Palacios SM. Antifeedant and insecticide properties of a limonoid from *Melia azedarach* (Meliaceae) with potential use for pest management. J Agric Food Chem 2003;51:369-374.

Casto BC, Kresty LA, Kraly CL, et al. Chemoprevention of oral cancer by black raspberries. Anticancer Res 2002;22:4005-4015.

Cernakova M, Kost'alova D, Kettmann V, Plodova M, Toth J, Drimal J. Potential antimutagenic activity of berberine, a constituent of *Mahonia aquifolium*. BMC Complement Altern Med 2002;2:2.

Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric *(Curcuma longa)*. J Altern Complement Med 2003;9:161-168.

Chakurski I, Matev M, Stefanov G, Koichev A, Angelova I. Treanntment of duodenal ulcers and gastroduodenitis with a herbal combination of Symphitum officinalis and Calendula officinalis with and without antacids. Vutr Boles. 1981b; 20(6):44-47.

Chakurski I, Matev M, Koichev A, Angelova I, Stefanov G. [Treatment of chronic colitis with an herbal combination of *Taraxacum officinale, Hypericum perforatum, Melissa officinalis, Calendula officinalis,* and *Foeniculum vulgare*.] Vutr Boles 1981b;20:51-54.

Chan TY. Interaction between warfarin and danshen *(Salvia miltiorrhiza)*. Ann Pharmacother 2001;35:501-504.

Chandler RF. Licorice, more than just a flavour. Can Pharm J 1985;118:420-424.

Chang HM, But PPH, eds. *Pharmacology and Applications of Chinese Materia Medica,* vol 1. Singapore: World Scientific Publishing; 1986:366-369.

Chang HM, But PPH, eds:*Pharmacology and Applications of Chinese Materia Medica,* vol 2. Singapore: World Scientific Publishing; 1987.

Chang CK, Lin MT. DL-Tetrahydropalmatine may act through inhibition of amygdaloid release of dopamine to inhibit an epileptic attack in rats. Neurosci Lett 2001;307:163-166.

Chauhan DP. *Chemotherapeutic Potential of Curcumin for Colorectal Cancer. Current Pharmaceutical Design.* Hilversum, Netherlands: Bentham Science Publishers BV; 2002:1695-1706.

Chen CF, Chen SM, Lin MT, Chow SY. In vivo and in vitro studies on the mechanism of cardiovascular effects of Wu-Chu-Yu (Evodiae fructus). Am J Chin Med 1981;9:39-47.

Chen QM, Ye YC, Chai FL, Jin KP. [Protoscolicidal effect of some chemical agents and drugs against *Echinococcus granulosus*.] Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi 1991;9:137-139.

Chen J, Stavro PM, Thompson LU. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. Nutr Cancer. 2002;43(2):187-192.

Cheng XD, Hou CH, Zhang XJ, et al. Effects of huangqi (hex) on inducing cell differentiation and cell death in K562 and HEL cells. Acta Biochim Biophys Sin (Shanghai) 2004;36:211-217.

Cheshier JE, Ardestani-Kaboudanian S, Liang B, et al. Immunomodulation by pycnogenol in retrovirus-infected or ethanol-fed mice. Life Sci 1996;58:87-96.

Cheung ZH, So KF, Lu Q, et al. Enhanced survival and regeneration of axotomized retinal ganglion cells by a mixture of herbal extracts. J Neurotrauma 2002;19:369-378.

Chew BP, Wong MW, Wong TS. Effects of lutein from marigold extract on immunity and growth of mammary tumors in mice. Anticancer Res 1996;16:3689-3694.

Chew EC. Yunnan bai yao–induced platelet release in suspensions of washed platelets. Comp Med East West 1977;5:271-274.

Choi SW, Son BW, Son YS, Park YI, Lee SK, Chung MH. The wound-healing effect of a glycoprotein fraction isolated from aloe vera. Br J Dermatol 2001;145:535-545.

Christina AJ, Joseph DG, Packialakshmi M, et al. Anticarcinogenic activity of *Withania somnifera* Dunal against Dalton's ascitic lymphoma. J Ethnopharmacol 2004;93:359-361.

Cibere J, Deng Z, Lin Y, et al. A randomized double blind, placebo controlled trial of topical *Tripterygium wilfordii* in rheumatoid arthritis: reanalysis using logistic regression analysis. J Rheumatol 2003;30:465-467.

Cicero AF, Derosa G, Brillante R, Bernardi R, Nascetti S, Gaddi A. Effects of Siberian ginseng *(Eleutherococcus senticosis maxim.)* on elderly quality of life: a randomized clinical trial. Arch Gerontol Geriatr Suppl 2004;9:69-73.

Clavin ML, Gorzalczany S, Mino J, et al. Antinociceptive effect of some Argentine medicinal species of Eupatorium. Phytother Res 2000;14:275-277.

Clouatre DL. Kava kava: examining new reports of toxicity. Toxicol Lett 2004;150:85-96.

Coats BC, Holland RE, Ahola R. *Creatures in Our Care: The Veterinary Uses of Aloe Vera*. Published by the authors. 1985.

Coldren CD, Hashim P, Ali JM, Oh SK, Sinskey AJ, Rha C. Gene expression changes in the human fibroblast induced by *Centella asiatica* triterpenoids. Planta Med 2003;69:725-732.

Cometa MF, Mazzanti G, Tomassini L, 1998. Sedative and spasmolytic effects of *Viburnum tinus* L. and its major pure compounds. Phytotherapy research, 12 (suppl.1): S89-S91.

Conklin KA. Dietary antioxidants during cancerchemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr Cancer 2000;37:1-18.

Cook W. The Physiomedical Dispensatory. 1869. Available online at Henriette's Herbal Homepage: http://www.henriettesherbal.com/eclectic/cook/index.htm

Costello CH, Butler CL. An investigation of Piscidia erythrina (Jamaica Dogwood). J Am Pharm Assoc 1948;37:89-96.

Cropley M, Cave Z, Ellis J, Middleton RW. Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. Phytother Res 2002;16:23-27.

Cruz T, Jimenez J, Zarzuelo A, Cabo MM. The spasmolytic activity of the essential oil of *Thymus baeticus* Boiss in rats. Phytother Res 1989;3:106-108.

Currier NL, Miller SC. *Echinacea purpurea* and melatonin augment natural-killer cells in leukemic mice and prolong life span. J Altern Complement Med 2001;7:241-251.

D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E, Lecchini S, Frigo GM, Crema A Double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. Journal of ethnopharmacology, 1986;16:15-22.

Dadkar VN, Ranadive NU, Dhar HL. Evaluation of antistress (adaptogen) activity of *Withania somnifera* (Ashwgandha). Ind J Clin Biochem 1987;2:101-108.

Danesch UC. *Petasites hybridus* (Butterbur root) extract in the treatment of asthma—an open trial. Altern Med Rev 2004;9:54-62.

Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. *Rhodiola rosea* in stress induced fatigue—a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine 2000;7:365-371.

Das P. Antiinflammatory and antiarthritc activity of varuna. Journal of Research Indian Medicine 1974;9:49.

Datta A, Sukul NC. Antifilarial effect of Zingiber officinale on Dirofilaria immitis. J Helminthol. 1987 Sep;61(3):268-270.

Daykin PW. *Veterinary and Applied Pharmacology and Therapeutics*. Bailliere: Tindall & Cox; 1960:78.

Deepak M, Handa SS. Antiinflammatory activity and chemical composition of extracts of Verbena officinalis. Phytother Res 2000;14:463-465.

DeFeudis FV. *Ginkgo biloba. From Chemistry to Clinic*. Wiesbaden, Germany: Ullstein Medical; 1998.

DeFeudis FV, Papadopoulos V, Drieu K. *Ginkgo biloba* extracts and cancer: a research area in its infancy. Fundam Clin Pharmacol 2003;17:405-417.

Dehpour AR, Zolfaghari ME, Samadian T, Kobarfard F, Faizi M, Assari M. Antiulcer activities of licorice and its derivatives in experimental gastric lesion induced by ibuprofen in rats. Int J Pharmaceut 1995;119:133-138.

de la Motte S, Bose-O'Reilly S, Heinisch M, Harrison F. Double-blind comparison of an apple pectin-chamomile extract preparation with placebo in children with diarrhea. Arzneimittelforschung 1997;47:1247-1249.

de Moura NF, Morel AF, Dessoy EC, et al. Alkaloids, amides and antispasmodic activity of *Zanthoxylum hyemale*. Planta Med 2002;68:534-538.

De Sanctis R, De Bellis R, Scesa C, Mancini U, Cucchiarini L, Dacha M. In vitro protective effect of *Rhodiola rosea* extract against hypochlorous acid–induced oxidative damage in human erythrocytes. Biofactors 2004;20:147-159.

De Smet PAGM, Keller K, Hänsel R, et al, eds. *Adverse Effects of Herbal Drugs*. Berlin, Germany: Springer Verlag; 1993.

Della Loggia R, Tubaro A, Redaelli C. Evaluation of the activity on the mouse CNS of several plant extracts and a combination of them. Riv Neurol 1981;51:297-310.

Della Loggia R, Traversa U, Scarcia V, Tubaro A. Depressive effects of *Chamomilla recutita* (L.) Rausch. tubular flowers, on central nervous system in mice. Pharmacological Research Communications 1982;14:153-162.

Della Loggia R, Zilli C, Del Negro P, Redaelli C, Tubaro A. Isoflavones as spasmolytic principles of *Piscidia erythrina*. Prog Clin Biol Res 1988;280:365-368.

Deng Y, Yang L. Effect of *Angelica sinensis* (Oliv.) on melanocytic proliferation, melanin synthesis and tyrosinase activity in vitro. Di Yi Junyi Daxue Xuebao 2003;23:239-241.

Deshpande P, Sahu M, Kumar P. *Crataeva nurvala* Hook and Forst (Varun): the Ayurvedic drug of choice in urinary disorders. Indian J Med Res 1982;76(suppl):46-53.

Desplaces A, Choppin J, Vogel G, Trost W. The effects of silymarin on experimental phalloidine poisoning. Arzneimittelforschung 1975;25:89-96.

Devasena T, Menon VP. Fenugreek affects the activity of beta-glucuronidase and mucinase in the colon. Phytother Res 2003;17:1088-1091.

Devi PU, Sharada AC, Solomon FE, Kamath MS. In vivo growth inhibitory effect of *Withania somnifera* (Ashwagandha) on a transplantable mouse tumor, sarcoma 180. Indian J Exp Biol 1992;30:169-172.

Devi PU, Sharada AC, Solomon FE. In vivo growth inhibitory and radiosensitizing effects of withaferin A on mouse *Ehrlich ascites* carcinoma. Cancer Lett 1995;95:189-193.

Dhananjay G, Jayadev R, Baquer NZ. Modulation of some gluconeogenic enzyme activities in diabetic rat liver and kidney: effect of antidiabetic compounds. Indian J Exp Biol 1999;37:2,196-199.

Dhawan K, Kumar S, Sharma A. Anxiolytic activity of aerial and underground parts of *Passiflora incarnata*. Fitoterapia 2001;72:922-926.

Dhawan K. Drug/substance reversal effects of a novel tri-substituted benzoflavone moiety (BZF) isolated from *Passiflora incarnata* Linn.—a brief perspective. Addict Biol 2003;8:379-386.

Dhawan K, Dhawan S, Sharma A. Passiflora: a review update. J Ethnopharmacol 2004;94:1-23.

Didry N, Pinkas M. A propos du Buchu. Plantes Méd et Phyothér 1982;16:249-252.

Dimitrov M, Georgiev P, Vitanov S. [Use of tribestan on rams with sexual disorders.] Vet Med Nauki 1987;24:102-110.

Doan DD, Nguyen NH, Doan HK, et al. Studies on the individual and combined diuretic effects of four Vietnamese traditional herbal remedies (*Zea mays, Imperata cylindrica, Plantago major* and *Orthosiphon stamineus*). J Ethnopharmacol 1992;36:225-231.

Dolara P, Corte B, Ghelardini C, et al. Local anaesthetic, antibacterial and antifungal properties of sesquiterpenes from myrrh. Planta Med 2000;66:356-358.

Dombradi CA, Foldeak S. Screening report on the antitumor activity of purified *Arctium lappa* extracts. Tumori 1966;52:173.

Duan P, Wang ZM. [Clinical study on effect of Astragalus in efficacy enhancing and toxicity reducing of chemotherapy in patients of malignant tumor.] Zhongguo Zhong Xi Yi Jie He Za Zhi 2002;22:515-517.

Dunford C. The use of honey-derived dressings to promote effective wound management. Prof Nurse. 2005 Apr;20(8):35-8. Review.

Duwiejua M, Zeitlin IJ, Waterman PG, Gray AI. Anti-inflammatory activity of *Polygonum bistorta, Guaiacum officinale* and *Hamamelis virginiana* in rats. J Pharm Pharmacol 1994;46:286-290.

Eickstedt KWV, Rahmann R. Psychopharmakolgische Wirkungen von Valepotriaten. Arzneim-Forsch 1969;19:316-319.

Ek O, Waurzyniak B, Myers DE, Uckun FM. Antitumor activity of TP3(anti-p80)-pokeweed antiviral protein immunotoxin in hamster cheek pouch and severe combined immunodeficient mouse xenograft models of human osteosarcoma. Clin Cancer Res 1998;4:1641-1647.

Elhajili M, Baddouri K, Elkabbaj S, Meiouat F, Settaf A. Diuretic activity of the infusion of flowers from *Lavendula officinalis*. [French] Reprod Nutr Dev 2001;41:393-399.

Ellingwood F. The American Materia Medica, Therapeutics and Pharmacognosy, 1919. Available online at Henriette's Herbal Homepage: http://www.henriettesherbal.com/index.html

EMEA (European Medicines Evaluation Agency). Herbal Medicinal Products Working Party Draft Core Summary of Product Characteristics for Valerian and Ispaghula. http://www.emea.eu.int/ Accessed February 20, 2002.

Eng ET, Ye J, Williams D, et al. Suppression of estrogen biosynthesis by procyanidin dimers in red wine and grape seeds. Cancer Res 2003;63:8516-8522.

Erdelmeier CA, Cinatl J Jr, Rabenau H, Doerr HW, Biber A, Koch E. Antiviral and antiphlogistic activities of *Hamamelis virginiana* bark. Planta Med 1996;62:241-245.

Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. Br J Anaesth 2000a;84:367-371.

Ernst E, Chrubasik S. Phyto-anti-inflammatories: a systematic review of randomized placebo controlled double blind trials. Rheumatic Dis Clin North Am 2000b;26:13-27.

Ernst E, Schmidt K. Ukrain—a new cancer cure? A systematic review of randomised clinical trials. BMC Cancer. 2005 Jul 1;5(1):69.

ESCP (European Scientific Cooperative on Phytotherapy). *Monographs on the Medicinal Uses of Plant Drugs,* Fascicules 1 and 2 (1996), Fascicules 3, 4, and 5 (1997), Fascicule 6 (1999). Exeter: European Scientific Cooperative on Phytotherapy.

Farnsworth NR, Kinghorn AD, Soefarto DD, et al. Siberian ginseng *(Elutherococcus senticosis):* current status as an adaptogen. In: Farnsworth NR, et al, eds. *Economic and Medicinal Plant Research,* vol 1. London: Academic Press; 1985:157.

Felter HW, Lloyd JU. King's American Dispensatory, 1898. Available online at Henriette's Herbal Homepage at: http://www.henriettesherbal.com/eclectic/kings/index.html

Felter HW. The Eclectic Materia Medica, Pharmacology and Therapeutics, 1922. Reprint by Eclectic Medical Publications, Sandy OR.

Ferger B, Boonen G, Haberlein H, Kuschinsky K. In vivo microdialysis study of (+/–)-kavain on veratridine-induced glutamate release. Eur J Pharmacol 1998;347:211-214.

Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL, et al. Randomized clinical trial of *Plantago ovata* seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). Am J Gastroenterol 1999;94:427-433.

Ferreira PR, Fleck JF, Diehl A, Barletta D, Braga-Filho A, Barletta A, Ilha L. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. Head Neck. 2004 Apr;26(4):313-321.

Fiebich BL, Grozdeva M, Hess S, et al. *Petasites hybridus* extracts in vitro inhibit COX-2 and PGE2 release by direct interaction with the enzyme and by preventing p42/44 MAP kinase activation in rat primary microglial cells. Planta Med 2005;71:12-19.

Fields AM, Richards TA, Felton JA, et al. Analysis of responses to valerian root extract in the feline pulmonary vascular bed. J Altern Complement Med 2003;9:909-918.

Fintelmann V, Menssen HG. Artichoke leaf extract. Current knowledge concerning its efficacy as a lipid-reducer and antidyspeptic agent. Dtsch Apoth Ztg 1996;136:1405-1414.

