The Value of Plants Used in Traditional Medicine for Drug Discovery

Daniel S. Fabricant and Norman R. Farnsworth

Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois-Chicago, Chicago, Illinois, USA

In this review we describe and discuss several approaches to selecting higher plants as candidates for drug development with the greatest possibility of success. We emphasize the role of information derived from various systems of traditional medicine (ethnomedicine) and its utility for drug discovery purposes. We have identified 122 compounds of defined structure, obtained from only 94 species of plants, that are used globally as drugs and demonstrate that 80% of these have had an ethnomedical use identical or related to the current use of the active elements of the plant. We identify and discuss advantages and disadvantages of using plants as starting points for drug development, specifically those used in traditional medicine. *Key words:* drug discovery, ethnomedicine, plants, traditional medicine. — *Environ Health Perspect* 109(suppl 1):69–75 (2001). *http://ehpnet1.niehs.nih.gov/docs/2001/suppl-1/69-75fabricant/abstract.html*

Fossil records date human use of plants as medicines at least to the Middle Paleolithic age some 60,000 years ago (*1*). From that point the development of traditional medical systems incorporating plants as a means of therapy can be traced back only as far as recorded documents of their likeness. However, the value of these systems is much more than a significant anthropologic or archeologic fact. Their value is as a methodology of medicinal agents, which, according to the World Health Organization (WHO), almost 65% of the world's population have incorporated into their primary modality of health care (*2*). The goals of using plants as sources of therapeutic agents are *a*) to isolate bioactive compounds for direct use as drugs, e.g., digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine; *b*) to produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and/or lower toxicity, e.g., metformin, nabilone, oxycodon (and other narcotic analgesics), taxotere, teniposide, verapamil, and amiodarone, which are based, respectively, on galegine, Δ^9-tetrahydrocannabinol, morphine, taxol, podophyllotoxin, khellin, and khellin; *c*) to use agents as pharmacologic tools, e.g., lysergic acid diethylamide, mescaline, yohimbine; and *d*) to use the whole plant or part of it as a herbal remedy, e.g., cranberry, echinacea, feverfew, garlic, ginkgo biloba, St. John's wort, saw palmetto. In this review we consider the past, present, and future value of employing information from plants used in traditional medical practices (ethnomedicine) for the discovery of new bioactive compounds.

The number of higher plant species (angiosperms and gymnosperms) on this planet is estimated at 250,000 (*3*), with a lower level at 215,000 (*4,5*) and an upper level as high as 500,000 (*6,7*). Of these, only about 6% have been screened for biologic activity, and a reported 15% have been evaluated phytochemically (*8*). With high throughput screening methods becoming more advanced and available, these numbers will change, but the primary discriminator in evaluating one plant species versus another is the matter of approach to finding leads. There are some broad starting points to selecting and obtaining plant material of potential therapeutic interest. However, the goals of such an endeavor are straightforward.

Plants have an advantage in this area based on their long-term use by humans (often hundreds or thousands of years). One might expect any bioactive compounds obtained from such plants to have low human toxicity. Obviously, some of these plants may be toxic within a given endemic culture that has no reporting system to document these effects. It is unlikely, however, that acute toxic effects following the use of a plant in these cultures would not be noticed, and the plant would then be used cautiously or not at all. Chronic toxic effects would be less likely to signal that the plant should not be used. In addition, chemical diversity of secondary plant metabolites that results from plant evolution may be equal or superior to that found in synthetic combinatorial chemical libraries.

It was estimated that in 1991 in the United States, for every 10,000 pure compounds (most likely those based on synthesis) that are biologically evaluated (primarily *in vitro*), 20 would be tested in animal models, and 10 of these would be clinically evaluated, and only one would reach U.S. Food and Drug Administration approval for marketing. The time required for this process was estimated as 10 years at a cost of $231 million (U.S.) (*9*).

Most large pharmaceutical manufacturers and some small biotechnology firms have the ability to screen 1,000 or more substances per week using high throughput *in vitro* assays. In addition to synthetic compounds from their own programs, some of these companies screen plant, microbial, and marine organisms.

Thus, the challenges facing these companies in acquiring organisms and extracts (*vide infra*) usually result in a failure to consider collection of plants, especially if the acquisitions are based on ethnomedical use. It is time-consuming to collect specific plants having an ethnomedical history. Despite these problems, one cannot discount the past importance of plants as sources of structurally novel drugs (Tables 1 and 2).

Ethnomedicine may be defined broadly as the use of plants by humans as medicines (*10,11*); but this use could be called more accurately ethnobotanic medicine. Traditional medicine is a broad term used to define any non-Western medical practice (*12*). Ethnopharmacology is a highly diversified approach to drug discovery involving the observation, description, and experimental investigation of indigenous drugs and their biologic activities. It is based on botany, chemistry, biochemistry, pharmacology, and many other disciplines (anthropology, archaeology, history, and linguistics) that contribute to the discovery of natural products with biologic activity (*13*). These three areas of endeavor will be the starting point for this review.

Approaches to Drug Discovery Using Higher Plants

Several reviews pertaining to approaches for selecting plants as candidates for drug discovery programs have been published (*8,14–27*); however, most concern screening plants for anticancer or anti-HIV activity. We outline these approaches briefly before concentrating on the ethnomedical approach, the major topic of this review. Examples from the literature are intended to be representative but not exhaustive.

Random selection followed by chemical screening. These so-called phytochemical screening approaches [i.e., for the presence of cardenolides/bufadenolides, alkaloids, triterpenes, flavonoids, isothiocyanates, iridoids, etc. (*17*)] have been used in the past and are

Address correspondence to D.S. Fabricant, College of Pharmacy, University of Illinois-Chicago, 833 S. Wood Street (M/C-877), Chicago, IL 60612 USA. Telephone: (312) 996-7253. Fax: (312) 413-5894. E-mail: dfabri1@uic.edu

Received 2 October 2000; accepted 22 November 2000.

currently pursued mainly in the developing countries. The tests are simple to perform, but false-positive and false-negative tests often render results difficult to assess (*17,28–30*). More important, it is usually impossible to relate one class of phytochemicals to specific biologic targets; for example, the alkaloids or flavonoids produce a vast array of biologic effects that are usually not predictable in advance.

