

Medicinal Herbs: NTP Extracts the Facts



The National Toxicology Program (NTP) has announced that it will design and initiate studies to identify and characterize possible adverse health effects that may be associated with prolonged use or higher doses of some of the most popular medicinal herbs, including *Ginkgo biloba*, *Echinacea angustifolia*, and *Panax quinquefolius* (American ginseng). The NTP studies a large variety of substances to which the population may be exposed in the environment, occupationally, in the food supply, or elsewhere.

Little has been scientifically confirmed regarding either the adverse or beneficial health effects of most of the 1,500-plus herbal products stocked in America's drug stores, grocery stores, and numerous other retail outlets that market these formulations. Many consumers mistakenly assume that because herbal preparations are natural, they are safer, gentler, and less "medicinal" than conventional drugs. Furthermore, they may neither think nor choose to tell their doctors they are using a particular herb and thus risk potential herb-drug interactions. The extent of the nation's self-medication is evidenced by the cornucopia of readily available remedies and the blossoming herbal product market, expected to reach \$5 billion next year.

Under the Dietary Supplement Health and Education Act of 1994, herbal products are not required to be proven safe before marketing. To date, there has been no legal requirement for the testing of herbal products either before or after marketing. Once marketed, the burden of proof is on the U.S. Food and Drug Administration to prove that a dietary supplement is unsafe before it can be removed from shelves. Thus, it falls to the government to test these formulations.

As part of its congressional mandate, the NTP studies biological or physical agents that might not be tested without federal involvement. This includes commercial agents first marketed prior to current testing requirements; orphan drugs, which are used to treat relatively rare diseases affecting fewer than 200,000 people and which might not be developed without federal involvement; and mixtures of chemicals for which evaluations are not required of industry. Medicinal herbs fall under each of these categories. Studies of medicinal herbs cannot be required of manufacturers unless they plan to market their products as drugs (rather than as dietary supplements).

Substances approved for NTP study undergo a series of assays to determine acute, subchronic, and chronic effects. In each case

the route of exposure is designed to simulate the anticipated route of human exposure. Initially the substance is administered daily for 14 days to determine palatability (if administered in food) and how well it is tolerated. The substance may next be administered for 90 days to simulate extended exposure and any related toxicity. Finally, it may be administered chronically for up to 2 years to determine its potential to induce chronic toxicity and/or carcinogenicity. The animal models usually used are Fischer 344 rats and B6C3F1 mice. Most substances tested in animals also undergo one or more assays for genetic toxicity, and additional assays testing for specific health effects such as reproductive toxicity, neurotoxicity, or immunotoxicity may be designed and administered if the test substance is suspected of affecting one or more of those systems. Assays may be terminated at any point if the results of these or other studies make it apparent that further testing is not needed.

To date, the NTP has received several nominations for medicinal plants to be studied. Currently, studies are under way for the herb *Hydrastis canadensis* (goldenseal). Studies on *Symphytum officinale* (comfrey) and pulegone, a chemical found in *Mentha pulegium* (pennyroyal), are being planned, and investigators are currently gathering materials for studies on ginkgo and echinacea. Other plants and substances approved for full studies include *Aloe vera*, ginseng, *Piper methysticum* (kava kava), *Silybum marianum* (milk thistle), and thujone, a compound found in several different spices and herbs. The studies will be conducted by members of the General Toxicology Group within the Toxicology Operations Branch of the Environmental Toxicology Program.

Goldenseal. The root of the goldenseal plant is traditionally used to treat wounds, ulcers, digestive problems, and eye and ear infections. Today, the herb is also used as a laxative, tonic, and diuretic. Goldenseal is used in feminine products such as vaginal douches and is claimed to help with menstrual disorders such as irregular cycle and excessive bleeding. Berberine, one of the chief active components in goldenseal, has antimicrobial and vasodilatory properties and may also be effective in preventing the growth of cancer cells. The other major component of goldenseal, hydrastine (which can be made from berberine), has abortifacient effects and has been shown to induce



Goldenseal

labor in pregnant women when taken orally. Large internal doses of goldenseal may cause convulsions and irritation of the mouth, throat, and stomach, tingling of the skin, paralysis, respiratory failure, and possibly death at very high doses. Chronic use may inhibit vitamin B absorption. Goldenseal was recommended to the NTP for study of reproductive toxicity, developmental toxicity, chronic toxicity, and carcinogenicity.