Fitzi J, Furst-Jucker J, Wegener T, Saller R, Reichling J, 2002. Phytotherapy of chronic dermatitis and pruritis of dogs with a topical preparation containing tea tree oil (Bogaskin®). Schweiz Arch Tierheilk 144(5):223-231.

Flausino OA Jr, Zangrossi H Jr, Salgado JV, Viana MB. Effects of acute and chronic treatment with *Hypericum perforatum* L. (LI 160) on different anxiety-related responses in rats. Pharmacol Biochem Behav 2002;71:251-257.

Floersheim GL, Eberhard M, Tschumi P, Duckert F. Effects of penicillin and silymarin on liver enzymes and blood clotting factors in dogs given a boiled preparation of Amanita phalloides. Toxicol Appl Pharmacol. 1978 Nov;46(2):455-62.

Forslund T, Fyhrquist F, Froseth B, Tikkanen I. Effects of licorice on plasma atrial natriuretic peptide in healthy volunteers. J Intern Med 1989;225:95-99.

Fratkin J. Leaky gut syndrome: treating intestinal candidiasis and dysbiosis. Proceedings of the American Holistic Medical Association Conference; May 1996; New York, NY.

Fronczek FR, Caballero P, Fischer NH, Fernandez S, Hernandez E, Hurtado LM. The molecular structure of 3′-demethoxynorisoguaiacin triacetate from creosote bush *(Larrea tridentata).* J Nat Prod 1987;50:497-499.

Fujikawa T, Soya H, Hibasami H, et al. Effect of *Acanthopanax senticosus* Harms on biogenic monoamine levels in the rat brain. Phytother Res 2002;16:474-478.

Fulder S. Garlic and the prevention of cardiovascular disease. Cardiol Pract 1989;7:30-35.

Gaffney BT, Hugel HM, Rich PA. The effects of *Eleutherococcus senticosus* and *Panax ginseng* on steroidal hormone indices of stress and lymphocyte subset numbers in endurance athletes. Life Sci 2001;70:431-442.

Gafner S, Bergeron C, Batcha LL, et al. Inhibition of [3H]-LSD binding to 5-HT7 receptors by flavonoids from *Scutellaria lateriflora.* J Nat Prod 2003;66:535-537.

Gauthaman K, Ganesan AP, Prasad RN. Sexual effects of puncturevine *(Tribulus terrestris)* extract (protodioscin): an evaluation using a rat model. J Altern Complement Med 2003;9:257-265.

Gebhardt R. Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke *(Cynara scolymus* L.*)* extracts. J Pharmacol Exp Ther 1998;286:1122-1128.

Georgiev P, Dimitrov M, Vitanov S. The effect of the preparation Tribestan on the plasma concentration of testosterone and spermatogenesis of lambs and rams. Vet Sb 1988;3:20-22.

Ghannam N, Kingston M, Al-Mshaal IA, et al. The antidiabetic activity of aloes; preliminary clinical and experimental observations. Horm Res 1986;24:288-294.

Ghazanfar SA. Handbook of Arabian medicinal plants. Boca Raton, FL, CRC Press, 1994.

Ghelardini C, Galeotti N, Salvatore G, Mazzanti G. Local anaesthetic activity of the essential oil of *Lavandula angustifolia*. Planta Med 1999;65:8,700-703.

Gholap S, Kar A. Effects of *Inula racemosa* root and *Gymnema sylvestre* leaf extracts in the regulation of corticosteroid induced diabetes mellitus: involvement of thyroid hormones. Pharmazie 2003;58:413-415.

Glatzel von H, Hackenberg K. Röntgenologische untersuchungen der wirkungen von bittermitteln auf die verdauunogsorgane. Planta Med 1967;15:223-232.

Gleitz J, Friese J, Beile A, Ameri A, Peters T. Anticonvulsive action of (+/–)-kavain estimated from its properties on stimulated synaptosomes and Na+ channel receptor sites. Eur J Pharmacol 1996a;315:89-97.

Gleitz J, Beile A, Peters T. (+/–)-Kavain inhibits the veratridine- and KCl-induced increase in intracellular Ca2+ and glutamate-release of rat cerebrocortical synaptosomes. Neuropharmacology 1996b;35:179-186.

Gleitz J, Beile A, Peters T. Kavain inhibits non-stereospecifically veratridine-activated Na+ channels [letter]. Planta Med 1996c;62:580-581.

Gloor M, Reichling J, Wasik B, Holzgang HE. Antiseptic effect of a topical dermatological formulation that contains *Hamamelis* distillate and urea. Forsch Komplementarmed Klass Naturheilkd 2002;9:153-159.

Goel V, Lovlin R, Barton R, et al. Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther 2004;29:75-83.

Gong QM, Wang SL, Gan C. [A clinical study on the treatment of acute upper digestive tract hemorrhage with wen-she decoction.] Zhong Xi Yi Jie He Za Zhi 1989;9:272-273,260.

Gong Z, Yuan Y, Lou K, Tu S, Zhai Z, Xu J. Mechanisms of Chinese herb emodin and somatostatin analogs on pancreatic regeneration in acute pancreatitis in rats. Pancreas 2002;25: 154-160.

Gorbacheva AV, et al. Anti-ulcerogenic characteristics of Filipendula ulmaria (L.) Maxim. [Russian] Rastitel'nye Resursy. Nauka, Sankt-Peterburg, St. Petersburg, Russia: 2002. 38:2,114-119.

Granados-Soto V. Pleiotropic effects of resveratrol. Drug News Perspect. 2003 Jun;16(5):299-307.

Grases F, Melero G, Costa-Bauza A, Prieto R, March JG. Urolithiasis and phytotherapy. Int Urol Nephrol 1994;26:507-511.

Grases F, Ramis M, Costa-Bauza A, March JG. Effect of *Herniaria hirsuta* and *Agropyron repens* on calcium oxalate urolithiasis risk in rats. J Ethnopharmacol 1995;45:211-214.

Gray RD, Haggart K, Lee DK, Cull S, Lipworth BJ. Effects of butterbur treatment in intermittent allergic rhinitis: a placebo-controlled evaluation. Ann Allergy Asthma Immunol 2004; 93:56-60.

Gresswell, George; Gresswell Charles, and Gresswell, Albert, 1887. The Veterinary Pharmacopeia, Materia Medical And Therapeutics. Bailliere, Tindall and Cox, London.

Grieve M. A Modern Herbal. Dover Publications NY 1931.

Griffiths P. The role of cranberry juice in the treatment of urinary tract infections. Br J Community Nurs 2003;8:557-561.

Grigoleit HG, Grigoleit P. Gastrointestinal clinical pharmacology of peppermint oil. Phytomedicine. 2005a Aug;12(8):607-611.

Grigoleit HG, Grigoleit P. Pharmacology and preclinical pharmacokinetics of peppermint oil. Phytomedicine. 2005b Aug;12(8):612-616.

Grochulski VA, Borkowski B. Influence of chamomile oil on experimental glomerulonephritis in rabbits. Planta Med 1972;21:289-292.

Grossarth-Maticek R, Kiene H, Baumgartner SM, Ziegler R. Use of Iscador, an extract of European mistletoe *(Viscum album),* in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Altern Ther Health Med 2001;7:57-66,68-72,74-6.

Grover JK, Yadav SP. Pharmacological actions and potential uses of *Momordica charantia:* a review. J Ethnopharmacol 2004;93: 123-132.

Guan YJ, Hu Z, Hou-Chung-Kuo Chung Hsi i Chieh Ho Tsa Chih M, [Effect of *Cordyceps sinensis* on T-lymphocyte subsets in chronic renal failure.] Chinese J Integrated Med 1992;12:323, 338-339.

Guerrini VH, Kriticos CM. Effects of azadirachtin on *Ctenocephalides felis* in the dog and the cat. Vet Parasitol 1998;74: 289-297.

Gumbinger HG, Winterhoff H, Sourgens H, et al. Formation of compounds with antigonadotropic activity from inactive phenolic precursors. Contraception 1981;23:661-666.

Guodong L, Zhongqi L. Effects of ginseng saponins on insulin release from isolated pancreatic islets of rats. Chin J Integr Trad Western Med 1987;7:326.

Gupta I, Gupta V, Parihar A, et al. Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res 1998;3:511-514.

Gupta R, Singhal S, Goyle A, Sharma VN. Antioxidant and hypocholesterolaemic effects of Terminalia arjuna tree-bark powder: a randomised placebo-controlled trial. J Assoc Physicians India 2001;49:231-235.

Gupta S, George P, Gupta V, et al. *Tylophora indica* in bronchial asthma—a double blind study. Ind J Med Res 1979;69:981-989.

Gupta SS, Variyar MC. Experimental studies on pituitary diabetes IV. Effect of *Gymnema sylvestre* and Cocciniaindica against the hyperglycemia response of somatotropin and corticotrophin hormones. Indian J Med Res 1964;52:200-207.

Gupta SS. Inhibitory effect of *Gymnema sylvestre* (Gurmar) on adrenaline induced hyperglycemia in rats. Indian J Med Sci 1961;15:883-887.

Gupte S. Use of berberine in treatment of giardiasis. Am J Dis Child 1975;129:866.

Guslandi M. Ulcer-healing drugs and endogenous prostaglandins. Int J Clin Pharmacol Ther Toxicol 1985;23:398-402.

Habtemariam S. Antiinflammatory activity of the antirheumatic herbal drug, gravel root (Eupatorium purpureum): further biological activities and constituents. Phytother Res 2001;15:687-690.

Hacker B, Medon PJ. Cytotoxic effects of *Eleutherococcus senticosus* aqueous extracts in combination with N6-(delta 2-isopentenyl)-adenosine and 1-beta-D-arabinofuranosylcytosine against L1210 leukemia cells. J Pharm Sci 1984;73:270-272.

Hajhashemi V, Ghannadi A, Sharif B. Anti-inflammatory and analgesic properties of the leaf extracts and essential oil of *Lavandula angustifolia* Mill. J Ethnopharmacol 2003;89:67-71.

Halcon L, Milkus K. *Staphylococcus aureus* and wounds: a review of tea tree oil as a promising antimicrobial. Am J Infect Control. 2004 Nov;32(7):402-408.

Halder A, Raychowdhury R, Ghosh A, De M. Black tea *(Camellia sinensis)* as a chemopreventive agent in oral precancerous lesions. J Environ Pathol Toxicol Oncol 2005;24:141-144.

Halliwell RE. Dietary allergy and intolerance in the dog: new concepts. ASAVA Dermatology 1995 Australian Veterinary Association Annual Conference Proceedings.

Hamada H, Hiramatsu M, Edamatsu R, Mori A. Free radical scavenging action of baicalein. Arch Biochem Biophys 1993; 306:261-266.

Hammer KA, Carson CF, Riley TV. In vitro activities of ketoconazole, econazole, miconazole, and Melaleuca alternifolia (tea tree) oil against Malassezia species. Antimicrob Agents Chemother. 2000 Feb;44(2):467-469.

Hänsel R, Wohlfart R Coper H. Narcotic action of 2-methyl-3-butene-2-ol contained in hops. Zhurnal der Natuerforschungen 1980;35:1096-1097.

Hänsel R, Wagener HH. Versuche, sedativ-hypnotische Wirkstoffe im Hopfen nachzuweisen. Arzneim Forsch/Dru Res 1967;17:79-81.

Harney JW, Barofsky IM, Leary JD. Behavioral and toxicological studies of cyclopentanoid monoterpenes from *Nepeta cataria*. Lloydia 1978;41:367-374.

Harvey RG. A comparison of evening primrose oil and sunflower oil for the management of papulocrustous dermatitis in cats. Vet Rec. 1993a;133(23):571-573.

Harvey RG. Effect of varying propositions of evening primrose oil and fish oil on cats with crusting dermatosis (miliary dermatitis). Vet Rec. 1993b;133(9):208-211.
Harris C, Pierce K, King G, Yates KM, Hall J, Tizard I. Efficacy of acemannan in treatment of canine and feline spontaneous neoplasms. Mol Biother 1991;3:207-213.
Hart BL, Leedy MG. Analysis of the catnip reaction: mediation by olfactory system, not vomeronasal organ. Behav Neural Biol. 1985 Jul;44(1):38-46.
Hartz AJ, Bentler S, Noyes R, et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. Psychol Med 2004; 34:51-61.
Hase K, Kasimu R, Basnet P, Kadota S, Namba T. Preventive effect of lithospermate B from *Salvia miltiorhiza* on experimental hepatitis induced by carbon tetrachloride or D-galactosamine/lipopolysaccharide. Planta Med. 1997 Feb;63(1):22-26.
Hasenohrl RU, Topic B, Frisch C, Hacker R, Mattern CM, Huston JP. Dissociation between anxiolytic and hypomnestic effects for combined extracts of *Zingiber officinale* and *Ginkgo biloba,* as opposed to diazepam. Pharmacol Biochem Behav 1998;59: 527-535.
Hawrelak J. Giardiasis pathophysiology and management. Alt Med Rev 2003;8:129-142.
Hayashi I, Ohotsuki M, Suzuki I, Watanabe T. Effects of oral administration of *Echinacea purpurea* (American herb) on incidence of spontaneous leukemia caused by recombinant leukemia viruses in AKR/J mice. Nihon Rinsho Meneki Gakkai Kaishi 2001;24:10-20.
Hazelhoff B, Malingre TM, Meijer DK. Antispasmodic effects of valeriana compounds: an in-vivo and in-vitro study on the guinea-pig ileum. Arch Int Pharmacodyn Ther 1982;257:274-287.
Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VL. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr 1999;69:231-236.
Helms S. Cancer prevention and therapeutics: Panax ginseng. Alt Med Rev 2004 9:259-274.
Hiai S, Yokoyama H, Oura H, Yano S. Stimulation of pituitary-adrenocortical system by ginseng saponin. Endocrinol Jpn. 1979 Dec;26(6):661-665.
Hirano T, Gotoh M, Oka T. Natural flavenoids and lignans are potent cytostatic agents against human leukemic HL-60 cells. Life Sci 1994;55:1061-1069.
Hobbs C. Sarsaparilla: a literature review. Herbalgram 1988;17: 10.
Hobbs C. Echinacea: a literature review. HerbalGram 1994; 30(suppl):33-47.
Hoffman D. The New Holistic Herbal Element, Brisbane, 1992.
Hoffman D (2004) Medical Herbalism, The Science Principles and Practices Of Herbal Medicine Healing Arts Press, Rochester, Vermont.
Hofmann D, Hecker M, Volp A. Efficacy of dry extract of ivy leaves in children with bronchial asthma—a review of randomized controlled trials. Phytomedicine 2003;10:213-220.
Holetz FB, et al. Screening of some plants used in the Brazilian folk medicine for the treatment of infectious diseases. Mem Inst Oswaldo Cruz 2002;97:1027-1031.
Hollander D. Intestinal permeability, leaky gut, and intestinal disorders. Curr Gastroenterol Rep 1999;1:410-416.
Homady MH. The influences of some medicinal plant extracts on the aggressivity and fertility of male mice. Philippine J Sci 2001;130:2,119-126.
Hook I, McGee A, Henman H. Evaluation of dandelion for diuretic activity and variation in potassium content. Int J Pharmacog 1993;31:29-34.
Hordegen P, Hertzberg H, Heilmann J, Langhans W, Maurer V. The anthelmintic efficacy of five plant products against gastrointestinal trichostrongylids in artificially infected lambs. Vet Parasitol 2003;117:51-60.
Horhammer L, Wagner H, Reinhardt H. New methods in pharmacognosy. XI. Chromatographic evaluation of commercial Viburnum drugs. Deutsche Apotheker Zeitung 1965;105:1371-1372.
Horhammer L, Wagner H, Reinhardt H. Chemistry, pharmacology, and pharmaceutics of the components from *Viburnum prunifolium* and *V. opulus*. Botanical Magazine (Tokyo) 1966; 79:510-525.
Hosford D, Mencia-Huerta JM, Page C, Braquet P. Natural antagonists of platelet-activating factor. Phytother Res 1988;2:1-17.
Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. N Engl J Med 1998;339:1085-1086.
Hsiang CY, Lai IL, Chao DC, Ho TY. Differential regulation of activator protein 1 activity by glycyrrhizin. Life Sci 2002;70: 1643-1656.
Hsieh CL, Tang NY, Chiang SY, Hsieh CT, Lin JG. Anticonvulsive and free radical scavenging actions of two herbs, *Uncaria rhynchophylla* (MIQ) Jack and *Gastrodia elata* Bl., in kainic acid-treated rats. Life Sci 1999;65:2071-2082.
Hsieh CL, Chiang SY, Cheng KS, et al. Anticonvulsive and free radical scavenging activities of *Gastrodia elata* Bl. in kainic acid-treated rats. Am J Chin Med 2001;29:331-341.
Hu S, Cai W, Ye J, Qian Z, Sun Z. Influence of medicinal herbs on phagocytosis by bovine neutrophils. Zentralbl Veterinarmed A 1992;39:593-599.
Hu S, Concha C, Johannisson A, Meglia G, Waller KP. Effect of subcutaneous injection of ginseng on cows with subclinical Staphylococcus aureus mastitis. J Vet Med B Infect Dis Vet Public Health. 2001 Sep;48(7):519-528.
Huang KC. *The Pharmacology of Chinese Herbs*. Boca Raton: CRC Press; 2000.
Huang MT, Ho CT, Wang ZY, et al. Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. Cancer Res 1994;54:701-708.
Huang WM, Yan H, Jin JM, Yu C, Zhang H. Beneficial effects of berberine on hemodynamics during acute ischemic left ventricular failure in dogs. Chin Med J 1992;105:1014-1019.
Hughes-Formella BJ, Filbry A, Gassmueller J, Rippke F. Anti-inflammatory efficacy of topical preparations with 10% hamamelis distillate in a UV erythema test. Skin Pharmacol Appl Skin Physiol 2002;15:125-132.
Hui KM, Huen MS, Wang HY, et al. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi. Biochem Pharmacol 2002;64:1415-1424.
Hussain Z, Waheed A, Qureshi RA, et al. The effect of medicinal plants of Islamabad and Murree region of Pakistan on insulin secretion from INS-1 cells. Phytother Res 2004;18:73-77.
Hwang BY, Roberts SK, Chadwick LR, Wu CD, Kinghorn AD. Antimicrobial constituents from goldenseal (the Rhizomes of *Hydrastis canadensis*) against selected oral pathogens. Planta Med 2003;69:623-627.
Iauk L, Lo Bue AM, Milazzo I, Rapisarda A, Blandino G. Antibacterial activity of medicinal plant extracts against periodontopathic bacteria. Phytother Res 2003;17:599-604.
Idris UE, Adam SE, Tartour G. The anthelmintic efficacy of *Artemisia herba-alba* against *Haemonchus contortus* infection in goats. Natl Inst Anim Health Q (Tokyo) 1982;22:138-143.
Iizuka N, Hazama S, Yoshimura K, et al. Anticachectic effects of the natural herb Coptidis rhizoma and berberine on mice bearing colon 26/clone 20 adenocarcinoma. Int J Cancer 2002;99:286-291.
Ikram M. Medicinal plants as hypocholesterolemic agents. J Pak Med Assoc 1980;30:278-282.