Random selection followed by one or more biologic assays. In the past, plant extracts were evaluated mainly in experimental animals, primarily mice and rats. The most extensive of these programs were sponsored by the National Cancer Institute (NCI) (*24,31–34*) in the United States and the Central Drug Research Institute (CDRI) in India (*35–41*). More than 35,000 species were screened *in vitro* and later *in vivo* at NCI from 1960 to 1981. Taxol and camptothecin (*42*) were discovered in this program as well as several other plant-derived compounds that were unsuccessful in human studies. In 1986 the NCI program abandoned this approach and continued to collect and screen plants using a battery of 60 human tumor cell lines and also initiated a screening of plants for anti-HIV activity *in vitro*. Calanolide A, currently in Phase I clinical trials, was developed from this program (*43,44*).

The CDRI evaluated approximately 2,000 plant species for several biologic activities, including antibacterial, antidiabetic, antifertility, antifungal, antihypercholesteremic, anti-inflammatory, antitumor, cardiovascular, central nervous-system depressant, cytotoxicity, diuretic, and others (*37*). To date no biologically active drugs for human use have arisen from that program, even though a large number of known and novel bioactive compounds were isolated from the active plants (*45*).

Follow-up of biologic activity reports. These reports showed that the plant extracts had interesting biologic activity, but the extracts were not studied for their active principles. The literature from the 1930s through the 1970s contains these types of reports.

Follow-up of ethnomedical (traditional medicine) uses of plants. Several types of ethnomedical information are available:

Plants used in organized traditional medical systems. Ayurveda, Unani, Kampo, and traditional Chinese medicine have flourished as systems of medicine in use for thousands of years. Their individual arrangements all emphasize education based on an established, frequently revised body of written knowledge and theory. These systems are still in place today because of their organizational strengths, and they focus primarily on multicomponent mixtures (*12*). Even though Western medical science views such systems

Table 1. Drugs derived from plants, with their ethnomedical correlations and sources.

Drug	Action or clinical use	Plant source
Acetyldigoxin	Cardiotonic	*Digitalis lanata* Ehrh.
Adoniside	Cardiotonic	*Adonis vernalis* L.
Aescin	Anti-inflammatory	*Aesculus hippocastanum* L.
Aesculetin	Antidysentery	*Fraxinus rhynchophylla* Hance
Agrimophol	Anthelmintic	*Agrimonia eupatoria* L.
Ajmalicine	Circulatory disorders	*Rauvolfia serpentina* (L.) Benth ex. Kurz
Allyl isothiocyanate	Rubefacient	*Brassica nigra* (L.) Koch
Andrographolide	Bacillary dysentery	*Andrographis paniculata* Nees
Anisodamine	Anticholinergic	*Anisodus tanguticus* (Maxim.) Pascher
Anisodine	Anticholinergic	*Anisodus tanguticus* (Maxim.) Pascher
Arecoline	Anthelmintic	*Areca catechu* L.
Asiaticoside	Vulnerary	*Centella asiatica* (L.) Urban
Atropine	Anticholinergic	*Atropa belladonna* L.
Berberine	Bacillary dysentery	*Berberis vulgaris* L.
Bergenin	Antitussive	*Ardisia japonica* Bl.
Bromelain	Anti-inflammatory; proteolytic agent	*Ananas comosus* (L.) Merrill
Caffeine	CNS stimulant	*Camellia sinensis* (L.) Kuntze
(+)-Catechin	Haemostatic	*Potentilla fragaroides* L.
Chymopapain	Proteolytic; mucolytic	*Carica papaya* L.
Cocaine	Local anaesthetic	*Erythroxylum coca* Lamk.
Codeine	Analgesic; antitussive	*Papaver somniferum* L.
Colchicine	Antitumor agent; antigout	*Colchicum autumnale* L.
Convallotoxin	Cardiotonic	*Convallaria majalis* L.
Curcumin	Choleretic	*Curcuma longa* L.
Cynarin	Choleretic	*Cynara scolymus* L.
Danthron	Laxative	*Cassia* spp.
Deserpidine	Antihypertensive; tranqulizer	*Rauvolfia canescens* L.
Deslanoside	Cardiotonic	*Digitalis lanata* Ehrh.
Digitalin	Cardiotonic	*Digitalis purpurea* L.
Digitoxin	Cardiotonic	*Digitalis purpurea* L.
Digoxin	Cardiotonic	*Digitalis lanata* Ehrh.
Emetine	Amoebicide; emetic	*Cephaelis ipecacuanha* (Brotero) A. Richard
Ephedrine	Sympathomimetic	*Ephedra sinica* Stapf.
Etoposide	Antitumour agent	*Podophyllum peltatum* L.
Gitalin	Cardiotonic	*Digitalis purpurea* L.
Glaucaroubin	Amoebicide	*Simarouba glauca* DC.
Glycyrrhizin	Sweetener	*Glycyrrhiza glabra* L.
Gossypol	Male contraceptive	*Gossypium* spp.
Hemsleyadin	Bacillary dysentery	*Helmsleya amabilis* Diels
Hydrastine	Hemostatic; astringent	*Hydrastis canadensis* L.
Hyoscamine	Anticholinergic	*Hyoscamus niger* L.
Kainic Acid	Ascaricide	*Digenea simplex* (Wulf.) Agardh
Kawain	Tranquilizer	*Piper methysicum* Forst. f.
Khellin	Bronchodilator	*Ammi visnaga* (L.) Lamk.
Lanatosides A, B, C	Cardiotonic	*Digitalis lanata* Ehrh.
Lobeline	Smoking deterrent; respiratory stimulant	*Lobelia inflata* L.
Monocrotaline	Antitumor agent	*Crotolaria sessiliflora* L.
Morphine	Analgesic	*Papaver somniferum* L.
Neoandrographolide	Bacillary dysentery	*Andrographis paniculata* Nees
Noscapine	Antitussive	*Papaver somniferum* L.
Ouabain	Cardiotonic	*Strophanthus gratus* Baill.
Papain	Proteolytic; mucolytic	*Carica papaya* L.
Phyllodulcin	Sweetener	*Hydrangea macrophylla* (Thunb.) DC
Physostigmine	Cholinesterase inhibitor	*Physostigma venenosum* Balf.
Picrotoxin	Analeptic	*Anamirta cocculus* (L.) W.&A.
Pilocarpine	Parasympathomimetic	*Pilocarpus jaborandi* Holmes
Podophyllotoxin	Condylomata acuminata	*Podophyllum peltatum* L.
Protoveratrines A & B	Antihypertensive	*Veratrum album* L.
Pseudoephedrine	Sympathomimetic	*Ephedra sinica* Stapf.
Pseudoephedrine, nor-	Sympathomimetic	*Ephedra sinica* Stapf.
Quinine	Antimalarial	*Cinchona ledgeriana* Moens ex. Trimen
Quisqualic Acid	Anthelmintic	*Quisqualis indica* L.
Rescinnamine	Antihypertensive; tranqulizer	*Rauvolfia serpentina* (L.) Benth ex. Kurz
Reserpine	Antihypertensive; tranqulizer	*Rauvolfia serpentina* (L.) Benth ex. Kurz
Rhomitoxin	Antihypertensive	*Rhododendron molle* G. Don
Rorifone	Antitussive	*Rorippa indica* (L.) Hochr.
Rotenone	Piscicide	*Lonchocarpus nicou* (Aubl.) DC.
Rotundine	Analgesic; sedative	*Stephania sinica* Diels
Salicin	Analgesic	*Salix alba* L.
Santonin	Ascaricide	*Artemisia maritima* L.