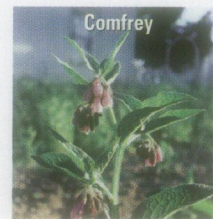
Comfrey. Applied externally, comfrey acts as an anti-inflammatory to promote healing of bruises, sprains, and open wounds. The roots and leaves of the plant contain the protein allantoin, which stimulates cell proliferation. Comfrey is said to help wounds to heal and broken bones to knit. It is also taken internally as an herbal tea to treat gastric ulcers, rheumatic pain, arthritis, bronchitis, and colitis. This is a matter of some concern because comfrey contains several pyrrolizidine alkaloids, primarily symphytine, which have been linked to liver and lung cancer in rats.

Because the hepatotoxic effects of pyrrolizidine alkaloids are well established in both animals and humans, there are no plans to reproduce earlier carcinogenicity studies on comfrey that linked the herb with liver cancer in rats. Rather, the study is anticipated to focus on the reproductive toxicity effects of the herb.

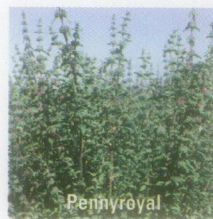
Pulegone. Pulegone is the active ingredient in pennyroyal and is also found in several other species of mint. Pennyroyal is traditionally used as a carminative, insect repellent, emmenagogue, and abortifacient. Prior studies have demonstrated hepatic, renal, and pulmonary toxicity in humans, as well as central nervous system toxicity resulting in seizure, coma, and death.

Pulegone was particularly recommended to the NTP for study because of its toxicity to the developing fetus. In addition to the standard toxicity assays, the substance will be studied for reproductive toxicity, chronic toxicity, and carcinogenicity.

Ginkgo. After several thousand years of use in China, ginkgo has recently enjoyed a swift rise to popularity in the United States. The extract of the ginkgo leaf contains a balance of flavone glycosides (including one suspected high-dose carcinogen, quercetin) and terpene lactones. Ginkgo acts as a blood

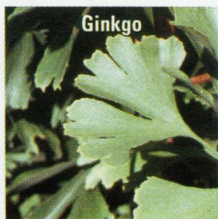


Comfrey



Pennyroyal

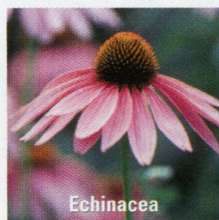
thinner; it improves circulation and is therefore used to treat migraine headaches, depression, and a range of lung and heart problems. In the United States, ginkgo is probably most popularly known for its purported memory-enhancing effects. However, although studies such as that published by researchers at Tarrytown's New York Institute for Medical Research in the 22–29 October 1997 issue of the *Journal of the American Medical Association* indicate that ginkgo may help stabilize and perhaps enhance cognitive function in dementia and Alzheimer disease patients, the herb has not been shown to improve memory in normal, healthy people.



Ginkgo

Ginkgo has been recommended to the NTP for studies of neurotoxicity, chronic toxicity, and carcinogenicity. At this point, the study is expected to focus on histopathological changes in the brain effected by the herb. A possible collaboration with the University of North Carolina at Chapel Hill is in the works.

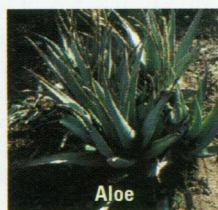
Echinacea. This member of the daisy family is one of the top medicinal herb sellers in the United States. Although once used for everything from snake bites to typhoid, echinacea is most commonly used today as an immunostimulant to treat the common cold, sore throat, and flu. Echinacea is not known to have any serious adverse side effects, although there have been



Echinacea

reports of skin rash and insomnia among users. The herb is available in many forms—dried root or leaf, liquid extract, powder, capsules, tablets, creams, gels, and injections (outside of North America). It has yet to be determined how echinacea is best administered or exactly how—or if—the plant's complex mixture of polysaccharides, flavonoids, essential oils, and other compounds actually produces beneficial effects. Echinacea was recommended to the NTP for study of immunotoxicity, subchronic toxicity, chronic toxicity, and carcinogenicity.