Ilarionova M, et al. Cytotoxic effect on leukemic cells of the essential oils from rosemary, wild geranium and nettle and concret of royal bulgarian rose. Anticancer Res 1992;12:1915.

Innes JF, Fuller CJ, Grover ER, Kelly AL, Burn JF. Randomised, double-blind, placebo-controlled parallel group study of P54FP for the treatment of dogs with osteoarthritis. Vet Rec 2003;152:457-460.

Inouye H, Takeda Y, Uobe K, Yamauchi K, Yabuuchi N, Kuwano S. Purgative activities of iridoid glycosides. Planta Med 1974; 25:285-288.

Ishani A, MacDonald R, Nelson D, Rutks I, Wilt TJ.Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. Am J Med. 2000 Dec 1;109(8):654-664.

Islam MS, Rahman MT, Rouf AS, Rahman F. Evaluation of neuropharmacological effects of *Rumex maritimus* Linn. (Polygonaceae) root extracts. Pharmazie 2003;58:738-741.

Ito H. Effects of the antitumor agents from various natural sources on drug-metabolizing system, phagocytic activity and complement system in sarcoma 180-bearing mice Jpn J Pharmacol 1986;40:435-443.

Itokawa H, Mihashi S, Watanabe K, et al. Studies on the constituents of crude drugs having inhibitory activity against contraction of the ileum caused by histamine or barium chloride. I. Screening test for the activity of commercially available crude drugs and the related plant materials. Shoyakugaku Zasshi 1983;37:223-228.

Ivetic V, Popovic M, Mimica-Dukic N, Barak O, Pilija V. St. John's Wort (Hypericum perforatum L.) and Kindling Epilepsy in Rabbit Phytomedicine. 2002 Sep;9(6):496-499.

Jacker H-J, et al. Zum antiexsudativen Verhalten einiger Triterpensaponine. Pharmazie 1982;37:380-382.

Jackson B, Hicks LE. Effect of cranberry juice on urinary pH in older adults. Home Healthc Nurse 1997;15:198-202.

Jackson CM, Lee DK, Lipworth BJ. The effects of butterbur on the histamine and allergen cutaneous response. Ann Allergy Asthma Immunol 2004;92:250-254.

Jager AK, Hutchings A, van Staden J. Screening of Zulu medicinal plants for prostaglandin-synthesis inhibitors. J Ethnopharmacol 1996;52:95-100.

Jagtap AG, Shirke SS, Phadke AS. Effect of polyherbal formulation on experimental models of inflammatory bowel diseases. J Ethnopharmacol 2004;90:195-204.

Jamieson DD, Duffield PH. The antinociceptive actions of kava components in mice. Clin Exp Pharmacol Physiol 1990;17: 495-507.

Jana S, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. J Psychiatry Neurosci 2001;26:21-29.

Janssen G, Bode U, Breu H, Dohrn B, Engelbrecht V, Gobel U. Boswellic acids in the palliative therapy of children with progressive or relapsed brain tumors. Klin Padiatr 2000;212:189-195.

Jarred RA, Keikha M, Dowling C, et al. Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones. Cancer Epidemiol Biomarkers Prev 2002;11:1689-1696.

Jarrett RH, Norman EJ, Squires RA. Liquorice and canine Addison's disease. N Z Vet J 2005;53:214.

Jeffrey SL, Belcher HJ. Use of Arnica to relieve pain after carpal-tunnel release surgery. Altern Ther Health Med 2002;8:66-68.

Jellin JM, Batz F, Hitchens K. Pharmacists Letter/Prescribers Letter Natural Medicines Comprehensive Database. Stockton, Calif: Therapeutic Research Faculty; 1999.

Jensen et al. cited on http://www.froytang.no/html/cattle.htm accessed July 2005.

Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy.The Cochrane Database of Systematic Reviews 2006,(1). available on for fee basis at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000145/frame.html

Jiang J, Xu Q. Immunomodulatory activity of the aqueous extract from rhizome of *Smilax glabra* in the later phase of adjuvant-induced arthritis in rats. J Ethnopharmacol 2003; 85:53-59.

Jones E. *Cancer: Its Causes, Symptoms and Treatment.* Wenatchee, Wash: Healing Mountain Publishing, Inc; 2001 (reprinted from 1911).

Jost M. Calendula as a healing plant for mastitis in dairy cows. Biodynamics 1984;152:7-19.

Kaemmerer K, Fink J. Untersuchungen von Eleutherococcus-Extrakt auf trophanabole Wirkungen bei Ratten. Der praktische Tierarzt 1980;61:748-753.

Kalin P. [The common butterbur (Petasites hybridus)—portrait of a medicinal herb.]Forsch Komplementarmed Klass Naturheilkd. 2003 Apr;10 (Suppl) 1:41-44.

Kamaldeep D, Suresh K, Anupam S. Evaluation of central nervous system effects of *Passiflora incarnata* in experimental animals. Pharmaceut Biol 2003;41:2,87-91.

Kamei J, Nakamura R, Ichiki H, Kubo M. Antitussive principles of *Glycyrrhizae radix,* a main component of the Kampo preparations Bakumondo-to (Mai-men-dong-tang). Eur J Pharmacol 2003;469:159-163.

Kamtchouing P, Mbongue Fandio GY, Dimo T, Jatsa HB. Evaluation of androgenic activity of *Zingiber officinale* and *Pentadiplandra brazzeana* in male rats. Asian J Androl 2002; 4:299-301.

Kang DG, Yun YG, Ryoo JH, Lee HS. Anti-hypertensive effect of water extract of danshen on renovascular hypertension through inhibition of the renin angiotensin system. Am J Chin Med 2002;30:87-93.

Kang H, Ahn KS, Cho C, Bae HS. Immunomodulatory effect of *Astragali radix* extract on murine TH1/TH2 cell lineage development. Biol Pharm Bull 2004;27:1946-1950.

Kaplan EI. The prophylactic effect of *Eleutherococcus senticosus* in craniocerebral trauma in animals. Lek Sredstva Dal'nego 1965;7:77-79.

Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol 2002;81:281-285.

Kardosova A, Ebringerova A, Alfoldi J, Nosal'ova G, Franova S, Hribalova V. A biologically active fructan from the roots of *Arctium lappa* L., var. Herkules. Int J Biol Macromol 2003; 33:135-140.

Karthikeyan K, Bai BR, Gauthaman K, Sathish KS, Devaraj SN. Cardioprotective effect of the alcoholic extract of *Terminalia arjuna* bark in an in vivo model of myocardial ischemic reperfusion injury. Life Sci 2003;73:2727-2739.

Kassir ZA. Endoscopic controlled trial of four drug regimens in the treatment of chronic duodenal ulceration. Irish Med J 1985;78:153-156.

Kast A, Hauser SP. [Helixor—mistletoe preparation for cancer therapy. Documentation No. 19.] Schweiz Rundsch Med Prax 1990;79:291-295.

Katiyar SK, Mukhtar H. Tea antioxidants in cancer chemoprevention. J Cell Biochem Suppl 1997;27:59-67.

Kaur P, Sharma M, Mathur S, et al. Effect of 1-oxo-5beta, 6beta-epoxy-witha-2-ene-27-ethoxy-olide isolated from the roots of *Withania somnifera* on stress indices in Wistar rats. J Altern Complement Med 2003;9:897-907.

Kawai T, Kinoshita K, Koyama K, Takahashi K. Anti-emetic principles of *Magnolia obovata* bark and *Zingiber officinale* rhizome. Planta Med 1994;60:17-20.

Keene JL, Noakes, DLG; Moccia, RD; Soto, CG. The efficacy of clove oil as an anaesthetic for rainbow trout, *Oncorhynchus mykiss* (Walbaum). Aquaculture Res 1998;29:2,89-101.

Kempe C, Gruning H, Stasche N, Hormann K. [Icelandic moss lozenges in the prevention or treatment of oral mucosa irritation and dried out throat mucosa.] [In German] Laryngorhinootologie 1997;76:186-188.

Kempski HW. On the causal therapy of chronic helminthic bronchitis. Med Klin. 1967 Feb 17;62(7):259-260.

Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). Pharmacol Biochem Behav 2002;72:953-964.

Kennedy DO, Scholey AB. Ginseng: potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav 2003a;75:687-700.

Kennedy DO, Wake G, Savelev S, et al. Modulation of mood and cognitive performance following acute administration of single doses of *Melissa officinalis* (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. Neuropsychopharmacology 2003b;28:1871-1881.

Kennedy DO, Little W, Scholey AB. Attenuation of laboratory-induced stress in humans after acute administration of *Melissa officinalis* (Lemon balm). Psychosom Med 2004;66:607-613.

Khan N, Sultana S Inhibition of two stage renal carcinogenesis, oxidative damage and hyperproliferative response by *Nigella sativa*. Eur J Cancer Prev 2005;14:159-168.

Khayyal MT, el-Ghazaly MA, Kenawy SA, Seif-el-Nasr M, Mahran LG, Kafafi YA, Okpanyi SN. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung 2001;51(7):545-53.

Kiefer D, Pantuso T. *Panax ginseng*. Am Fam Physician 2003;68: 1539-1542.

Kim DH, Moon YS, Jung JS, et al. Effects of ginseng saponin administered intraperitoneally on the hypothalamo-pituitary-adrenal axis in mice. Neurosci Lett 2003;343:62-66.

Kim H, Lee E, Lee S, Shin T, Kim Y, Kim J. Effect of *Rehmannia glutinosa* on immediate type allergic reaction. Int J Immunopharmacol 1998;20:231-240.

Kim KS, Rhee KH, Yoon JH, Lee JG, Lee JH, Yoo JB. *Ginkgo biloba* extract (EGb 761) induces apoptosis by the activation of caspase-3 in oral cavity cancer cells. Oral Oncol 2005;41:383-389.

Kim MJ, Kim HN, Kang KS, et al. Methanol extract of *Dioscoreae rhizoma* inhibits pro-inflammatory cytokines and mediators in the synoviocytes of rheumatoid arthritis. Int Immunopharmacol 2004;4:1489-1497.

Kim DC, Kim SH, Choi BH, etal, Curcuma longa extract protects against gastric ulcers by blocking H2 histamine receptors. Biol Pharm Bull. 2005 Dec;28(12):2220-2224.

Kim MJ, Kim HN, Kang KS, Baek NI, Kim DK, Kim YS, Jeon BH, Kim SH.Methanol extract of Dioscoreae Rhizoma inhibits pro-inflammatory cytokines and mediators in the synoviocytes of rheumatoid arthritis. Int Immunopharmacol. 2005b Mar;5(3):629.

Kim-Park S, Ku DD. Garlic elicits a nitric oxide-dependent relaxation and inhibits hypoxic pulmonary vasoconstriction in rats. Clin Exp Pharmacol Physiol 2000;27:780-786.

Kimura Y, Sumiyoshi M. Effects of various *Eleutherococcus senticosus* cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice. J Ethnopharmacol 2004;95:447-453.

King GK, Yates KM, Greenlee PG, et al. The effect of acemannan immunostimulant in combination with surgery and radiation therapy on spontaneous canine and feline fibrosarcomas. J Am Anim Hosp Assoc 1995;31:439-447.

Kingwatanakul P, Alon US. Cranberries and urinary tract infection. Child Hosp Q 1996;8:69-72.

Kirk H. Index of Treatment in Small-Animal Practice. The Williams and Wilkins Company, Baltimore, 1948.

Kitts D, Hu C. Efficacy and safety of ginseng. Public Health Nutr 2000;3:473-485.

Klaas CA, Wagner G, Laufer S, et al. Studies on the anti-inflammatory activity of phytopharmaceuticals prepared from Arnica flowers. Planta Med 2002;68:385-391.

Kline RM, Kline JJ, DiPalma J, Barbero G. Enteric coated, pH dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr. 2001;138:125-128.

Klouchek-Popova E, Popov A, Pavlova N, Krusteva S. Influence of the physiological regeneration and epithelialization using fractions isolated from *Calendula officinalis*. Acta Physiol Pharmacol Bulg 1982;8:63-67.

Knuesel O, Weber M, Suter A. *Arnica montana* gel in osteoarthritis of the knee: an open, multicenter clinical trial. Adv Ther 2002;19:209-218.

Kobayashi Y, Nakano Y, Inayama K, Sakai A, Kamiya T. Dietary intake of the flower extracts of German chamomile (*Matricaria recutita* L.) inhibited compound 48/80-induced itch-scratch responses in mice. Phytomedicine 2003;10:657-664.

Kobayashi Y, Takahashi R, Ogino F. Antipruritic effect of the single oral administration of German chamomile flower extract and its combined effect with antiallergic agents in ddY mice. J Ethnopharmacol 2005;101:308-312.

Koc RK, Akdemir H, Kurtsoy A, et al. Lipid peroxidation in experimental spinal cord injury. Comparison of treatment with *Ginkgo biloba,* TRH and methylprednisolone. Res Exp Med (Berl) 1995;195:117-123.

Koch HP, Lawson LD, eds. *Garlic. The Science and Therapeutic Application of* Allium sativum *L. and Related Species*. 2nd ed. Baltimore, Md: Williams and Wilkins; 1996.

Koh JH, Kim KM, Kim JM, Song JC, Suh HJ. Antifatigue and antistress effect of the hot-water fraction from mycelia of *Cordyceps sinensis*. Biol Pharm Bull 2003;26:691-694.

Konopa J, Jereczek, E., Matuszkiewicz, A., et al. Screening of antitumor substances from plants. Arch Immunol Ther Exp 1957;15:129.

Kovar KA, Gropper B, Friess D, Ammon HP. Blood levels of 1,8-cineole and locomotor activity of mice after inhalation and oral administration of rosemary oil. Planta Med 1987;53:315-318.

Krack A, Sharma R, Figulla HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. Eur Heart J 2005;26:2368-2374.

Kraft K. Therapeutisches Profil eines Spitzwegerichekraut-Fluidextraktes bei akuten repsiratorischen Erkrankungen im Kindes- und Erwachsenenalter. In: Loew D, Rietbrock N, Hrsg. *Phytopharmaka III: Forschung und klinische Anwendung*. Darmstadt: Steinkopff Verlag; 1997a:199-209.

Kraft K. Artichoke leaf extract—recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts. Phytomedicine 1997b;4:369-378.

Krazhan IA, Garazha NN. Treatment of chronic catarrhal gingivitis with polysorb-immobilized calendula. Stomatologiia (Mosk). 2001;80(5):11-13.

Kreydiyyeh SI, Usta J. Diuretic effect and mechanism of action of parsley. J Ethnopharmacol 2002;79:353-357.

Krishnaswamy K, Goud VK, Sesikeran B, Mukundan MA, Krishna TP. Retardation of experimental tumorigenesis and reduction in DNA adducts by turmeric and curcumin. Nutr Cancer 1998;30:163-166.