(Continued)

as lacking credibility, undeniably they are used widely by most people on this planet. Adverse effects from those widely used plants are not well documented in the literature, and efficacy of these plants and plant mixtures is more difficult to assess by Western scientific methods.

Herbalism, folklore, and shamanism. These center on an apprenticeship system of information passed to the next generation through a shaman, curandero, traditional healer, or herbalist. The plants that are used are often kept secret by the practitioner, so little information about them is recorded; thus there is less dependence on scientific evidence as in systems of traditional medicine that can be subject to scrutiny. The shaman or herbalist combines the roles of pharmacist and medical doctor with the cultural/spiritual/religious beliefs of a region or people, which are often regarded as magic or mysticism. This approach is widely practiced in Africa and South America (*45*).

Ethnomedical information can be acquired from various sources such as books on medical botany (*46*) and herbals (*47*); review articles (usually involving surveys of medicinal plants by geographic region or ethnic culture) (*48–66*); notes placed on voucher herbarium specimens by the botanist at the time of collection (*67*); field work (*68*); and computer databases, e.g., NAPRALERT (*69–71*) and USDA–Duke (*72,73*).

Use of databases. The NAPRALERT database (*69–71*) currently contains information on 43,879 species of higher plants covering ethnomedical, chemical, and pharmacologic (including clinical studies) uses. Of these, 13,599 species contain ethnomedical data, distributed among 3,607 genera and 273 plant families. Thus it is possible to correlate ethnomedical use with experimental biochemical or pharmacologic activities (*in vitro*, *in vivo*, or in humans) to identify plants having both types of activity for a given effect—e.g., anticancer, antidiabetic, antimalarial.

Other approaches. Our group was interested in identifying plants that could yield intensely sweet compounds. In addition, we searched the literature for Latin binomials that would imply sweetness—e.g., *saccharum, dulcis, dulcificum, dulcifica, dulce, sacchartus, saccharoides*. (*74*). We actually tasted small segments from leaves of 184 *Stevia* herbarium specimens from the John G. Searle Herbarium of the Field Museum of Natural History in Chicago, Illinois. Of these, 18 species and varieties of *Stevia* had a sweet taste, but none were sweeter than *Stevia rebaudiana*, the source of stevioside, the intensely sweet kaurene glycoside. (*75*).

Table 1. *Continued.*

Drug	Action or clinical use	Plant source
Scillarin A	Cardiotonic	*Urginea maritima* (L.) Baker
Scopolamine	Sedative	*Datura metel* L.
Sennosides A & B	Laxative	*Cassia* spp.
Silymarin	Antihepatotoxic	*Silybum marianum* (L.) Gaertn.
Stevioside	Sweetener	*Stevia rebaudiana* Bertoni
Strychnine	CNS stimulant	*Strychnos nux-vomica* L.
Teniposide	Antitumor agent	*Podophyllum peltatum* L.
Tetrahydropalmatine	Analgesic; sedative	*Corydalis ambigua* (Pallas) Cham. & Schltal.
Theobromine	Diuretic; bronchodilator	*Theobroma cacao* L.
Theophylline	Diuretic; bronchodilator	*Camellia sinensis* (L.) Kuntze
Trichosanthin	Abortifacient	*Thymus vulgaris* L.
Tubocurarine	Skeletal muscle relaxant	*Chondodendron tomentosum* R. & P.
Valepotriates	Sedative	*Valeriana officinalis* L.
Vincamine	Cerebral stimulant	*Vinca minor* L.
Xanthotoxin	Leukoderma; vitiligo	*Ammi majus* L.
Yohimbine	Aphrodisiac	*Pausinystalia yohimbe* (K.Schum.) Pierre
Yuanhuacine	Abortifacient	*Daphne genkwa* Seib. & Zucc.
Yuanhuadine	Abortifacient	*Daphne genkwa* Seib. & Zucc.