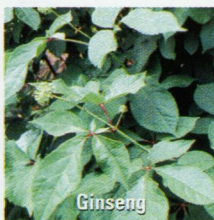
Aloe. The gel of the succulent aloe plant has been used as a balm for minor burns since the time of the ancient Egyptians. Aloe is also taken internally



Aloe

to treat constipation, colitis, peptic ulcers, and diabetes. Thanks to its highly touted powers as a skin moisturizer, aloe now appears in an extensive array of cosmetic products such as soaps, lotions, and skin creams. Several aloe juice health drinks are being marketed as general tonics. Aloe was recommended to the NTP for study in the Tg.AC transgenic mouse. No special toxicity studies were indicated.

Ginseng. Ginseng has long been a popular remedy in Eastern medicine; its Latin name *Panax* is derived from the same root as “panacea,” which gives some idea of the esteem in which this herb is held among its users. Ginseng is used as a mood enhancer, stress reducer, and aphrodisiac. It is also used to treat upset stomach, depression, diabetes, and hypertension.



Ginseng

Reports of so-called ginseng abuse syndrome, a condition symptomized by nervousness, hypertension, insomnia, skin eruptions, diarrhea, and depression that was first described in the 13 April 1979 issue of the *Journal of the American Medical Association*, have been largely debunked. Ginseng was recommended to the NTP for testing of reproductive toxicity, neurotoxicity, chronic toxicity, and carcinogenicity.

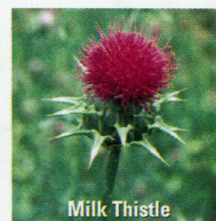
Kava kava. Among the peoples of Oceania, kava kava has a long history of recreational, medicinal, and ceremonial use. Today, the herb is quickly becoming popular in the West as a calmative and antidepressant. The same psychoactive properties that induce restful sleep and promote sociability also make kava kava a likely candidate for abuse;



Kava Kava

chronic heavy use of the herb has been associated with skin problems, liver and kidney dysfunction, and possible hypertension. Kava kava has been recommended to the NTP for genotoxicity, reproductive toxicity, neurotoxicity, chronic toxicity, and carcinogenic testing.

Milk thistle. Milk thistle is used to treat a number of liver conditions including cirrhosis and hepatitis, and has been shown to stimulate protein synthesis within the liver, leading to tissue regeneration. Milk thistle is noted for its potency as an antidote to the toxins of the death cap mushroom, which attack the liver and can cause death if not treated promptly.



Milk Thistle

The herb has also been used historically to treat depression and to increase breast milk production; today it is a staple for pregnant and nursing mothers

who embrace the alternative medicine approach. Milk thistle has been recommended to the NTP for genotoxicity, metabolism, reproductive toxicity, chronic toxicity, and carcinogenicity testing.

Thujone. Thujone is a monoterpene found in several different herbs, including sage, cedar, tansy, and wormwood. Thujone is believed to be the culprit behind the hallucinations, tremors, convulsions, and paralysis that result from drinking the wormwood-based liqueur absinthe. Although the use of thujone in food is banned in the United States, the compound appears in over 20 approved flavorings and food additives. In addition, several readily available nonfood items (including medicinal products such as Vicks VapoRub, fragrances, and perfume additives) contain thujone. Thujone has been recommended to the NTP for genotoxicity, neurotoxicity, reproductive toxicity, chronic toxicity, and carcinogenicity testing.



Wormwood

The NTP continually solicits and receives new nominations for substances to be studied from numerous sources including academia, industry, other government agencies, and the general public. Three committees are involved in reviewing nominations for NTP studies: the Interagency Coordinating Committee for Evaluation of Chemicals (ICCEC, which is made up of scientists representing 11 federal health agencies), the NTP Board of Scientific Counselors (which reviews each nominee's background information and the recommendations made by the ICCEC), and the NTP Executive Committee (which considers the recommendations of the other two committees and formally accepts or rejects each nomination). As public exposure to herbal products continues to grow and usage trends of medicinal plants become more apparent, the NTP will continue to characterize the acute and chronic effects of these products along with those of other chemicals and agents that industry cannot be required to study.