Kudi AC, Myint SH, 1999. Antiviral activity of some Nigerian medicinal plant extracts. J Ethnopharmacol 1999 Dec 15;68(1-3):289-294.

Kumar V, Singh PN, Bhattacharya SK. Anti-inflammatory and analgesic activity of Indian *Hypericum perforatum* L. Indian J Exp Biol 2001;39:339-343.

Kuo CL, Chou CC, Yung BYM. Berberine complexes with DNA in the berberine-induced apoptosis in human leukemic HL-60 cells. Cancer Lett 1995;93:193-200.

Kupchan SM, Karim A. Tumor inhibitors. 114. *Aloe emodin:* antileukemic principle isolated from *Rhamnus frangula* L. Lloydia 1976;39:223-224.

Kurashige S, Akuzawa Y, Endo F. Effects of astragali radix extract on carcinogenesis, cytokine production, and cytotoxicity in mice treated with a carcinogen, N-butyl-N′-butanolnitrosoamine. Cancer Invest 1999;17:30-35.

Kwon YS, Jang KH, Jang IH. The effects of Korean red ginseng (ginseng radix rubra) on liver regeneration after partial hepatectomy in dogs. J Vet Sci. 2003 Apr;4(1):83-92.

Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003-1011.

Lahiri-Chatterjee M, Katiyar SK, Mohan RR, Agarwal R. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumour promotion in the SENCAR mouse skin tumorigenic model. Cancer Res 1999;59:622-632.

Lambert JD, Yang CS. Mechanisms of cancer prevention by tea constituents. J Nutr. 2003 Oct;133(10):3262S-3267S.

Lamson DW, Brignall MS. Antioxidants in cancer therapy: their actions and interactions with oncologic therapies. Altern Med Rev 1999;4:304-329.

Lamson DW, Brignall MS. Antioxidant and cancer therapy II: quick reference guide. Altern Med Rev 2000;5:152-163.

Langmead L, Dawson C, Hawkins C, Banna N, Loo S, Rampton DS. Antioxidant effects of herbal therapies used by patients with inflammatory bowel disease: an in vitro study. Aliment Pharmacol Ther 2002;16:197-205.

Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. Aliment Pharmacol Ther 2004a;19:739-747.

Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro. Aliment Pharmacol Ther 2004b;19:521-527.

Larsson B, Jonasson A, Fianu S. Prophylactic effect of UVA-E in women with recurrent cystitis: a preliminary report. Curr Ther Res 1993;53:441-443.

Lau BHS Adetumbi MA, and Sanchez A *Allium sativum* (garlic) and atherosclerosis: a review. Nutr Res 1983;3:119-128.

Lau BH, Ruckle HC, Botolazzo T, Lui PD. Chinese medicinal herbs inhibit growth of murine renal cell carcinoma. Cancer Biother 1994;9:153-161.

Lau CB, Ho CY, Kim CF, et al. Cytotoxic activities of Coriolus versicolor (Yunzhi) extract on human leukemia and lymphoma cells by induction of apoptosis. Life Sci 2004;75:797-808.

Lee KM Jung JS, Song DK, et al. Effects of Humulus lupulus extract on the central nervous system in mice. Planta Med 1993; 59: A691.

Lee SM, Li ML, Tse YC, et al. *Paeoniae radix,* a Chinese herbal extract, inhibits hepatoma cell growth by inducing apoptosis in a p53 independent pathway. Life Sci 2002;71:2267-2277.

Lee DK, Carstairs IJ, Haggart K, Jackson CM, Currie GP, Lipworth BJ. Butterbur, an herbal remedy, attenuates adenosine monophosphate induced nasal responsiveness in seasonal allergic rhinitis. Clin Exp Allergy 2003;33:882-886.

Lee DK, Haggart K, Robb FM, Lipworth BJ. Butterbur, an herbal remedy, confers complementary anti-inflammatory activity in asthmatic patients receiving inhaled corticosteroids. Clin Exp Allergy 2004a;34:110-114.

Lee DK, Gray RD, Robb FM, Fujihara S, Lipworth BJ. A placebo-controlled evaluation of butterbur and fexofenadine on objective and subjective outcomes in perennial allergic rhinitis. Clin Exp Allergy 2004b;34:646-649.

Lee AN, Werth VP. Activation of autoimmunity following use of immunostimulatory herbal supplements. Arch Dermatol 2004c;140:723-727.

Leeney H. *Home Doctoring for Animals*. London: MacDonald & Martin; 1921.

Legnani C, Frascaro M, Guazzaloca G, Ludovici S, Cesarano G, Coccheri S. Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. Arzneimittelforschung 1993;43:119-122.

Lehrl S. Clinical efficacy of kava extract WS 1490 in sleep disturbances associated with anxiety disorders. Results of a multicenter, randomized, placebo-controlled, double-blind clinical trial. J Affect Disord 2004;78:101-110.

Lenartz D, Dott U, Menzel J, Schierholz JM, Beuth J. Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res 2000;20:2073-2076.

Lenau H, Muller A, Maier-Lewz H. Efficacy and Tolerance of a mixture of plant extracts and alpha tocopherol acetate in patients with irritable bladder and or urinary incontinence. Therapiewoche 1984;34:6054-6059.

Leng-Peschlow E. *Plantago ovata* seeds as dietary fibre supplement: physiological and metabolic effects in rats. Br J Nutr 1991;66:331349.

Leung AY. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*. New York-Chichester: Wiley; 1980.

Lewis WH, Zenger VE, Lynch RG. No adaptogen response of mice to ginseng and *Eleutherococcus* infusions. J Ethnopharmacol 1983;8:209-214.

Li W, Zhou CH, Lu QL. [Effects of Chinese materia medica in activating blood and stimulating menstrual flow on the endocrine function of ovary-uterus and its mechanisms.] Zhongguo Zhong Xi Yi Jie He Za Zhi 1992;12:165-168,134.

Li MH, Zhang HL, Yang BY. [Effects of ginkgo leave concentrated oral liquor in treating asthma.] Zhongguo Zhong Xi Yi Jie He Za Zhi 1997;17:216-218.

Li N, Chen X, Han C, Chen J. [Chemopreventive effect of tea and curcumin on DMBA-induced oral carcinogenesis in hamsters.] Wei Sheng Yan Jiu 2002;31:354-357.

Li CZ, Cao ZG, Yang R, Shang ZH, Jin LJ, Cobert EF. [Effects of baicalin on the expression of pro-MMP-1 and MMP-3 in human gingival fibroblasts and periodontal ligament cells.] Zhonghua Kou Qiang Yi Xue Za Zhi 2004;39:197-200.

Li YP, Wang YM. Evaluation of tussilagone: a cardiovascular-respiratory stimulant isolated from Chinese herbal medicine. Gen Pharmacol. 1988;19(2):261-263.

Lin JH, Lo YY, Shu NS, et al. Control of preweaning diarrhea in piglets by acupuncture and Chinese medicine. Am J Chin Med 1988;16:75-80.

Lin RT. [An experimental study of dan sheng improving the mandibular bone fracture healing.] Zhonghua Kou Qiang Yi Xue Za Zhi 1992;27:215-216,256.

Lin CC, Lu JM, Yang JJ, Nabba T, Hatton M. Anti-inflammatory and radical scavenge effects of *Arctium lappa*. Am J Chin Med 1996a;24:127-137.

Lin CC, Shieh DE. The anti-inflammatory activity of *Scutellaria rivularis* extracts and its active components, baicalin, baicalein and wogonin. Am J Chin Med 1996b;24:31-36.

Lin MT, Wang JJ, Young MS. The protective effect of dl-tetrahydropalmatine against the development of amygdala kindling seizures in rats. Neurosci Lett 2002;320:113-116.

Lin J, Dong HF, Oppenheim JJ, Howard OM. Effects of astragali radix on the growth of different cancer cell lines. World J Gastroenterol. 2003 Apr;9(4):670-673.

Lis-Balchin M, Hart S, Simpson E. Buchu *(Agathosma betulina* and *A. crenulata,* Rutaceae*)* essential oils: their pharmacological action on guinea-pig ileum and antimicrobial activity on microorganisms. J Pharm Pharmacol 2001;53:579-582.

Lis-Balchin M, Hart S. Studies on the mode of action of the essential oil of lavender (*Lavandula angustifolia* P. Miller). Phytother Res 1999;13:540-542.

Lissoni P, Giani L, Zerbini S, Trabattoni P, Rovelli F. Biotherapy with the pineal immunomodulating hormone melatonin versus melatonin plus aloe vera in untreatable advanced solid neoplasms. Nat Immun 1998;16:27-33.

Liu J, Liang P, Yin C, et al. Effects of several Chinese herbal aqueous extracts on human sperm motility in vitro. Andrologia 2004;36:78-83.

Lloyd JU. History of the Vegetable Drugs of the Pharmacopoeia of the United States, 1911. Available online at Henriette's Herbal Homepage: http://www.henriettesherbal.com/eclectic/lloyd-hist/index.html

Lo HC, Tu ST, Lin KC, Lin SC. The anti-hyperglycemic activity of the fruiting body of *Cordyceps* in diabetic rats induced by nicotinamide and streptozotocin. Life Sci 2004;74:2897-2908.

Loeper ME. Mistletoe *(Viscum album)*. The Longwood Herbal Task Force, The Centre for Holistic Pediatric Education and Research, 1999. Available at: www.mcp.edu/hebal/default.htm. Accessed June 2005.

Long D, Ballentine NH, Marks JG, Jr. Treatment of poison ivy/oak allergic contact dermatitis with an extract of jewelweed. Am J Contact Dermatitis 1997;8:150-153.

Lorenz J, Ferlinz R. Expektoranzien: pathophysiologie und therapie der mukostase. Arzneimitteltherapie 1985;3:22-27.

Louis M, Kowalski SD. Use of aromatherapy with hospice patients to decrease pain, anxiety, and depression and to promote an increased sense of well-being. Am J Hosp Palliat Care 2002;19:381-386.

Lu H, Liu GT. Anti-oxidant activity of dibenzocyclooctene lignans isolated from Schisandraceae. Planta Med 1992;58:311-313.

Lu Y, Chen D, Deng J, Tian L. Effect of *Smilax china* on adjunctive arthritis mouse. Zhong Yao Cai. 2003;26:344-346.

Lupattelli G, Marchesi S, Lombardini R, Roscini AR, Trinca F, Gemelli F, Vaudo G, Mannarino E. Artichoke juice improves endothelial function in hyperlipemia. Life Sci. 2004 Dec 31;76(7):775-782.

Madabushi R, Frank B, Drewelow B, Derendorf H, Butterweck V. Hyperforin in St. John's wort drug interactions. Eur J Clin Pharmacol. 2006 Feb 14;:1-9

Madar Z, Stark AH. New legume sources as therapeutic agents. Br J Nutr 2002;88(suppl 3):S287-S292.

Magistretti MJ, Conti, Cristoni A. Antiulcer activity of an anthocyanidin from *Vaccinium myrtillus*. Arzneimittelforschung 1988;38:686-690.

Magliulo E, Scevola D, Carosi GP. Investigations on the actions of silybin on regenerating rat liver. Effects on Kupffer's cells. Arzneimittelforschung 1979;29:1024-1028.

Magura EI, Kopanitsa MV, Gleitz J, Peters T, Krishtal OA. Kava extract ingredients, (+)-methysticin and (+/–)-kavain inhibit voltage-operated Na+-channels in rat CA1 hippocampal neurons. Neuroscience 1997;81:345-351.

Mahady GB, Pendland SL, Yun GS, Lu ZZ, Stoia A. Ginger (*Zingiber officinale* Roscoe) and the gingerols inhibit the growth of Cag A+ strains of *Helicobacter pylori*. Anticancer Res 2003;23:3699-3702.

Makino T, Ito M, Kiuchiu F, Ono T, Muso E, Honda G. Inhibitory effect of decoction of *Perilla frutescens* on cultured murine mesangial cell proliferation and quantitative analysis of its active constituents. Planta Med 2001;67:24-28.

Malhotra CL, Mehta VL, Das PK, Dhalla NS. Studies on Withania-ashwagandha, Kaul. V. The effect of total alkaloids (ashwagandholine) on the central nervous system. Indian J Physiol Pharmacol 1965;9:127-136.

Malik ZA, Siddiqui S. Hypotensive effect of freeze dried garlic *(Allium sativum)* sap in dog. J Pak Med Assoc 1981;31:12-13.

Manez S, Recio MC, Gil I, et al. A glycosyl analogue of diacylglycerol and other antiinflammatory constituents from Inula viscosa. J Nat Prod 1999;62:601-604.

Mann C, Staba EJ. The chemistry, pharmacology, and commercial formulations of chamomile. In: Craker LE, Simon JE, eds. *Herbs, Spices, and Medicinal Plants: Recent Advances in Botany, Horticulture, and Pharmacology,* vol 1. Arizona: Oryx Press; 1986:235-280.

Manning R. *The Illustrated Stock Doctor.* Sydney: Pacific Publishing Company; 1883.

Mao SP, Cheng KL, Zhou YF [Modulatory effect of *Astragalus membranaceus* on Th1/Th2 cytokine in patients with herpes simplex keratitis.] Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24:121-123.

Maquart FX, Chastang F, Simeon A, Birembaut P, Gillery P, Wegrowski Y. Triterpenes from *Centella asiatica* stimulate extracellular matrix accumulation in rat experimental wounds. Eur J Dermatol 1999;9:289-296.

Marcilhac A, Dakine N, Bourhim N, et al. Effect of chronic administration of *Ginkgo biloba* extract or Ginkgolide on the hypothalamic-pituitary-adrenal axis in the rat. Life Sci 1998;62:2329-2340.

Maros T, Racz G, Katonai B, Kovacs VV. Wirkungen der *Cynara scolymus*—Extrakte auf die Regeneration der Rattenleber. Arzneimittelforschung 1966;16:127-129.

Marsella R, Nicklin CF, Melloy C. The effects of capsaicin topical therapy in dogs with atopic dermatitis: a randomized, double-blinded, placebo-controlled, cross-over clinical trial. Vet Dermatol 2002;13:131-139.

Martarelli D, Martarelli B, Pediconi D, Nabissi MI, Perfumi M, Pompei P. Hypericum perforatum methanolic extract inhibits growth of human prostatic carcinoma cell line orthotopically implanted in nude mice. Cancer Lett. 2004 Jul 8;210(1):27-33.

Martin N, Bardisa L, Pantoja C, Roman R, Vargas M. Experimental cardiovascular depressant effects of garlic *(Allium sativum)* dialysate. J Ethnopharmacol 1992;37:145-149.

Martin HB, McCallum M, Stofer WD, Eichinger MR. Kavain attenuates vascular contractility through inhibition of calcium channels. Planta Med 2002;68:784-789.

Martin KW, Ernst E. Herbal medicines for treatment of bacterial infections: a review of controlled clinical trials. J Antimicrob Chemother 2003;51:241-246.

Martinez Conesa C, Vicente Ortega V, Yanez Gascon MJ, Garcia Reverte JM, Canteras Jordana M, Alcaraz Banos M. [Experimental model for treating pulmonary metastatic melanoma using grape-seed extract, red wine and ethanol.] Clin Transl Oncol 2005;7:115-121.

Marzocco S, Piacente S, Pizza C, et al. Inhibition of inducible nitric oxide synthase expression by yuccaol C from Yucca schidigera roezl. Life Sci 2004;75:1491-1501.

Massoco CO, Silva MR, Gorniak SL, Spinosa MS, Bernardi MM. Behavioral effects of acute and long-term administration of catnip *(Nepeta cataria)* in mice. Vet Hum Toxicol 1995;37:530-533.

Matev M, Angelova I, Koichev A, Leseva M, Stefanov G. [Clinical trial of a *Plantago major* preparation in the treatment of chronic bronchitis.] Vutr Boles 1982;21:133-137.

Mathur R, Gupta SK, Singh N, Mathur S, Kochupillai V, Velpandian T. Evaluation of the effect of *Withania somnifera* root extracts on cell cycle and angiogenesis.: J Ethnopharmacol. 2006 Jan 9.

Matsuda H, Nakamura S, Shiomoto H, Tanaka T, Kubo M. [Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. IV. Effect of 50% methanolic extract from *Arctostaphylos uva-ursi* (L.) Spreng. (bearberry leaf) on melanin synthesis.] Yakugaku Zasshi 1992a;112:276-282.

Matsuda H, Nakamura S, Tanaka T, Kubo M. [Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. V. Effect of water extract from *Arctostaphylos uva-ursi* (L.) Spreng. (bearberry leaf) on the antiallergic and antiinflammatory activities of dexamethasone ointment.] Yakugaku Zasshi 1992b;112:673-677.

Matsuda H, Yamazaki M, Asanuma Y, Kubo M. Promotion of hair growth by *Ginseng radix* on cultured mouse vibrissal hair follicles. Phytother Res 2003;17:797-800.