Data adapted from Farnsworth et al. (*2*).

Table 2. Plant-derived drugs and their sources not developed on the basis of ethnomedical information.

Drug	Plant source
Allantoin	Several plants
Anabasine	*Anabasis aphylla* L.
Benzyl benzoate	Several plants
Borneol	Several plants
Camphor	*Cinnamonum camphora* (L.) J.S. Presl
Camptothecin	*Camptotheca acuminata* Decne.
Cissampeline	*Cissampelos pareira* L.
Colchicaine amide	*Colchicum autumnale* L.
Demecolcine	*Colchicum autumnale* L.
L-Dopa	*Mucuna deeringiana* (Bort) Merr.
Galanthamine	*Lycoris squamigera* Maxim.
Glaucine	*Glaucium flavum* Crantz
Glaziovine	*Ocotea glazovii* Mez
Hesperidin	*Citrus spp.*
Huperzine A	*Huperzia serrata* (Thunb. ex Murray) Trevis.
Menthol	*Mentha spp.*
Methyl salicylate	*Gaultheria procumbens* L.
Nicotine	*Nicotiana tabacum* L.
Nordihydroguaiaretic acid	*Larrea divaricata* Cav.
Pachycarpine	*Sophora pachycarpa* Schrenk ex C.A. Meyer
Palmatine	*Coptis japonica* Makino
Papaverine	*Papaver somniferum* L.
Pinitol	Several plants
Quinidine	*Cinchona ledgeriana* Moens ex. Trimen
Rutin	*Citrus* spp.
Sanguinarine	*Sanguinaria candensis* L.
Sparteine	*Cytisus scoparius* (L.) Link
Taxol	*Taxus brevifolia* Nutt.
Tetrahydrocannabinol	*Cannabis sativa* L.
Tetrandrine	*Stephania tetrandra* S.Moore
Thymol	*Thymus vulgaris* L.
Vasicine (peganine)	*Adhatoda vasica* Nees
Vinblastine	*Catharanthus roseus* (L.) G. Don
Vincristine	*Catharanthus roseus* (L.) G. Don

Data adapted from Farnsworth et al. (*2*).

The Value of Ethnomedicine

A few examples document the value of using ethnomedical information to initiate drug discovery efforts. We were requested by the WHO Traditional Medicine Programme (TRM) several years ago to provide evidence that ethnomedical information did indeed lead to useful drug discovery. We sent letters to the WHO–TRM centers throughout the world asking for their assistance in identifying all plant-derived pure compounds used as drugs in their respective countries. In addition, we surveyed pharmacopoeias of developed and developing countries to identify all such useful drugs. Next we surveyed the scientific literature to find the original papers reporting isolation of these compounds from their respective plants. This was done to determine whether the chemical efforts were stimulated by ethnomedical claims and to correlate current uses for the compounds with such ethnomedical claims (*2*).

A total of 122 compounds were identified; 80% of these compounds were used for the same (or related) ethnomedical purposes (Table 1). Further, it was discovered that these compounds were derived from only 94 species of plants (*2*).

Because these compounds are derived from only 94 species of plants, and a conservative estimate of the number of flowering plants occurring on the planet is 250,000, there should be an abundance of drugs remaining to be discovered in these plants. The question is, what is the best approach to discover plants that contain potential drugs?

Several years ago we were visited by a Mexican physician who presented us with small pieces (30 g) of the roots of a Mexican plant alleged to alleviate toothache pain. One of us (NRF) placed a piece of the root in his mouth and experienced a pronounced local anesthetic effect lasting for about 60 min. Before receiving a voucher specimen of the plant for identification purposes, we made a 50% ethanol extract of the roots and evaluated it in the acetic acid–induced writhing inhibition test in mice (i.g.). A subfraction, showing one major spot following thin layer chromatography, gave an ED_{50} of 19.04 mg/kg (i.g.). Morphine showed an ED_{50} of 2.0 mg/kg (i.g.). Within 2 days a pure compound was isolated in high yield, identified and synthesized within 1 week. The pure compound was active in this assay, but 40% of the mice died within 40 min of administration at a dose of 40 mg/kg (i.g.). The ED_{50} of this compound was 6.98 mg/kg (i.g.). The plant was then identified as *Heliopsis longipes* (A. Gray) Blake, and the isolated bioactive compound was identified as the previously known isobutylamide, affinin (spilanthol) (*76*).

The investigation of this plant was initiated by an ethnomedical report (*76*) of the use of the plant as an analgesic (actually, a local anesthetic). With combined efforts of a pharmacognosist, chemist, pharmacologist, and botanist, the bioactive constituent was identified in less than 2 weeks.

In 1985 the WHO Special Programme of Research and Training in Human Reproduction embarked on a program called "The Task Force on Plants for Fertility Regulation" (*77*). The charge was to select plants on the basis of ethnomedical claims related to human reproduction, e.g., abortifacient, contraceptive, ecbolic, emmenagogue. Safety with long-term use was presumed. The ultimate goal was to discover orally active, pure substances that were nonestrogenic, nonsteroidal, and nontoxic anti-implantation agents. Work was to take place initially in designated centers in the United States, England, South Korea, Brazil, India, and Hong Kong, with additional centers later established in the People's Republic of China and Thailand. Our initial effort involved searching all available literature for plants and natural compounds having any of these biologic effects and storing this information in our NAPRALERT database for eventual analysis (*71*). We were able to identify approximately 4,000 plant species. A computer analysis of the data produced about 300 species that were scheduled for collection and testing. About 250 species were evaluated for anti-implantation activity in rats (with confirmation in hamsters) and approximately 50 were of sufficient interest to start chemical isolation studies. Several active compounds were identified, the most promising being an indole alkaloid named yuehchukene (YCK) (*78*) from the plant *Murraya paniculata* (L.) Jack (Figure 1), used in China to regulate fertility. Unfortunately, YCK showed a low level of estrogenicity and was not further explored. The WHO program was terminated shortly thereafter.