Mazzanti MF, Cometa G, Tomassini L. Sedative and spasmolytic effects of *Viburnum tinus* L. and its major pure compounds. Phytother Res 1998;12:S89-S91.

McDaniel S, Goldman GD. Consequences of using escharotic agents as primary treatment for nonmelanoma skin cancer. Arch Dermatol 2002;138:1593-1596.

McHarg T, Rodgers A, Charlton K. Influence of cranberry juice on the urinary risk factors for calcium oxalate kidney stone formation. BJU Int 2003;92:765-768.

Mechirova E, Domorakova I.NADPH-diaphorase activity in the spinal cord after ischemic injury and the effects of pretreatment with *Ginkgo biloba* extract (EGb 761). Acta Histochem 2002;104:427-430.

Mehlhorn H, Schmahl G, Schmidt J. Extract of the seeds of the plant Vitex agnus castus proven to be highly efficacious as a repellent against ticks, fleas, mosquitoes and biting flies. Parasitol Res. 2005 Mar;95(5):363-5. Epub 2005 Jan 29.

Mehta AK, Binkley P, Gandhi SS, Ticku MK. Pharmacological effects of *Withania somnifera* root extract on GABAA receptor complex. Indian J Med Res 1991;94:312-315.

Merriam EA, Campbell BD, Flood LP, Welsh CJR, McDaniel HR, Busbee DL. Enhancement of immune function in rodents using a complex plant carbohydrate which stimulates macrophage secretion of immunoreactive cytokines. In: Klatz RM, ed. *Advances in Anti-Aging Medicine,* vol 1. Larchmont, NY: Mary Ann Liebert, Inc.; 1995:181-203.

Meybe R, ed. *The Complete New Herbal*. London: Elm Tree Books; 1988.

Milkowska-Leyck K, Filipek B, Strzelecka H. Pharmacological effects of lavandulifolioside from *Leonurus cardiaca*. J Ethnopharmacol 2002;80:85-90.

Milks, HJ. Practical Veterinary Pharmacology, Materia Medica and Therapeutics. Alex Eger, Inc., Chicago, 1949.

Miller DM, Brodell RT. Human papillomavirus infection: treatment options for warts. Am Fam Physician 1996;53:135-143,148-150.

Miller AL. Botanical influences on cardiovascular disease. Altern Med Rev 1998;3:422-431.

Mills S. *The Complete Guide to Modern Herbalism*. London: Thorsons; 1989:22.

Mills S. Acupharmacology: a fundamental approach to herbal therapeutics, part 2. Mod Phytother 1997;3.

Mills S, Bone K. *Principles and Practice of Phytomedicine*. Sydney: Churchill Livingston; 2000.

Min KT, Koo BN, Kang JW, Bai SJ, Ko SR, Cho ZH. Effect of ginseng saponins on the recombinant serotonin type 3A receptor expressed in xenopus oocytes: implication of possible application as an antiemetic. J Altern Complement Med. 2003 Aug;9(4):505-510.

Mitchell J, Rook A. *Botanical Dermatology—Plants and Plant Products Injurious to the Skin*. Vancouver: Greengrass; 1979.

Mittman P. Randomized,double-blind study of freeze-dried *Urtica dioica* in the treatment of allergic rhinitis. Planta Med 1990;56:44-47.

Mittra S, Datta A, Singh SK, Singh A. 5-Hydroxytryptamine-inhibiting property of Feverfew: role of parthenolide content. Acta Pharmacol Sin 2000;21:1106-1114.

Miyamoto K, Katsuragi T, Abdu P, Furukawa T. Effects of baicalein on prostanoid generation from the lung and contractile responses of the trachea in guinea pig. Am J Chin Med 1997;25:37-50.

Moalic S, Liagre B, Corbiere C, et al. A plant steroid, diosgenin, induces apoptosis, cell cycle arrest and COX activity in osteosarcoma cells. FEBS Lett 2001;506:225-230.

Momin RA, Nair MG. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from *Apium graveolens* Linn. seeds. Phytomedicine 2002;9:312-318.

Moon EJ, Lee YM, Lee OH, et al. A novel angiogenic factor derived from *Aloe vera* gel: beta-sitosterol, a plant sterol. Angiogenesis 1999;3:117-123.

Mooreville M, Fritz RW, Mulholland SG. Enhancement of the bladder defense mechanism by an exogenous agent. J Urol 1983;130:607-609.

Moorhead LD. Contributions to the physiology of the stomach. XXVIII. Further studies on the action of the bitter tonic on the secretion of gastric juice. J Pharmacol Exp Ther 1915;7:577-589.

Morazzoni P, Bombardelli E. *Silybum marianum (Carduus marianus)*. Fitoterapia 1995;66:3-42.

Morisset T, Cote NG, Panisset JC. Evaluation of the healing activity of hydrocotyle tincture in the treatment of wounds. Phytother Res 1987;1:117-121.

Morris J, Burke V, Mori TA, Vandongen R, Beilin LJ. Effects of garlic extract on platelet aggregation: a randomized placebo-controlled double-blind study. Clin Exp Pharmacol Physiol 1995;22:414-417.

Mors WB, do Nascimento MC, Pereira BMR, Pereira NA. Plant natural products active against snake bite—the molecular approach. Phytochemistry 2000;55:627-642.

Motomura N, Sakurai A, Yotsuya Y. Reduction of mental stress with lavender odorant. Percept Mot Skills 2001;93:713-718.

Moxley RA, Schneider NR. Apparent toxicosis associated with lily-of-the-valley *(Convallaria majalis)* ingestion in a dog. J Am Vet Med Assoc 1989;195:485-487.

Mukherjee PK, Verpoorte R, Suresh B. Evaluation of in-vivo wound healing activity of *Hypericum patulum* (Family: hypericaceae) leaf extract on different wound model in rats. J Ethnopharmacol 2000;70:315-321.

Mukhopadhyay A, Basu N, Ghatak N, Gujral PK. Antiinflammatory and irritant activities of curcumin analogues in rats. Agents Actions 1982;12:508-515.

Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. Med Sci Monit. 2004 Apr;10(4):RA55-62.

Mulla MS, Su T. Activity and biological effects of neem products against arthropods of medical and veterinary importance. J Am Mosq Control Assoc 1999;15:133-152.

Muller-Limmroth W, Frohlich HH. [Effect of various phytotherapeutic expectorants on mucociliary transport.] Fortschr Med 1980;98:95-101.

Munday PL, Wilson SK. Comparative efficacy of clove oil and other chemicals in anaesthetization of *Pomacentrus amboinensis,* a coral reef fish. J Fish Biol 1997;51:931-938.

Murch SJ, Simmons CB, Saxena PK. Melatonin in feverfew and other medicinal plants. Lancet 1997;350:1598-1599.
Murphy LL, Lee TJ. Ginseng, sex behavior, and nitric oxide. Ann N Y Acad Sci 2002;962:372-377.
Murray MT. The Healing Power of Herbs. 2nd ed. Rocklin California: Prima Publishing; 1995:56.
Nadkarni AK, Dr KM. Nadkarni's Indian Materia Medica, vol 1. 3rd ed. Reprinted Bombay: Popular Prakashan; 1976.
Nagata M. Efficacy of commercial hypoallergenic diets in canine allergic dermatosis. Jpn J Vet Dermatol 1999;5:25-29.
Nagle TM, Torres SM, Horne KL, Grover R, Stevens MTA Randomized, Double-Blind, Placebo-Controlled Trial to Investigate the Efficacy and Safety of a Chinese Herbal Product (P07P) for the Treatment of Canine Atopic Dermatitis. Vet Dermatol 12[5]:265-274.
Nagourney RA. Garlic: medicinal food or nutritional medicine? J Medicinal Foods 1998;1:13-28.
Nammi S, Gudavalli R, Babu BS, Lodagala DS, Boini KM. Possible mechanisms of hypotension produced 70% alcoholic extract of Terminalia arjuna (L.) in anaesthetized dogs. BMC Complement Altern Med. 2003 Oct 16;3:5.
Nathan PJ, Clarke J, Lloyd J, et al. The acute effects of an extract of *Bacopa monnieri* (Brahmi) on cognitive function in healthy normal subjects. In: *Human Psychopharmacology, Clinical and Experimental*. Chichester, United Kingdom: John Wiley & Sons; 2001:345-351.
Newall CA, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Health-Care Professionals*. London: Pharmaceutical Press; 1996:124-126.
Ng TB, Li WW. Effects of ginsenosides, lectins and *Momordica charantia* insulin–like peptide on corticosterone production by isolated rat adrenal cells. J Ethnopharmacol 1987;21: 21-29.
Ni JD, Ding RK, Lu GH. [Protective effect of dansheng injection on experimental rabbits' spinal cord injury.] Hunan Yi Ke Da Xue Xue Bao 2002;27:507-508.
Nicholson JA, Darby TD, Jarboe CH. Viopudial, a hypotensive and smooth muscle antispasmodic from *Viburnum opulus*. Proc Soc Exp Biol Med 1972;140:457-461.
Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia 2000;71(suppl 1):S1-S5.
Noorlander DO. US Patent 4670263 1987: Nontoxic, germicide and healing compositions. Cited in Australian College of Phytotherapy notes.
Nosal'ova G, Strapkova A, Kardosova A, Capek P, Zathurecky L, Bukovska E. Antitussive efficacy of the complex extract and the polysaccharide of marshmallow (*Althaea officinalis* L. var. Robusta). Pharmazie 1992;47:224-226.
Obertreis B, Ruttkowski T, Teucher T. Benke B, Schmitz H. Ex vivo, in vitro inhibition of lipopolysaccharide stimulated tumour necrosis factor alpha and interleukin 1 beta secretion in human whole blood by extractum urticae diocae folorum. Arzneimittelforschung 1996;46(4):389-394.
Obertreis B, Giller K, Teucher T. Benke B, Schmitz H. Anitinflammatory effect of *Urtica dioica* folia extract in comparison to caffeic malic acid. Arzneimitteforschung 1996;46:52-56.
Office of Technology Assessment (OTA). Essiac. Unconventional Cancer Treatments: A Report of the Office of Technology Assessment to the United States Congress. Washington, D.C.: US Government Printing Office, 1990. Report No.: Reprinted by the Commonweal Research Institute.
Ogle CW, Dai S, Ma JC. The haemostatic effects of the Chinese herbal drug Yunnan Bai Yao: a pilot study. Am J Chin Med 1976;4:147-152.
Ogle CW, Dai S, Cho CH. The hemostatic effects of orally administered Yunnan Bai Yao in rats and rabbits. Comp Med East West 1977;5:155-160.
Ohashi Y, Tsuchiya Y, Koizumi K, Sakurai H, Saiki I. Prevention of intrahepatic metastasis by curcumin in an orthotopic implantation model. Oncology. 2003;65(3):250-258.
Ohtaki Y, et al. Deoxycholic Acid as an Endogenous Risk Factor for Hepatocarcinogenesis and Effects of Gomisin A, a Lignan Component of Schizandra Fruits. Anticancer Res. Mar 1996; 16(2):751-755.
Ohyama K, Akaike T, Hirobe C, Yamakawa T.. (a) Cytotoxicity and apoptotic inducibility of *Vitex agnus-castus* fruit extract in cultured human normal and cancer cells and effect on growth. Biol Pharmaceut Bull. 2003;26:10-18.
Okeniyi JA, Olubanjo OO, Ogunlesi TA, Oyelami OA. Comparison of healing of incised abscess wounds with honey and EUSOL dressing. J Altern Complement Med. 2005 Jun;11(3):511-513.
Okimasu E, Moromizato Y, Watanabe S, et al. Inhibition of phospholipase A2 and platelet aggregation by glycyrrhizin, an antiinflammation drug. Actu Med Okayama 1981;37:457-463.
Ooi VE, Liu F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. Curr Med Chem 2000;7:715-729.
Osterhoudt KC, Lee SK, Callahan JM, Henretig FM. Catnip and the alteration of human consciousness. Vet Hum Toxicol 1997;39:373-375.
Ozaki Y. Vasodilative effects of indole alkaloids obtained from domestic plants, *Uncaria rhynchophylla* Miq. and *Amsonia elliptica* Roem. et Schult. Nippon Yakurigaku Zasshi 1990;95:47-54.
Paez X, Hernandez L. Topical hemostatic effect of a common ornamental plant, the geraniaceae *Pelargonium zonale*. J Clin Pharmacol 2003;43:291-295.
Paladini AC, Marder M, Viola H, Wolfman C, Wasowski C, Medina JH. Flavonoids and the central nervous system: from forgotten factors to potent anxiolytic compounds. J Pharm Pharmacol 1999;51:519-526.
Panda S, Kar A. Changes in thyroid hormone concentrations after administration of ashwagandha root extract to adult male mice. J Pharm Pharmacol 1998;50:1065-1068.
Panda S, Kar A. *Withania somnifera* and *Bauhinia purpurea* in the regulation of circulating thyroid hormone concentrations in female mice. J Ethnopharmacol 1999;67:233-239.
Pandian RS, Anuradha CV, Viswanathan P. Gastroprotective effect of fenugreek seeds (Trigonella foenum graecum) on experimental gastric ulcer in rats. J Ethnopharmacol. 2002 Aug;81(3):393-397.
Panossian A, Wikman G, Wagner H. Plant adaptogens III.* Earlier and more recent aspects and concepts on their mode of action. Phytomedicine 1999;6:287-300.
Panossian AG, Oganessian AS, Ambartsumian M, Gabrielian ES, Wagner H, Wikman G. Effects of heavy physical exercise and adaptogens on nitric oxide content in human saliva. Phytomedicine. 1999b;6:17-26.
Pantoja CV, Chiang LC, Norris BC, Concha JB. Diuretic, natriuretic and hypotensive effects produced by *Allium sativum* (garlic) in anaesthetized dogs. J Ethnopharmacol 1991;31:325-331.
Patočka J. Biologically active pentacyclic triterpenes and their current medicine: signification. J Appl Biomed 2003;1:7-12.
Patzelt-Wenczler R, Ponce-Poschl E. Proof of efficacy of Kamillosan® cream in atopic eczema. Eur J Med Res 2000;5:171-175.
Paulova J, Dvorak M, Kolouch F, Vanova L, Janeckova L. [Verification of the hepatoprotective and therapeutic effect of silymarin in experimental liver injury with tetrachloromethane in dogs]: overeni hepatoprotektivniho a terapeutickeho ucinku silymarinu pri experimentalnim poskozeni jater tetrachlormetanem u psu. Vet Med (Praha) 1990;35:629-635.
Pawlowski Z, Chwirot E. (1970). 5th Int Knogr Infektionskr: 277.
Peeters E, Driessen B, Steegmans R, Henot D, Geers R. Effect of

supplemental tryptophan, vitamin E, and a herbal product on responses by pigs to vibration. J Anim Sci. 2004 Aug; 82(8):2410-2420.

Peigen X, Keji C. Recent advances in clinical studies of Chinese medicinal herbs. 1. Drugs affecting the cardiovascular system. Phytother Res 1987;1:53-57.

Peng A, Gu Y, Lin SY. Herbal treatment for kidney disease. Ann Acad Med Singapore 2005;34:44-51.

Peoa, N., Aurx, A. and Sumano, H.: A comparative trial of garlic, its extract and ammonium-potassium tartrate as anthelmintics in carp. J. Ethnopharmacol. 24: 199-203, 1988.

Percival SS. Use of echinacea in medicine. Biochem Pharmacol 2000;60:155-158.

Peredery O, Persinger MA. Herbal treatment following post-seizure induction in rat by lithium pilocarpine: *Scutellaria lateriflora* (Skullcap), *Gelsemium sempervirens* (Gelsemium) and *Datura stramonium* (Jimson Weed) may prevent development of spontaneous seizures. Phytother Res 2004;18:700-705.

Perfumi M, Santoni M, Ciccocioppo R, Massi M. Blockade of gamma-aminobutyric acid receptors does not modify the inhibiton of ethanol intake induced by *Hypericum perforatum* in rats. Alcohol Alcohol 2002;37:540-546.

Petersen FJ. Materia Medica and Clinical Therapeutics, 1905. Available online at Henriette's Herbal Homepage: http://www.henriettesherbal.com/eclectic/petersen/index.html

Petrowicz O, Gebhardt R, Donner M, et al. Effects of artichoke leaf extract (ALE) on lipoprotein metabolism in vitro and in vivo. Atherosclerosis 1997;129:147.

Piao BK, Wang YX, Xie GR, et al. Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small cell lung cancer patients. A prospective randomized controlled clinical trial. Anticancer Res 2004;24:303-309.

PinDer D. Antioxidant activity of burdock (*Arctium lappa* linne): its scavenging effect on free radical and active oxygen. J Am Oil Chem Soc 1998;75:4,455-461.

Pittler MH, Ernst E. Kava extract for treating anxiety. The Cochrane Database of Systematic Reviews 2003.

Pizzorno JE, Murray MT. *Hydrastis canadensis, Berberis vulgaris, Berberis aquifolium* and other berberine containing plants. In: *Textbook of Natural Medicine*. Seattle: John Bastyr College Publications; 1985 (looseleaf).

Pocta J. Therapeutic use of lobeline Spofa. Cas Lek Cesk 1970;109:865 [in Czech].

Polesuk J, Ameodeo JM, Ma TS (1973) Microchemical Investigation of Medicinal Plants. X. Analysis of the Chinese Herbal Drug Yunnan Bai Yao. Mikrochim Acta 4, 507-517.

Poncemacotela M, Navarro-Alegria I, Martinez-Gordillo MN, Alvarez-Chacon R. In vitro effect against giardia of 14 plant extracts. Rev Invest Clin 1994;46:343-347. [In Spanish]

Prabhakar Y, Kumar S. *Crataeva nurvala:* an Ayurvedic remedy for urological disorders Br J Phytother 1997;4:103-109.

Prakash AO, Mather S, Mather R. Effect of feeding *Gymnema sylvestre* leaves on blood glucose in berylliumnitrate treated rats. J Ethnopharmacol 1986;18:143-146.

Preininger V. The pharmacology and toxicology of the Papaveraceae alkaloids. In: Manske RHF, Holmes HL, eds. *The Alkaloids,* vol 15. New York: Academic Press; 1975:239.

Pryme IF, Bardocz S, Pusztai A, Ewen SW, Pfuller U. A mistletoe lectin (ML-1)-containing diet reduces the viability of a murine non-Hodgkin lymphoma tumor. Cancer Detect Prev 2004;28:52-56.

Rackova L, Majekova M, Kost'alova D, Stefek M. Antiradical and antioxidant activities of alkaloids isolated from *Mahonia aquifolium*. Structural aspects. Bioorg Med Chem. 2004;12: 4709-4715.

Rácz-Kotilla, Racz G, Solomon A. The action of *Taraxacum officinale* extracts on the body weight and diuresis of laboratory animals. Planta Med 1974;26:212-217.

Rafatullah S, Tariq M, Al-Yahya MA, Mossa JS, Ageel AM. Evaluation of turmeric (Curcuma longa) for gastric and duodenal antiulcer activity in rats. J Ethnopharmacol. 1990 Apr;29(1): 25-34.

Rahman K, Billington D. Dietary supplementation with aged garlic extract inhibits ADP-induced platelet aggregation in humans. J Nutr 2000;130:2662-2665.

Rahman MT, Alimuzzaman M, Ahmad S, Chowdhury AA. Antinociceptive and antidiarrhoeal activity of *Zanthoxylum rhetsa*. Fitoterapia 2002;73:340-342.

Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh HK. Adaptogenic effect of *Bacopa monniera* (Brahmi). Pharmacol Biochem Behav 2003a;75:823-830.

Rai D, Bhatia G, Sen T, Palit G. Anti-stress effects of *Ginkgo biloba* and *Panax ginseng:* a comparative study. J Pharmacol Sci 2003b;93:458-464.

Ramamoorthy L, Tizard IR. Induction of apoptosis in a macrophage cell line RAW 264.7 by acemannan, a β-(1,4)-acetylated mannan. Molecular Pharma 1998;53:415-421.

Ramaswamy AS, et al. Pharmacological studies on *Centella asiatica* Linn. *(Brahma manduki)* (N.O. Umbelliferae). J Res Indian Med 1970;4:160-175.

Randall C, Randall H, Dobbs F, Hutton C, Sanders H. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. J R Soc Med 2000;93:305-309.

Reichling J, Schmokel H, Fitzi J, Bucher S, Saller R. Dietary support with Boswellia resin in canine inflammatory joint and spinal disease. Schweiz Arch Tierheilkd 2004;146:71-79.

Reid G, Sobel JD. Bacterial adherence in the pathogenesis of urinary tract infection: a review. Rev Infect Dis 1987;9:470-487

Reider N, Komericki P, Hausen BM, Fritsch P, Aberer W. The seamy side of natural medicines: contact sensitization to arnica (*Arnica montana* L.) and marigold (*Calendula officinalis* L.). Contact Dermatitis 2001;45:269-272.

Remington JP, Wood HC. The Dispensatory of the United States of America 1918. Available at: www.henriettesherbal.com. Accessed June 2005.

Reynolds JEF, ed. Martindale: The Extra Pharmacopoeia. 28th ed. London: The Pharmaceutical Press; 1982.

Reynolds JEF, ed. Martindale: The Extra Pharmacopoeia. 29th ed. London: The Pharmaceutical Press; 1989.

Ribes G, Sauvaire Y, Da Costa C, et al. Effects of fenugreek seeds on endocrine pancreatic secretions in dogs. Ann Nutr Metab 1984;28:37-43.

Ribes G, Sauvaire Y, Da Costa C, Baccou JC, Loubatieres-Mariani MM. Anitidiabetic effects of subfractions from fenugreek seeds in diabetic dogs. Proc Soc Exp Biol Med 1986;182:159-166.

Riccioppo Neto F. Electropharmacological effects of berberine on canine cardiac Purkinje fibres and ventricular muscle and atrial muscle of the rabbit. Br J Pharmacol 1993;108:534-537.

Richardson MA, Russell NC, Sanders T, Barrett R, Salveson C. Assessment of outcomes at alternative medicine cancer clinics: a feasibility study. J of Alternative & Complementary Medicine. 2001;7(1):19-32.

Richardson MA, Ramirez T, Tamayo C, Perez C, Palmer JL. Flor-Essence Herbal tonic use in North America. Herbalgram 2000;50:40-6.

Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle *(Urtica dioica),* an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. FEBS Lett 1999;442:89-94.

Rieli Mendes F, Mattei R, de Araujo Carlini EL. Activity of *Hypericum brasiliense* and *Hypericum cordatum* on the central nervous system in rodents. Fitoterapia 2002;73:462-471.

Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. Am J Health Syst Pharm. 2002 Mar 1;59(5):417-422.

Riggs DR, DeHaven JI, Lamm DL. *Allium sativum* (garlic) treatment for murine transitional cell carcinoma. Cancer 1997;79:1987-1994.

Roberts A, Williams JM. The effect of olfactory stimulation on fluency, vividness of imagery and associated mood: a preliminary study. Br J Med Psychol 1992;65:197-199.

Rogala E, Skopinska-Rozewska E, Sawicka T, Sommer E, Prosinska J, Drozd J. The influence of *Eleuterococcus senticosus* on cellular and humoral immunological response of mice. Pol J Vet Sci 2003;6(3 suppl):37-39.

Rolland A, Fleurentin J, Lanhers MC, et al. Behavioural effects of the American traditional plant *Eschscholzia californica:* sedative and anxiolytic properties. Planta Med. 19915:212-216.

Rolland A, Fleurentin J, Lanhers MC, Misslin R, Mortier F. Neurophysiological effects of an extract of *Eschscholzia californica* Cham (Papaveraceae). Phytother Res 2001;15:377-381.

Roodenrys S, Booth D, Bulzomi S, et al. Chronic effects of Brahmi *(Bacopa monnieri)* on human memory. Neuropsychopharmacology 2002;27:279-281.

Rudakewich M, Ba F, Benishin CG. Neurotrophic and neuroprotective actions of ginsenosides Rb(1) and Rg(1). Planta Med 2001;67:533-537.

Sairam K, Rao CV, Goel RK. Effect of *Centella asiatica* Linn on physical and chemical factors induced gastric ulceration and secretion in rats. Indian J Exp Biol 2001a;39:137-142.

Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of *Bacopa monniera* in gastric ulcer models. Phytomedicine 2001b;8:423-430.

Sairam K, et al. Antidepressant activity of standardized extract of *Bacopa monniera* in experimental models of depression in rats. Phytomedicine 2002;9:207-211.

Samuelsen AB. The traditional uses, chemical constituents and biological activities of *Plantago major* L. A review. J Ethnopharmacol 2000;71:1-21.

Sancho R, Lucena C, Macho A, et al. Immunosuppressive activity of capsaicinoids: capsiate derived from sweet peppers inhibits NF-kappaB activation and is a potent antiinflammatory compound in vivo. Eur J Immunol 2002;32:1753-1763.

Sander O, Herborn G, Rau R. [Is H15 (resin extract of Boswellia serrata, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study.] Z Rheumatol 1998;57:11-16.

Sandler BI. The influence of Eleutherococcus extract on cerebral circulation in patients with acute cranio-cerebral trauma after rheoencephalography, 1972;11:109-113 Lek Sredstva Dal'nego, Vostoka, USSR.

Sandler BI, Sandler TV. Influence of Eleutherococcus on ceratin clinico-biochemical indexes in the blood of patients with acute craniocerebral trauma. 1972;11:114-19. Lek Sredstva Dal'nego, Vostoka, USSR.

Santini F, Vitti P, Ceccarini G, et al. In vitro assay of thyroid disruptors affecting TSH stimulated adenylate cyclase activity. J Endorcrinol Invest 2003;26:950-955.

Sastravaha G, Yotnuengnit P, Booncong P, Sangtherapitikul P. Adjunctive periodontal treatment with *Centella asiatica* and *Punica granatum* extracts. A preliminary study. J Int Acad Periodontol 2003;5:106-115.

Satoh K, Yasuda I, Nagai F, Ushiyama K, Akiyama K, Kano I. The effects of crude drugs using diuretic on horse kidney (Na+ + K+)-adenosine triphosphatase. Yakugaku Zasshi. 1991 Feb; 111(2):138-145.

Satoh H, Nishida S. Electropharmacological actions of *Ginkgo biloba* extract on vascular smooth and heart muscles. Clin Chim Acta 2004;342:13-22.

Satrija F, Nansen P, Bjorn H, Murtini S, He S. Effect of papaya latex against *Ascaris suum* in naturally infected pigs. J Helminthol 1994;68:343-346.

Satyanarayana S, et al. Evaluation of herbal preparations for hypoglycemic activity in normal and diabetic rabbits. Pharmaceut Biol. 2003;41:6,466-472.

Scarff DH, Lloyd DH. Double blind, placebo controlled, crossover study of evening primrose oil in the treatment of canine atopy. Vet Rec. 1992;131(5):97-99

Schapowal A. Petasites Study Group. Randomized controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. BMJ 2002;324:144-146.

Schempp CM, Winghofer B, Ludtke R, Simon-Haarhaus B, Schopf E, Simon JC. Topical application of Saint John's Wort (*Hypericum perforatum* L.) and of its metabolite hyperforin inhibits the allostimulatory capacity of epidermal cells. Br J Dermatol 2000;142:979-984.

Schirrmacher K, et al. Effects of (+/–)-kavain on voltage-activated inward currents of dorsal root ganglion cells from neonatal rats. Eur Neuropsychopharmacol 1999;9:171-176.

Schliebs R, Liebmann A, Bhattacharya SK, Kumar A, Ghosal S, Bigl VLC, Singh BB, Dagenais S. Systemic administration of defined extracts from *Withania somnifera* (Indian Ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain. Neurochem Int 1997;30: 181-190.

Schmidgall J, Schnetz E, Hensel A. Evidence for bioadhesive effects of polysaccharides and polysaccharide-containing herbs in an ex vivo bioadhesion assay on buccal membranes. Planta Med. 2000 Feb;66(1):48-53.

Schmidt CF, et al. Experiments with Chinese drugs. 1. Tang-kuei. Chin Med J 1924;38:362.

Schmidt D, Sobota A. An examination of the anti-adhernce activity of cranberry juice on urinary and nonurinary bacterial isolates. Microbios 1988;55:173-181.

Scholar EM, Wolterman K, Birt DF, Bresnick E. The effect of diets enriched in cabbage and collards on murine pulmonary metastasis. Nutr Cancer 1989;12:121-126.

Schramm HM. Iscador Clinical Documentation Summary and Expert Report, January 15, 2001.

Schulz V, Hänsel R, Tyler V. *Rational Phytotherapy.* 4th ed. Berlin: Springer; 2001.

Schulze-Tanzil G, de SP, Behnke B, Klingelhoefer S, Scheid A, Shakibaei M. Effects of the antirheumatic remedy hox alpha—a new stinging nettle leaf extract—on matrix metalloproteinases in human chondrocytes in vitro. Histol Histopathol 2002;17:477-485.

Scott DW, Miller WH, Decker GA, Wellington JR. Comparison of the clinical efficacy of two commercial fatty acid supplements (Efa Vet and DVM Derm caps), evening primrose oil, and cold water marine fish oil in the management of allergic pruritis in dogs: A double blinded study. Cornell Vet. 1992;82(3):319-329.

Seifen E, Adams RJ, Riemer RK. Sanguinarine: a positive inotropic alkaloid which inhibits cardiac Na+,K+-ATPase. Eur J Pharmacol 1979;60:373-377.

Seitz U, Ameri A, Pelzer H, Gleitz J, Peters T. Relaxation of evoked contractile activity of isolated guinea-pig ileum by (+/–)-kavain. Planta Med 1997;63:303-306.

Self H. Hilton Herbs—Latest News: Equine Cushing's disease results, 2003 Available online at: http://www.

hiltonherbs.com/news_details.cfm?itemid=171&cfid=562777&cftoken=19285394 (accessed 7-6-05).

Seo K, Jung S, Park M, Song Y, Choung S. Effects of leucocyanidines on activities of metabolizing enzymes and antioxidant enzymes. Biol Pharm Bull 2001;24:592-593.

Seth SD, Jagdeesh G. Cardiac action of *T.terrestris* L. Indian J Med Res 1976;64:1821.

Shanmugasundaram KR, Panneerselvam C, Samudram P, Shanmugasundaram ER. Enzyme changes and glucose utilisation in diabetic rabbits: the effect of Gymnema sylvestre R. Br J Ethnopharmacol 1983;7:205-234.

Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. J Ethnopharmacol 1990;30:265-279.

Shao CR, Chen FM, Tang YX. [Clinical and experimental study on *Ligusticum wallichii* mixture in preventing and treating bronchial asthma.] Zhongguo Zhong Xi Yi Jie He Za Zhi 1994;14:465-468.

Sharada AC, Solomon FE, Devi PU, Udupa N, Srinivasan KK. Antitumor and radiosensitizing effects of withaferin A on mouse Ehrlich ascites carcinoma in vivo. Acta Oncol 1996;35:95-100.

Sharifi AM, Darabi R, Akbarloo N. Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. J Ethnopharmacol 2003a;86:219-224.

Sharifi AM, Darabi R, Akbarloo N. Study of antihypertensive mechanism of *Tribulus terrestris* in 2K1C hypertensive rats: role of tissue ACE activity. Life Sci 2003b;73:2963-2971.

Sharma RD. An evaluation of hypocholesterolemic factor of fenugreek seeds *(T. foenum graecum)* in rats. Nutr Rep Int 1986;33:669-677.

Sharma ML, Bani S, Singh GB. Anti-arthritic activity of boswellic acids in bovine serum albumin (BSA)-induced arthritis. Int J Immunopharmacol 1989;11:647-652.

Sharma SS, Kochupillai V, Gupta SK, Seth SD, Gupta YK. Antiemetic efficacy of ginger *(Zingiber officinale)* against cisplatin-induced emesis in dogs. J Ethnopharmacol 1997;57:93-96.

Sheets MA, Unger BA, Giggleman GF Jr, Tizard IR. Studies of the effect of acemannan on retrovirus infections: clinical stabilization of feline leukemia virus-infected cats. Mol Biother 1991;3:41-45.

Sheldon JP. *Dairy Farming: Being the Theory Practice, and Methods of Dairying*. London: Cassell and Company; 1880 (575 pages).

Sheng Y, Pero RW, Amiri A, Bryngelsson C. Induction of apoptosis and inhibition of proliferation in human tumor cells treated with extracts of Uncaria tomentosa. Anticancer Res 1998;18:3363-3368.

Sherry CJ, Hunter PS. The effect of an ethanol extract of catnip *(Nepeta cataria)* on the behavior of the young chick. Experientia 1979;35:237-238.

Shi M, Chang L, He G. Stimulating action of Carthamus tinctorius L., Angelica sinensis (Oliv.) Diels and Leonurus sibiricus L. on the uterus. Zhongguo Zhong Yao Za Zhi. 1995 Mar;20(3): 173-175, 192

Shi JF, Zhu HW, Zhang C, Bian F, Shan JP, Lu WI. Therapeutic effect of Astragalus on patients with chronic glomerulonephritis. Acta University Medicinalis Secondae Shanghai 2002;22:245-248.

Shi Jing-Shan1, Yu Jun-Xian, Chen Xiu-Ping, Xu Rui-Xia. Pharmacological actions of *Uncaria* alkaloids, rhynchophylline and isorhynchophylline. Acta Pharmacol Sin 2003;24:97-101.

Shi M, Chang L, He G. Stimulating action of Carthamus tinctorius L., Angelica sinensis (Oliv.) Diels and Leonurus sibiricus L. on the uterus. Chung Kuo Chung Yao Tsa Chih 1995;20:173-175.