Perhaps the first company in the United States to investigate plants strictly through the ethnomedical approach was Shaman Pharmaceuticals in South San Francisco, California. (*79*) Their approach was to send botanist/physician teams to tropical areas to assess firsthand the use of plants by traditional healers and to collect interesting plants and assess them for validity in the Shaman laboratories. Initial interest was directed toward antifungal and antiviral agents (*80*); several active compounds were discovered but were either toxic or failed in the clinic. Efforts were then directed toward antidiarrheal activity. SP-303, an oligomeric proanthocyanidin (*81*), was shown to be clinically efficacious and is currently marketed as a dietary supplement for diarrhea. In addition, a major effort was directed toward discovery of novel antidiabetic agents, which resulted in the discovery of several patented compounds: cryptolepine (*82–84*), maprouneacin (*85*), 3β,30-dihydroxylupen-20(29)-en-2-one (*86*), harunganin (*87*), vismin (*87*), and quinones SP18904 and SP18905 (*88*). The most interesting discovery was nordihydroguaiaretic acid (ndga) (*89*) (Figure 2) which, besides being active orally in db/db diabetic mice, also lowered cholesterol levels. In 1999 Shaman terminated their research in drug discovery.

In 1985 we proposed an approach, based on ethnomedical information, to experimentally pursue plants as a source of

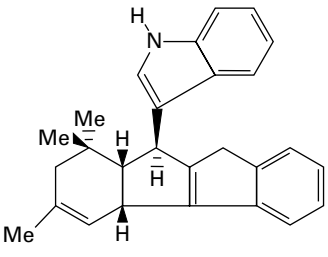

Figure 1. Structure of yuehchukene.

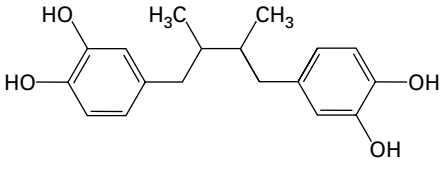

Figure 2. Structure of nordihydroguaiaretic acid (ndga).

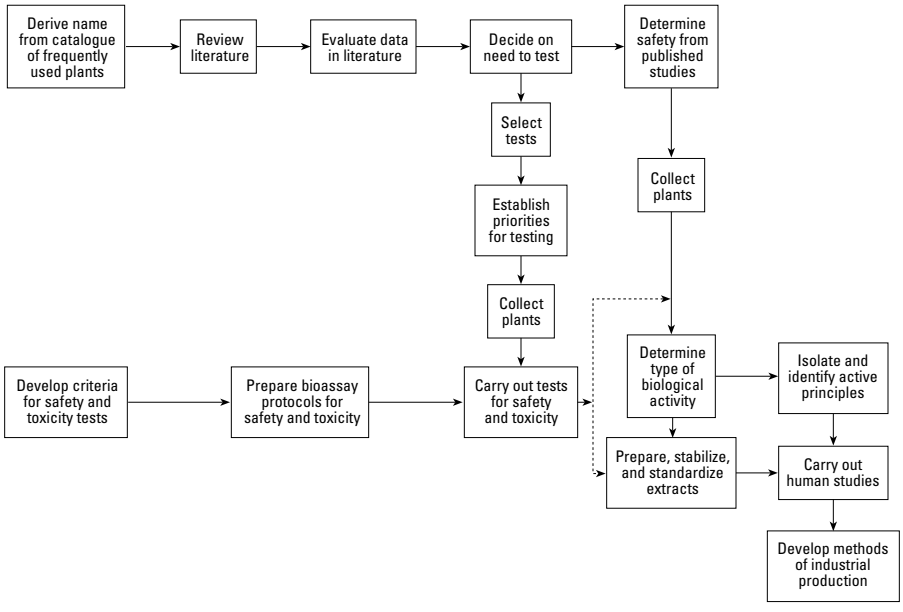

Figure 3. Flow chart of sequence for the study of plants used in traditional medicine. Adapted from Farnsworth et al. (*2*).

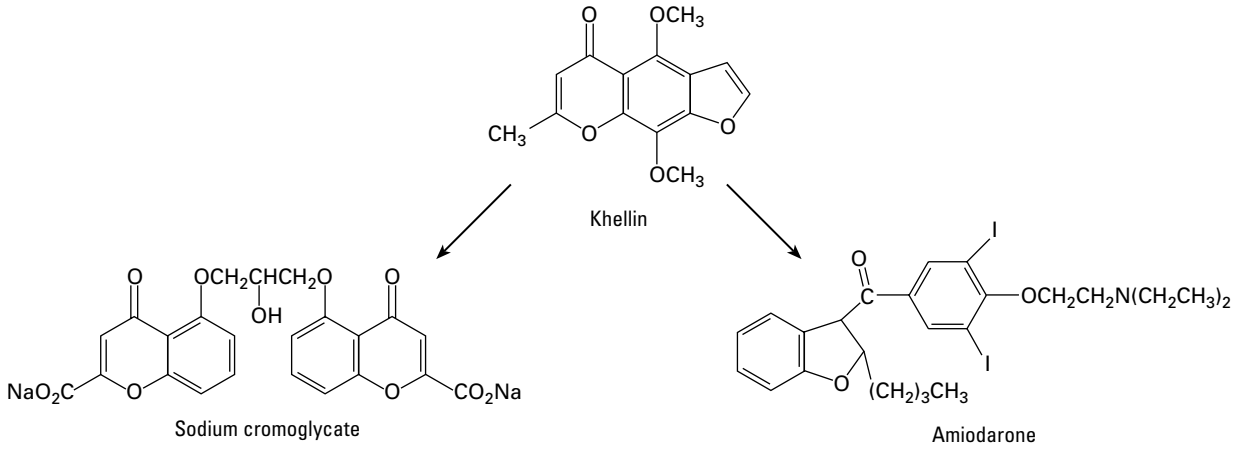

Figure 4. Structural relationship of amiodarone and sodium cromoglycate to khellin.

drugs. The approach was designed primarily for implementation by developing countries, where lack of hard currency often prevents sophisticated types of research from being conducted. The possibility of drug development in the form of stable, standardized crude extracts and eventual development of the active principles from these plants was envisioned (*2*) (Figure 3).