Shidoji Y, Ogawa H. Natural occurrence of cancer-preventive geranylgeranoic acid in medicinal herbs. J Lipid Res 2004;45(6): 1092-1093. Epub April 1, 2004.

Shin WL. Sedative action of flavonoids and saponins from the seeds of *Zizyphus vulgaris* var. spinosa Bunge. Saengyak Hakhoechi 1981;12:23-27.

Shiota G, et al. Rapid Induction of Hepatocyte Growth Factor mRNA after Administration of Gomisin A, a Lignan Component of Shizandra Fruits. Res Commun Mol Pathol Pharmacol. Nov1996; 94(2):141-146.

Shipochliev T. [Uterotonic action of extracts from a group of medicinal plants.] Vet Med Nauki 1981;18:94-98.

Shivpuri DN, Menon MPS, Prakash D. A crossover double-blind study on *Tylophora indica* in the treatment of asthma and allergic rhinitis. J Allergy 1969;43:145-150.

Shivpuri DN, Singhal SC, Parkash D. Treatment of asthma with an alcoholic extract of *Tylophora indica:* a cross-over, double-blind study. Ann Allergy 1972;30:407-412.

Shukla B, Visen PK, Patnaik GK, Dhawan BN. Choleretic effect of andrographolide in rats and guinea pigs. Planta Med. 1992 Apr;58(2):146-149.

Sievenpiper JL, Arnson JT, Vidgen E, et al. A systematic quantitative analysis of the literature of the high variability in Ginseng (*Panax* spp). Diabetes Care 2004;27:839-840.

Sindrup SH, Madsen C, Bach FW, Gram LF, Jensen TS. St. John's wort has no effect on pain in polyneuropathy. Pain 2001;91: 361-365.

Singh A, Saxena E, Bhutani KK. Adrenocorticosterone alterations in male, albino mice treated with *Trichopus zeylanicus, Withania somnifera* and *Panax ginseng* preparations. Phytother Res. 2000;14:122-125.

Singh B, Chandan BK, Gupta DK. Adaptogenic activity of a novel withanolide-free aqueous fraction from the roots of *Withania somnifera* Dun. (Part II). Phytother Res 2003a;17:531-536.

Singh B, Saxena AK, Chandan BK, Gupta DK, Bhutani KK, Anand KK. Adaptogenic activity of a novel, withanolide-free aqueous fraction from the roots of *Withania somnifera* Dun. Phytother Res 2001;15:311-318.

Singh BB, Mishra LC, Vinjamury SP, Aquilina N, Singh VJ, Shepard N. The effectiveness of *Commiphora mukul* for osteoarthritis of the knee: an outcomes study. Altern Ther Health Med 2003b;9:74-79.

Singh N, Singh SP, Nath R etal. Prevention of induced lung adenomas by Withania somnifera (L) Dunal in albino mice. Int J Crude Drug Res 1986 24:90-100.

Singh NP, Lai HC. Artemisinin induces apoptosis in human cancer cells. Anticancer Res 2004;24:2277-2280.

Singh R. Evaluation of antilithic properties of varun *(Crataeva nurvala),* an indigenous drug. J Res Indian Med 1991;10: 35-39.

Singh RB, Niaz MA, Ghosh S. Hypolipidemic and antioxidant effects of *Commiphora mukul* as an adjunct to dietary therapy in patients with hypercholesterolemia. Cardiovasc Drugs Ther 1994;8:659-664.

Singh RP, Dhanalakshmi S, Agarwal C, Agarwal R. Silibinin strongly inhibits growth and survival of human endothelial cells via cell cycle arrest and downregulation of survivin, Akt and NF-kappaB: implications for angioprevention and antiangiogenic therapy. Oncogene. 2005 Feb 10;24(7):1188-1202.

Singh YN, Singh NN. Therapeutic potential of kava in the treatment of anxiety disorders. CNS Drugs. 2002;16:731-743.

Singletary K. Inhibition of DMBA-induced mammary tumorigenesis by rosemary extract. FASEB J 1991;5:5A927.

Skalisz LL, Beijamini V, Andreatini R. Effect of *Hypericum perforatum* on marble-burying by mice. Phytother Res 2004;18:399-402.

Soh C. The effects of natural food preservative substances on the development and survivial of intestinal Helminth eggs and larvaeII Action on Ancylostoma caninum larvae. American Jounral of tropical medicine and hygiene 1960 9:8-10

Song Z, Kharazmi A, Wu H, et al. Effects of ginseng treatment on neutrophil chemiluminescence and immunoglobulin G subclasses in a rat model of chronic *Pseudomonas aeruginosa* pneumonia. Clin Diagn Lab Immunol 1998;5:882-887.

Sotnikova R, Kettmann V, Kostalova D, Taborska E. Relaxant properties of some aporphine alkaloids from *Mahonia aquifolium*. Methods Find Exp Clin Pharmacol 1997;19:589-597.

Soto CG, Burhanuddin S. Clove oil as a fish anaesthetic for measuring length and weight of rabbitfish *(Siganus lineatus)*. Aquaculture 1995;136:149-152.

Spain Ward P. History of Hoxsey treatment. Contract report submitted to US Congress, Office of Technology Assessment, May 1988.

Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effects of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomedicine 2000;85-89.

Srimal RC. Dhawan BN pharmacology of diferuloyl methane (curcumin), a nonsteroid antiinflammatopry agent. J Pharm Pharmacol 1973;25:447-452.

Srivastava R, Srimal RC. Modification of certain inflammation induced biochemical changes by curcumin. Indian J Med Res 1985;81:215-223.

Staumont G, Fioramonti J, Frexinos J, Bueno L. Changes in colonic motility induced by sennosides in dogs: evidence of a prostaglandin mediation. Gut 1988;29:1180-1187.

Stephensen 1974 cited on http://www.froytang.no/html/cattle.htm accessed July 2005.

Stewart PM, Wallace AM, Valentino R, et al. Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. Lancet 1987;ii:821-824.

Stevenson PC, Simmonds MS, Sampson J, Houghton PJ, Grice P. Wound healing activity of acylated iridoid glycosides from *Scrophularia nodosa*. Phytother Res 2002;16:33-35.

Stocker HR. Sedative und hypnogene Wirkung des Hopfens. Schweizer Brauerei Rundschau 1967;78:80-80.

Stoss M, Michels C, Peter E, Beutke R, Gorter RW. Prospective cohort trial of Euphrasia single-dose eye drops in conjunctivitis. J Altern Complement Med 2000;6:499-508.

Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M. Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. Neurology 2001;56:1219-1221.

Stull CL, Spier SJ, Aldridge BM, Blanchard M, Stott JL. Immunological response to long-term transport stress in mature horses and effects of adaptogenic dietary supplementation as an immunomodulator. Equine Vet J 2004;36:583-589.

Subbotina MD, Timchenko VN, Vorobyov MM, Konunova YS, Aleksandrovih YS, Shushunov S. Effect of oral administration of tormentil root extract (Potentilla tormentilla) on rotavirus diarrhea in children: a randomized, double blind, controlled trial. Pediatr Infect Dis J. 2003 Aug;22(8):706-711

Suguna L, Sivakumar P, Chandrakasan G. Effects of *Centella asiatica* extract on dermal wound healing in rats. Indian J Exp Biol 1996;34:1208-1211.

Suleyman H, Demirezer LO, Kuruuzum UA. Analgesic and antipyretic activities of *Rumex patientia* extract on mice and rabbits. Pharmazie 2001;56:815-817.

Sun Y, Hersh EM, Talpaz M, Lee SL, Wong W, Loo TL, Mavligit GM. Immune restoration and/or augmentation of local graft versus host reaction by traditional Chinese medicinal herbs. Cancer 1983:52(1):70-73.

Sundaram SG, Milner JA. Impact of organosulfur compounds in garlic on canine mammary tumor cells in culture. Cancer Lett 1993;74:85-90.

Sunila ES, Kuttan G. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. J Ethnopharmacol 2004;90:339-346.

Surh YJ, Lee E, Lee JM. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. Mutat Res 1998;402:259-267.

Suzuki M, Yoshino K, Maeda-Yamamoto M, Miyase T, Sano M. Inhibitory effects of tea catechins and O-methylated derivatives of (-)-epigallocatechin-3-O-gallate on mouse type IV allergy. J Agric Food Chem 2000;48:5649-5653.

Swaim SF, Riddell KP, McGuire JA. Effects of topical medications on the healing of open pad wounds in dogs. J Am Anim Hosp Assoc 1992;28:499-502.

Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. Evaluation of traditional plant treatments for diabetes: studies in streptozotocin diabetic mice. Acta Diabetol Lat 1989;26:51-55.

Szelenyi I, Isaac O, Thiemer K. [Pharmacological experiments with compounds of chamomile. III. Experimental studies of the ulcerprotective effect of chamomile (author's transl)]. Planta Med. 1979;35:218-227.

Szentmihályi K, Kery A, Then M, et al. Potassium-sodium ratio for the characterization of medicinal plant extracts with diuretic activity. Phytother Res 1998;12:163-166.

Tachikawa E, Kudo K. Proof of the mysterious efficacy of ginseng: basic and clinical trials: suppression of adrenal medullary function in vitro by ginseng. J Pharmacol Sci 2004;95:140-144.

TajuddinA S, Latif A, Qasmi IA:. Aphrodisiac activity of 50% ethanolic extracts of *Myristica fragrans* (Houtt) (nutmeg) and *Syzygium aromaticum* (L.) (Merr and Perry) (clove) in male mice: a comparative study. BMC Complementary and Alternative Medicine 2003;3:6.

Tamaya MD, et al. Possible mechanism of steroid action of the plant herb extracts glycyrrhizin, glycyrrhetinic acid, and paeoniflorin: Inhibition by plant herb extracts of steroid protein binding in the rabbit. Am J Obstet Gynecol 1986;155:1134-1139.

Tanner AG, Owen ER, Seal DV. Successful treatment of chronically infected wounds with sugar paste. Eur J Clin Microbiol Infect Dis. 1988 Aug;7(4):524-525.

Tao X, Lipsky PE. The Chinese anti-inflammatory and immunosuppressive herbal remedy *Tripterygium wilfordii* Hook F. Rheum Dis Clin North Am 2000;26:29-50, viii.

Tao X, Younger J, Fan FZ, Wang B, Lipsky PE. Benefit of an extract of *Tripterygium wilfordii* Hook F in patients with rheumatoid arthritis: a double-blind, placebo-controlled study. Arthritis Rheum 2002l;46:1735-1743.

Taylor LH, Kobak KA. An open-label trial of St. John's Wort *(Hypericum perforatum)* in obsessive-compulsive disorder. J Clin Psychiatry 2000;61:575-578.

Terris MK, Issa MM, Tacker JR. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. Urology 2001;57:26-29.

Thiruvengadam KV, Haranatii K, Sudarsan S, et al. *Tylophora indica* in bronchial asthma: a controlled comparison with a standard anti-asthmatic drug. J Indian Med Assoc 1978;71:172-176.

Thompson Coon JS, Ernst E. Herbs for serum cholesterol reduction: a systematic view. J Fam Pract 2003;52:468-478.

Tian J, Chen XM, Li LS. Effects of *Cordyceps sinensis* on renal cortical Na-K-ATPase activity and calcium content in gentamicin nephrotoxic rats. J Am Soc Nephrol 1991a;2:670.

Tian J, Chen XM, Li LS. Use of *Cordyceps sinensis* in gentamicin induced ARF: a preliminary animal experimentation and observation of cell culture. JAMA 1991b;2:670. Abstract 83P.

Tian J, Yang JY, Li LS. Observation of effects of *Cordyceps sinensis* in isolated perfused kidney of gentamicin nephrotoxic rats. J Am Soc Nephrol 1991c;2:671.

Tilak JC, Banerjee M, Mohan H, Devasagayam TP. Antioxidant availability of turmeric in relation to its medicinal and culinary uses. Phytother Res 2004;18:798-804.

Tisserand R, Balacs T. *Essential Oil Safety.* Edinburgh: Churchill Livingstone; 1995.

Tita B, Bello U, Faccendini P, Bartolini, R., Bolle, P. Taraxacum officinale W.: pharmacological effect of ethanol extract. Pharmacol Res 1993;27:23-24.

Titus Nelson N, 1862. The American Eclectic Practice Of Medicine, As Applied To The Diseases Of Domestic Animals. Baker and Godwin, New York. Also available online at the David Winston's Herbal Therapeutics Research homepage: http://www.herbaltherapeutics.net/DomesticAnimal Diseases.pdf

Toda N, Usui H, Nishino N, Fujiwara M. Cardiovascular effects of capsaicin in dogs and rabbits. J Pharm Exp Ther 1972;181:512-521.

Tohda C, Kuboyama T, Komatsu K. Dendrite extension by methanol extract of Ashwagandha (roots of *Withania somnifera*) in SK-N-SH cells. Neuroreport 2000;11:1981-1985.

Topic B, Hasenöhrl RU, Häcker R, Huston JP Enhanced conditioned inhibitory avoidance by a combined extract of *Zingiber officinale* and *Ginkgo biloba*. Phytother Res 2002;16:312-315.

Tort L, Puigcerver, M.; Crespo, S.; Padrós, F. Cortisol and haematological response in sea bream and trout subjected to the anaesthetics clove oil and 2-phenoxyethanol. Aquaculture Res 2002;33:11,907-910.

Touvay C, Etienne A, Braquet P. Inhibition of antigen-induced lung anaphylaxis in the guinea-pig by BN 52021 a new specific PAF-acether receptor antagonist isolated from Ginkgo biloba. Agents Actions 1986;17:371-372.

Treasure J. Urtica semen reduces serum creatinine levels. J Am Herbalists Guild 2003;4:22-25.

Tripathi RM, Sen PC, Das PK. Further studies on the mechanism of the anti-anaphylactic action of Albizzia lebbeck, an Indian indigenous drug. J Ethnopharmacol 1979a;1:397-400.

Tripathi RM, Sen PC, Das PK. Studies on the mechanism of action of *Albizzia lebbeck,* an Indian indigenous drug used in the treatment of atopic allergy. J Ethnopharmacol 1979b;1:385-396.

Trovato A, Raneri E, Kouladis M, Tzakou O, Taviano MF, Galati EM. Anti-inflammatory and analgesic activity of *Hypericum empetrifolium* Willd. (Guttiferae). Farmaco 2001;56:455-457.

Tsukada K, Tokunaga K, Iwama T, Mishima Y, Tazawa K, Fujimaki M. Cranberry juice and its impact on peristomal skin conditions for urostomy patients. Ostomy Wound Manage 1994;40: 60-62, 64, 66-68.

Tsung PK. *Allergy and Chinese Herbal Medicine,* Monograph. Long Beach, Calif: Oriental Healing Arts Institute; 1987.

Tyler VE. *The Honest Herbal.* 3rd ed. Philadelphia: Strickley; 1993.

Uddin S, Hussain AR, Manogaran PS, et al. Curcumin suppresses growth and induces apoptosis in primary effusion lymphoma. Oncogene 2005;24:7022-7030.

Udintsev SN, Shakhov VP, Borovskoi IG, Ibragimova SG. The effect of low concentrations of adaptogen solutions on the functional activity of murine bone marrow cells in vitro. Biofizika 1991;36:105-108.

Uehara M, Sugiura J, Sakurai K. A trial of oolong tea in the management of recalcitrant atopic dermatitis Arch Dermatol 2001;137:42-43.

Uglyanitsa KN, Nefyodov LI, Doroshenko YM, et al. Ukrain: a novel antitumor drug. Drugs Exp Clin Res 2000;26:341-356.

Umehara K, Nakamura M, Miyase T, Kuroyanagi M, Ueno A. Studies on differentiation inducers. VI. Lignan derivatives from *Arctium fructus*. Chem Pharm Bull (Tokyo) 1996;44:2300-2304.

Umezu T. Behavioral effects of plant-derived essential oils in the Geller type conflict test in mice. Jpn J Pharmacol. 2000;83: 2,150-153.

Upton R, Hawthorn Berry (Crataegus spp): Analytical, Quality Control and Therapeutic Monograph. American Herbal Pharmacopeia, Scotts Valley, CA. 1999.

Usow V. Farmakologiia i toxikologiia. 1958;21:31-34.

Vacca DD, Walsh RA. The antibacterial activity of an extract obtained from *Ascophyllum nodosum*. J Am Pharm Assoc 1954;43:24-26.

Van Den Broucke CO, Lemli JA. Spasmolytic activity of the flavonoids from *Thymus vulgaris*. Pharm World Sci 1983;5:9-14.

Van den Hoven R, Zappe H, Zitterl-Eglseer K, Jugl M, Franz C. Study of the effect of Bronchipret on the lung function of five Austrian saddle horses suffering recurrent airway obstruction (heaves). Vet Rec 2003;152:555-557.

Varalakshmi P, Shamila Y, Latha E. Effect of *Crataeva nurvala* in experimental urolithiasis. J Ethnopharmacol 1990;28:313-321.

Vazquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. J Ethnopharmacol 1996;55:69-75.

Velasco G, Galve-Roperh I, Sanchez C, Blazquez C, Guzman M. Hypothesis: cannabinoid therapy for the treatment of gliomas? Neuropharmacology 2004;47:315-323.

Viana AF, Heckler AP, Fenner R, Rates SM. Antinociceptive activity of *Hypericum caprifoliatum* and *Hypericum polyanthemum* (Guttiferae). Braz J Med Biol Res 2003;36:631-634. Epub April 22, 2003.

Vikas Kumar, Singh PN, Muruganandam AV, Bhattacharya SK. Effect of Indian *Hypericum perforatum* Linn. on animal models of cognitive dysfunction. J Ethnopharmacol. 2000;72:1-2,119-128.

Vikas Kumar, Singh PN, Bhattacharya SK. Anti-stress activity of Indian *Hypericum perforatum* L. Indian J Exp Biol 2001;39: 4,344-349.

Viola H, Wasowski C, Levi M, Wolfman C, *Silveira R,* Dajas F, Medina J, Paladini A. Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptor-ligand with anxiolytic effects. Planta Med 1995;61:213-216.

Vogel G; Tuchweber B; Trost W; Mengs U. Protection by silibinin against *Amanita phalloides* intoxication in beagles. Toxicol Appl Pharmacol 1984;73:355-362.

Volate SR, Davenport DM, Muga SJ, Wargovich MJ. Modulation of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin). Carcinogenesis 2005;26:1450-1456.

Vykusova B. New technologies and new species in aquaculture. Proceedings of a Special International Conference. Vurh Vodnany 2003;39:1-2,1-148.

Wagner H, Horhammer L, Frank U. Lithospermic acid, the antihormonally active principle of *Lycopus europaeus* L. and *Symphytum officinale* L. Arzneimittelforschung 1970;20:705-712.

Wagner H, Jurcic K. On the spasmolytic activity of valeriana extracts. Planta Med 1979;37:84-86.

Walker AF, Marakis G, Morris AP, Robinson PA. Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension. Phytother Res 2002;16:48-54.

Wang SM Lee LJ, Lin WW, Chang CM, Effects of a water-soluble extract of *Cordyceps sinensis* on steroidogenesis and capsular morphology of lipid droplets in cultured rat adrenocortical cells. J Cell Biochem 1998;69:483-489.

Wang X, Wei L, Ouyang JP, et al. Effects of an angelica extract on human erythrocyte aggregation, deformation and osmotic fragility. Clin Hemorrheol Microcirc 2001;24:201-205.

Wang H, Li J, Yu L, Zhao Y, Ding W. Antifibrotic effect of the Chinese herbs, *Astragalus mongholicus* and *Angelica sinensis,* in a rat model of chronic puromycin aminonucleoside nephrosis. Life Sci 2004;74:1645-1658.

Wang LS, Zhou G, Zhu B, Wu J, Wang JG, Abd El-Aty AM, Li T, Liu J, Yang TL, Wang D, Zhong XY, Zhou HH, St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole. Clin Pharmacol Ther 75:191, 2004

Ward P, Fasitsas S, Katz SE. Inhibition, resistance development, and increased antibiotic and antimicrobial resistance caused by nutraceuticals. J Food Prot 2002;65:528-533.

Wasser SP, Weis AL. Therapeutic effects of substances occurring in higher Basidiomycetes mushrooms: a modern perspective. Crit Rev Immunol 1999;19:65-96.

Wei F, Zou S, Young A, Dubner R, Ren K. Effects of four herbal extracts on adjuvant-induced inflammation and hyperalgesia in rats. J Altern Complement Med 1999;5:429-436.

Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, Cleton FJ, Osanto S. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer. 2004 Jul;40(11):1713-1723.

Weiss RF, Volker F. *Herbal Medicine.* 2nd ed. Stuttgart, Germany: Thieme; 1988.

Weizman Z, Alkrinawi S, Goldfarb D, Bitran C. Efficacy of herbal tea preparation in infantile colic. J Pediatr. 1993 Apr;122(4):650-652.

Wende K, Krenn L, Unterrieder I, Lindequist U. Red clover extracts stimulate differentiation of human osteoblastic osteosarcoma HOS58 cells. Planta Med 2004;70:1003-1005.

Werk, W. 1994, "Wasser ausleiten: elektrolytneutral", Erfahrungsheilkunde, vol. 11, pp. 712-714

Weseler A, Geiss HK, Saller R, Reichling J. Antifungal effect of Australian tea tree oil on Malassezia pachydermatis isolated from canines suffering from cutaneous skin disease. Schweiz Arch Tierheilkd. 2002 May;144(5):215-221.

Westerhof W, Das PK, Middelkoop E, Verschoor J, Storey L, Regnier C. Mucopolysaccharides from psyllium involved in wound healing. Drugs Exp Clin Res 2001;27:165-175.

White DJ, Billingham C, Chapman S, et al. Podophyllin 0.5% or 2.0% v podophyllotoxin 0.5% for the self treatment of penile warts: a double blind randomised study. Genitourin Med 1997;73:184-187.

Widy-Tyszkiewicz E, Piechal A, Joniec I, Blecharz-Kin K. Long term administration of *Hypericum perforatum* improves spatial learning and memory in the water maze. Biol Pharm Bull 2002;25:1289-1294.

Wilburn AJ, King DS, Glisson J, Rockhold RW, Wofford MR. The natural treatment of hypertension. J Clin Hypertens (Greenwich) 2004;6:242-248.

Willard T. The Wild Rose Scientific Herbal Wild Rose College of Natural Healing Calgary 1991 p95.

Williamson EW, Evans FJ. Bradford, England: Health Science Press; 1975.

Willuhn G. Violae tricoloris herba. In: Bissett NG, ed. *Herbal Drugs and Phytopharmaceuticals.* Stuttgart: Medpharm; 1994: 527-529.

Wimer BM, Mann PL. Apparent pokeweed mitogen cure of metastatic gum melanoma in an older dog. Cancer Biother Radiopharm 2000;15:201-205.

Winking M, Sarikaya S, Rahmanian A, Jödicke A, Böker DK. Boswellic Acids Inhibit Glioma Growth: A New Treatment Option? J. Neuro-Onc 46(2):97-103, 2000.

Winslow K. Veterinary Materia Medica and Therapeutics, 1908. William R. Jenkins, New York.

Winston D. Herbal Therapeutics: Specific Indications for Herbs and Herb Formulas, ed 8, Herbal Therapeutics Research Library, Broadway, NJ, 2003.

Winterhoff H, Gumbinger HG, Vahlensieck U, et al. Endocrine effects of *Lycopus europaeus* L. following oral application. Arzneimittelforschung 1994;44:41-45.

Wohlfart R, Hänsel R, Schmidt H. An investigation of sedative-hypnotic principles in hops, Part 3. Planta Med 1982;45: 224.

Wohlfart R, Hänsel R, Schmidt H. The sedative-hypnotic principle of hops. Planta Med 1983;48:120-123.

Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. Altern Ther Health Med 2003;9:74-78.

Woo KC, Park YS, Jun DJ, et al. Phytoestrogen cimicifugoside-mediated inhibition of catecholamine secretion by blocking nicotinic acetylcholine receptor in bovine adrenal chromaffin cells. J Pharmacol Exp Ther 2004;309:641-649. Epub February 2, 2004.

Wood M. *Herbalism: Basic Doctrines, Energetics, and Classification.* Berkeley, Calif: North Atlantic Books; 2004.

Wren RC. Potter's New Cyclopedia of Botanical Drugs and Preparations, 1907 (revised, 1988) Potter & Clarke, 1985.

Wu G, Yamamoto K, Mori T, Inatomi H, Nagasawa H. Improvement by guan-mu-tong *(Caulis aristolochiae manshuriensis)* of lactation in mice. Am J Chin Med 1995;23:159-165.

Wuttke W, Jarry H, Christoffel V, Spengler B, Seidlova-Wuttke D. Chaste tree *(Vitex agnus-castus):* pharmacology and clinical indications. Phytomedicine 2003;10:348-357.

Wynn S, Marsden S. *Manual of Natural Veterinary Medicine.* Sydney: Mosby; 2003:158.

Xia Z, Gu J, Ansley DM, Xia F, Yu J. Antioxidant therapy with *Salvia miltiorrhiza* decreases plasma endothelin-1 and thromboxane B2 after cardiopulmonary bypass in patients with congenital heart disease. J Thorac Cardiovasc Surg 2003;126:1404-1410.

Xie SS. Immunoregulatory effect of polysaccharide of *Acanthopanax senticosus* (PAS). I. Immunological mechanism of PAS against cancer. [In Chinese] Zhonghua Zhong Liu Za Zhi 1989;11:338-340.

Yamaguchi N, Yoshida J, Ren LJ, et al. Augmentation of various immune reactivities of tumor-bearing hosts with an extract of Cordyceps sinensis. Biotherapy 1990;2:199-205.

Yamamoto H, Ogawa T. Antimicrobial activity of perilla seed polyphenols against oral pathogenic bacteria. Biosci Biotechnol Biochem 2002;66:921-924.

Yan ZY. Effect of radix Salviae miltiorrhizae on gastric mucosal barrier. Zhonghua Wai Ke Za Zhi. 1990 May;28(5):298-301, 319.

Yan L, Yee JA, Li D, McGuire MH, Thompson LU. Dietary flaxseed supplementation and experimental metastasis of melanoma cells in mice. Cancer Lett 1998;124:181-186.

Yang IW, Chou CC, Yung BYM. Dose-dependent effects of berberine on cell cycle pause and apoptosis in Balb/c 3T3 cells. Naunyn-Schmiedeberg's Arch Pharmacol 1996;354:102-106.

Yang CS, Liao J, Yang GY, Lu G. Inhibition of lung tumorigenesis by tea. Exp Lung Res 2005;31:135-144.

Yokozawa T, Liu ZW, Chen CP. Protective effects of *Glycyrrhizae radix* extract and its compounds in a renal hypoxia (ischemia)-reoxygenation (reperfusion) model. Phytomedicine 1999;6: 6,439-445.

Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, Chokechaijaroenporn O. Antidiabetic activity of Aloe juice. I. Clinical trial in new cases of diabetes mellitus. Phytomedicine 1996:3:241-243.

Yoshida Y, Wang MQ, Liu JN, Shan BE, Yamashita U. Immunomodulating activity of Chinese medicinal herbs and *Oldenlandia diffusa* in particular. Int J Immunopharmacol 1997;19:359-370.

Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S. Antiangiogenic activity of curcumin in hepatocellular carcinoma cells implanted nude mice. Clin Hemorheol Microcirc 2005;33(2):127-135.

Youn HJ, Noh JW. Screening of the anticoccidial effects of herb extracts against *Eimeria tenella*. Vet Parasitol 2001;96:257-263.

Yuan Y, Hou S, Lian T, Han Y. [Studies of *Rehmannia glutinosa* Libosch. f. hueichingensis as a blood tonic.] Zhongguo Zhong Yao Za Zhi 1992;17:366-368.

Yuan A, Liu C, Huang X. [Treatment of 34 cases of chronic aplastic anemia using prepared *Rehmannia* polysaccharide associated with stanozolol.] Zhongguo Zhong Xi Yi Jie He Za Zhi 1998;18:351-353.

Yuan SL, Wang XJ, Wei YQ. [Anticancer effect of tanshinone and its mechanisms.] Ai Zheng 2003;22:1363-1366.

Yuan CS, Mehendale SR, Wang CZ, et al. Effects of *Corydalis yanhusuo* and *Angelicae dahuricae* on cold pressor-induced pain in humans: a controlled trial. J Clin Pharmacol 2004;44:1323-1327.

Yun TK. Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. Mutat Res 2003;523:63-74.

Yun JH, Pang EK, Kim CS, et al. Inhibitory effects of green tea polyphenol (-)-epigallocatechin gallate on the expression of matrix metalloproteinase-9 and on the formation of osteoclasts. J Periodontal Res 2004;39:300-307.

Yushu H, Yuzhen C. The effect of *Panax ginseng* extract (GS) on insulin and corticosteroid receptors. J Trad Chin Med 1988;8:293-295.

Yang SH, Lin JK, Huang CJ, Chen WS, Li SY, Chiu JH. Silibinin inhibits angiogenesis via Flt-1, but not KDR, receptor up-regulation. J Surg Res. 2005 Sep;128(1):140-146.

Zafar Iqbal, A Jabbar, MS Akhtar, G Muhammad, M Lateef. In vitro anthelmintic activity of *Allium sativum, Zingiber officinale, Cucurbita mexicana* and *Ficus religiosa*. Int J Agric Biol 2001;3:454-457.

Zanoli P, Rivasi M, Baraldi C, Baraldi M. Pharmacological activity of hyperforin acetate in rats. Behav Pharmacol 2002;13: 645-651.

Zarkova S. Tribestan experimental and clinical investigations. Sofia, Bulgaria: Sopharma Chemical Pharmaceutical Research Institute 1981.

Zarkova S. Steroid saponins of *Tribulus terrestis* L having a stimulant effect on the sexual functions. Rev Port Ciencias Vet 1984;79:117-126.

Zeng XH, Zeng XJ, Li YY. Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2003;92:173-176.

Zenner L, Callait MP, Granier C, Chauve C. In vitro effect of essential oils from Cinnamomum aromaticum, Citrus limon and Allium sativum on two intestinal flagellates of poultry, Tetratrichomonas gallinarum and Histomonas meleagridis. Parasite. 2003 Jun;10(2):153-157.

Zhang WR, et al. Protective effect of Ginkgo extract on rat brain with transient middle cerebral artery occlusion. Neurol Res 2000;22:517-521.

Zhang X. Influence of *Cordyceps sinensis* on pancreatic islet beta cells in rats with experimental liver fibrogenesis. [In Chinese] Chung Hua Kan Tsang Ping Tsa Chih 2003a;11:93-94.

Zhang M, Ning G, Shou C, Lu Y, Hong D, Zheng X. Inhibitory effect of jujuboside A on glutamate-mediated excitatory signal pathway in hippocampus. Planta Med 2003b;69:692-695.

Zhang R, Zhou J, Jia Z, Zhang Y, Gu G. Hypoglycemic effect of *Rehmannia glutinosa* oligosaccharide in hyperglycemic and alloxan-induced diabetic rats and its mechanism. J Ethnopharmacol 2004;90:39-43.

Zhang XP, Li ZF, Liu XG, et al. Effects of emodin and baicalein on rats with severe acute pancreatitis. World J Gastroenterol 2005;11:2095-2100.

Zhao KS, Mancini C, Doria G. Enhancement of the immune response in mice by *Astragalus membranaceus* extracts. Immunopharmacology 1990;20:225-233.

Zhao J, Sharma Y, Agarwal R. Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradecanoylphorbol 13-acetate caused modulation of anti oxidant and inflammatory enzymes and cyclooxygenase 2 and interleukin-1 alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumour promotion. Mol Carcinogen 1999;26:321-333.

Zhao YQ, Li GQ, Guo CX, Lian X. Evaluation of the effect of TNF alpha RBC immunological function and improvement on renal function by Astragalus root in patients with chronic renal failure. J Mudanjiang Coll 2000;21:5-6.

Zhou JG. Tianjin medical journal, 1960, 2:131.

Zhou DH, Lin LZ. [Effect of Jinshuibao capsule on the immunological function of 36 patients with advanced cancer.] Chungkuo Chung His I Chieh Ho Tsa Chih 1995;15:476-478.

Zhou Q. Journal of Chinese Materia Medica. 1999;30(5):386-388.

Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical use and molecular mechanisms of action of extract of *Ginkgo biloba* leaves in cardiovascular diseases. Cardiovasc Drug Rev 2004a;22:309-319.

Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen CJ. Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. Med Sci Monit 2004b;10:RA187-RA192. Epub July 23, 2004b.

Zhou YM, Huang ZQ, Hu MH, et al. Clinical study on the effect of Shengxueling on idiopathic thrombocytopenic purpura. Chin J Integr Med 2005;11:60-64.

Zhu DPQ. Dong guai. Am J Chin Med 1987;15:117-125.

Zhu YP. *Chinese Materia Media: Chemistry, Pharmacology, and Applications*. Australia: Harwood Academic Publishers; 1998a: 445-448.

Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis*. Part II. J Altern Complement Med 1998b;4:429-457.

Zi X, Simoneau AR. Flavokawain A, a novel chalcone from kava extract, induces apoptosis in bladder cancer cells by involvement of Bax protein-dependent and mitochondria-dependent apoptotic pathway and suppresses tumor growth in mice. Cancer Res 2005;65:3479-3486.

Ziauddin M, Phansalkar N, Patki P, et al. Studies on the immunemodulatory effects of ashwagandha. J Ethnopharmacol 1996;50:69-76.

Zou L, Harkey MR, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity, Life Sci 71:1579, 2002