Some examples of drugs from plants that served as models for the next generation of drugs are exemplified as follows: Khellin [from *Ammi visnaga* (L.) Lamk.] was used as a bronchodilator in the United States until it was shown to produce nausea and vomiting after prolonged use. In 1955 a group of chemists in England set about to synthesize khellin analogs as potential bronchodilators with fewer side effects. This eventually led to the discovery of chromolyn (used as sodium chromoglycate), which stabilized cell membranes in the lungs to prevent the allergen-induced release of the substance ultimately causing bronchoconstriction in allergic asthma patients (*90*). Further studies elsewhere led to the synthesis of amiodarone, a useful antiarrythmia agent (*90*). The structural relationship can be seen in Figure 4.

Papaverine, useful as a smooth muscle relaxant, provided the basic structure for verapamil, a drug used to treat hypertension (*90*) (Figure 5).

Galegine was isolated as an active antihyperglycemic agent from the plant *Galega officinalis* L. This plant was used ethnomedically for the treatment of diabetes. Galegine provided the template for the synthesis of metformin and opened up interest in the synthesis of other biguanidine-type antidiabetic drugs (Figure 6) (*90*).

It is extremely difficult to assess the value of any approach to the use of higher plants to develop new drugs. Artuso (*91*) has outlined the entire process: formulating an appropriate strategy, obtaining biologic extracts, screening

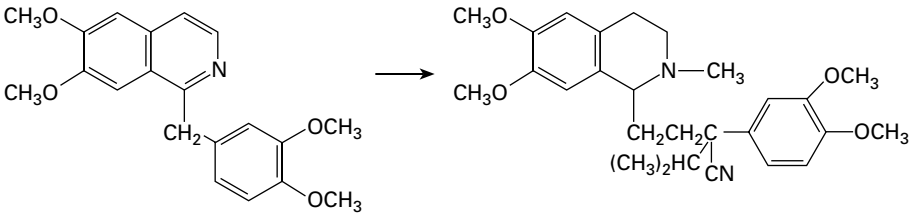

Figure 5. Structural relationship of verapamil to papaverine.

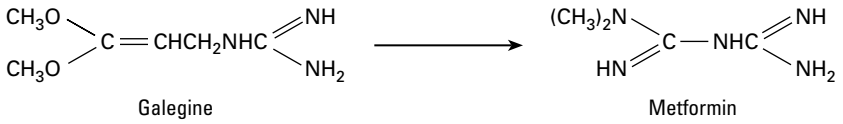

Figure 6. Structural relationship of metformin to galegine.

those extracts, isolating active compounds, conducting preclinical tests and chemical modification, submitting an Investigational New Drug Application, performing clinical trials, submitting a New Drug Application, and beginning commercial production. He estimates the entire process would take 10–20 years or more. Using complex mathematical formulae, he discusses what the expected payoff would be relative to such variables as the number of available plant species on earth, the amount of biodiversity in the tropical rain forests, and extinction rates. An element that all estimated projections fail to consider is that any of the 250,000 higher plant species on earth could conceivably produce a new drug, leaving all other criteria, projections, and speculations aside. The reason is that the introduction of novel mechanism-based *in vitro* bioassays is virtually limitless, and therefore any plant, regardless of the extent of prior biologic or chemical study, could prove interesting as a potential new drug source. For example, from 1960 to 1981 NCI collected and screened approximately 35,000 plant species for anticancer activity (*32*). Eventually, all residual extracts from these 35,000 species were destroyed after they were assessed for anticancer activity. Thus, in speculating that about 6% of the 250,000 plant species on earth have been evaluated as a source of drugs (*8*), should one count the 35,000 species screened by NCI for anticancer activity within the number of 6%? We think not. Thus, because it is improbable that one could collect all the 250,000 higher plant species to screen for one or more biologic activities, and because the number of bioassays that one could screen these species for is unlimited, one must select judiciously those species most likely to produce useful activity. In addition, the biologic targets must represent the activities that correlate best with the rationale for plant selection. It would appear that selection of plants based on long-term human use (ethnomedical) in conjunction with appropriate biologic assays that correlate with the ethnomedical uses would be most appropriate.

There are advantages and disadvantages of using plants as the starting point in any drug development program. If one elects to use

information suggesting that specific plants may yield useful drugs based on long-term use by humans (ethnomedicine) one can rationalize that any isolated active compounds from the plants are likely to be safer than active compounds from plants with no history of human use. Also, plants are a renewable source of starting material in many but not all cases. It is universally believed that plants provide an unlimited source of novel and complex chemical structures that most likely would never be the subject of a beginning synthetic program, e.g., vinblastine, vincristine, taxol, *d*-tubocurarine, digoxin. If the active principles derived from plants have novel structures and useful biologic activity, patent protection can be assured. We have shown here that most useful drugs derived from plants have been discovered by follow-up of ethnomedical uses (Table 1). Further, the trend today, especially in an industrial setting, is to seek bioactive compounds from plants that will serve as lead compounds for synthetic or semisynthetic development, to assure patent protection. Thus, this diminishes the need to isolate novel bioactive structures from plants, since the ultimate goal is to use the active compounds to produce synthetic derivatives with lower toxicity and higher efficacy.

Several pitfalls can emerge when deciding to use plants, through either random selection or ethnomedical claims involving the targeted disease.

First, plants as biologic systems have inherent potential variability in their chemistry and resulting biologic activity. In our experience, perhaps 25% of all plants showing promising biologic activity in our assay systems fail to have the activity confirmed on subsequent re-collections. This could be due to variability in the chemistry of plants or in the bioassay systems used, or mix-ups in labeling of plant samples or their taxonomic identifications. We have previously discussed and provided examples of these problems and their solutions (*17,18,21,29*).

Second, the Convention on Biological Diversity in 1992 expected the parties to the convention to *a*) develop national biodiversity protection plans and programs for sustainable use; *b*) inventory and monitor components of biologic diversity that are threatened, endangered, or of economic, cultural, or scientific value; *c*) establish a system of protected areas with appropriate guidelines for their selection and management; *d*)establish and maintain facilities for *ex situ* conservation; *e*) establish programs for scientific research and technical training related to identification, conservation, and sustainable use of biological diversity; and *f*) integrate consideration of conservation and sustainable use of biologic resources into national decision making (*92*).

Since 1992, the countries with the most biologic diversity—i.e., where tropical rain forests predominate—have either prohibited collection of plant material for export or promulgated regulations that make it difficult to collect plant samples (or other biologic specimens). Several issues are tied in with the restrictions set forth by countries, including preservation of genetic material, intellectual property rights, and compensation for discoveries arising from their genetic resources. These problems and potential solutions have been discussed thoroughly (*92–97*). We have found that in areas where regulations permit plant collection and export, at least 2 years are required to negotiate and obtain permission to collect plant materials.

Third, collecting plant samples randomly in a specific geographic area can be done simply and rapidly. With a team of four to five people, at least 200 samples of 0.5–1.0 kg (dry weight) each can be collected daily. However, collecting plants on the basis of their ethnomedical claims requires considerable preliminary planning to determine *a*) where each plant grows, *b*) what the abundance of each plant is, *c*) whether any of the plants are threatened or endangered, *d*) what local arrangements must be made to collect the plants, e.g. permits, and *e*) whether local botanists familiar with the flora of the region are available to assist. Thus, the number of plant collections possible, based on the ethnomedical approach in a given day or week, becomes much smaller.

In summary, the industrial approach most likely to be used to evaluate plants for bioactive compounds will be based on random collection followed by automated, robotized, *in vitro* screening. The ethnomedical approach lends itself more to being carried out in academic institutions. Since plant-derived drug discovery efforts began, the ethnomedical approach has been more successful. However, the random collection of plants, which provides the highest biodiversity, is forging ahead as the method of choice. The latter approach requires significantly more financial resources than the former.

Conclusions and Perspectives

The body of existing ethnomedical knowledge has led to great developments in health care. With the rapid industrialization of the planet and the loss of ethnic cultures and customs, some of this information will no doubt disappear. An abundance of ethnomedical information on plant uses can be found in the scientific literature but has not yet been compiled into a usable form. Collection of ethnomedical information remains primarily an academic endeavor of little interest to most industrial groups.

The use of ethnomedical information has contributed to health care worldwide, even though efforts to use it have been sporadic. Are we loath to continue plant-derived drug discovery efforts because we anticipate that current industrial technology, i.e., mass screening, will provide novel drugs at a greater rate than will the ethnomedical information already at hand? "Those who cannot remember the past are condemned to repeat it" (*98*).

References and Notes

1. Solecki R. Shanidar IV, a Neanderthal flower burial in northern Iraq. Science 190:880–881 (1975).
2. Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. Bull W H O 63:965–981 (1985).
3. Ayensu ES, DeFilipps RA. Endangered and Threatened Plants of the United States. Washington, DC:Smithsonian Institution, 1978.
4. Cronquist A. An Integrated System of Classification of Flowering Plants. New York:Columbia University Press, 1981.
5. Cronquist A. The Evolution and Classification of Flowering Plants. Bronx, NY:New York Botanical Garden, 1988.
6. Tippo O, Stern WL. Humanistic Botany. New York:W.W. Norton, 1977.
7. Schultes RE. The future of plants as sources of new biodynamic compounds. In: Plants in the Development of Modern Medicine (Swain T, ed). Cambridge, MA:Harvard University Press, 1972;103–124.
8. Verpoorte R. Pharmacognosy in the new millennium: leadfinding and biotechnology. J Pharm Pharmacol 52:253–262 (2000).
9. Vagelos PR. Are prescription drug prices high? Science 252:1080–1084 (1991).
10. Farnsworth NR. The role of ethnopharmacology in drug development. Ciba Found Symp 154:2–11 (1990).
11. Farnsworth NR. Ethnopharmacology and drug development. Ciba Found Symp 185:42–51 (1994).
12. Bannerman RHO, Burton J, Ch'en W-C. Traditional Medicine and Health Care Coverage: A Reader for Health Administrators and Practitioners. Geneva:World Health Organization, 1983.
13. Rivier L, Bruhn J. Editorial. J Ethnopharmacol 1 (1979).
14. Phillipson JD, Anderson LA. Ethnopharmacology and Western medicine. J Ethnopharmacol 25:61–72 (1989).
15. Kinghorn AD. The discovery of drugs from higher plants. Biotechnology 26:81–108 (1994).
16. Vlietinck AJ, Vanden Berghe DA. Can ethnopharmacology contribute to the development of antiviral drugs? J Ethnopharmacol 32:141–153 (1991).
17. Farnsworth NR. Biological and phytochemical screening of plants. J Pharm Sci 55:225–276 (1966).
18. Farnsworth NR, Bingel AS. Problems and prospects of discovering new drugs from higher plants by pharmacological screening. In: New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity (Wagner H, Wolff P, eds). Berlin:Springer, 1977;1–22.
19. Harvey A. Strategies for discovering drugs from previously unexplored natural products. Drug Discov Today 5:294–300 (2000).
20. Farnsworth NR. Screening plants for new medicines. In: Biodiversity (Wilson EO, ed). Washington DC:National Academy Press, 1988;83–97.
21. Farnsworth NR, Henry LK, Svoboda GH, Blomster RN, Yates MJ, Euler KL. Biological and phytochemical evaluation of plants. I: Biological test procedures and results from 200 accessions. Lloydia 29:101–122 (1966).
22. Farnsworth NR. The role of medicinal plants in drug development. In: Natural Products in Drug Development, Alfred Benzon Symposium, 20 August 1983, Copenhagen, Denmark: Munksgaard, 1984;17–30.
23. Spjut RW, Perdue RE Jr. Plant folklore: a tool for predicting sources of antitumor activity? Cancer Treat Rep 60:979–985 (1976).
24. Suffness M, Douros J. Current status of the NCI plant and animal product program. J Nat Prod 45:1–14 (1982).
25. Turner DM. Natural product source material use in the pharmaceutical industry: the Glaxo experience. J Ethnopharmacol 51:39–43; Discussion 44 (1996).
26. Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery. Nat Prod Rep 17:215–234 (2000).
27. Clark AM. Natural products as a resource for new drugs. Pharm Res 13:1133–1144 (1996).

28. Segelman AB, Farnsworth NR, Quimby MW. Biological and phytochemical evaluation of plants. III: False-negative saponin test results induced by the presence of tannins. Lloydia 32:52–58 (1968).
29. Farnsworth NR, Pilewski NA, Draus FJ. Studies on false-positive alkaloid reactions with Dragendorff's reagent. Lloydia 25:296–310 (1962).
30. Roper EC, Blomster RN, Farnsworth NR, Draus FJ. Studies on alkaloid detecting reagents. II: Stability and sensitivity of modified Dragendorff's reagents. Planta Med 13:98–103 (1965).
31. Cragg GM, Newman DJ, Snader KM. Natural products in drug discovery and development. J Nat Prod 60:52–60 (1997).
32. Cragg GM, Boyd MR, Cardellina JH, Newman DJ, Snader KM, McCloud TG. Ethnobotany and drug discovery: the experience of the US National Cancer Institute. Ciba Found Symp 185:178–190 (1994).
33. Douros J, Suffness M. The National Cancer Institute's Natural Products Antineoplastic Development Program. Recent Results Cancer Res 70:21–44 (1980).
34. Douros J, Suffness M. New natural products under development at the National Cancer Institute. Recent results. Cancer Res 76:153–175 (1981).
35. Bhakuni DS, Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN. Screening of Indian plants for biological activity. II. Indian J Exp Biol 7:250–262 (1969).
36. Bhakuni DS, Dhar ML, Dhar MM, Dhawan BN, Gupta B, Srimal RC. Screening of Indian plants for biological activity. III. Indian J Exp Biol 9:91–102 (1971).
37. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian plants for biological activity. I. Indian J Exp Biol 6:232–247 (1968).
38. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Srimal RC, Tandon JS. Screening of Indian plants for biological activity. IV. Indian J Exp Biol 11:43–54 (1973).
39. Dhar ML, Dhawan BN, Prasad CR, Rastogi RP, Singh KK, Tandon JS. Screening of Indian plants for biological activity. V. Indian J Exp Biol 12:512–523 (1974).
40. Dhawan BN, Patnaik GK, Rastogi RP, Singh KK, Tandon JS. Screening of Indian plants for biological activity. VI. Indian J Exp Biol 15:208–219 (1977).
41. Dhawan BN, Dubey MP, Mehrotra BN, Rastogi RP, Tandon JS. Screening of Indian plants for biological activity. IX. Indian J Exp Biol 18:594–606 (1980).
42. Wall ME, Wani MC. Camptothecin and taxol: from discovery to clinic. J Ethnopharmacol 51:239–254 (1996).
43. Calanolide looks promising. AIDS Patient Care STDS 14:225–226 (2000).
44. Kashman Y, Gustafson KR, Fuller RW, Cardellina JH, McMahon JB, Currens MJ, Buckheit RW Jr, Hughes SH, Cragg GM, Boyd MR. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum* [published erratum appears in J Med Chem 36(8):1110 (1993)]. J Med Chem 35:2735–2743 (1992).
45. Rastogi RP, Dhawan BN. Research on medicinal plants at the Central Drug Research Institute, Lucknow (India). Indian J Med Res 76(suppl):27–45 (1982).
46. Lewis WH, Elvin-Lewis MPF. Medical Botany: Plants Affecting Man's Health. New York:Wiley, 1977.
47. Cruz M, Badiano J, Trueblood EWE. The Badianus Manuscript, Codex Barberini, Latin 241, Vatican Library: An Aztec Herbal of 1552. Baltimore, MD:Johns Hopkins Press, 1940.
48. Siddiqui TO, Javed K, Alam MM. Folk-medicinal claims of western Uttar Pradesh, India. Hamdard Med 43:59–60 (2000).
49. Shinwari MI, Khan MA. Folk use of medicinal herbs of Margalla Hills National Park, Islamabad. J Ethnopharmacol 69:45–56 (2000).
50. Rossato SC, Leitao-Filho HD, Begossi A. Ethnobotany of Caicaras of the Atlantic Forest Coast (Brazil). Econ Bot 53:387–395 (1999).
51. Pieroni A. Medicinal plants and food medicines in the folk traditions of the upper Lucca Province, Italy. J Ethnopharmacol 70:235–273 (2000).
52. Ong HC, Nordiana M. Malay ethno-medico botany in Machang, Kelantan, Malysia. Fitoterapia 70:502–513 (1999).
53. Noumi E, Dibatko TW. Medicinal plants used for peptic ulcer in the Bangangte region, western Cameroon. Fitoterapia 71:406–412 (2000).
54. Ertug F. An Ethnobotanical Study in Central Anatolia (Turkey). Econ Bot 54:155–182 (2000).
55. El-Kamali HH, El-Khalifa KK. Folk medicinal plants of riverside forests of the Southern Blue Nile district, Sudan. Fitoterapia 70:493–497 (1999).
56. Mebs D. Notes on the traditional use of plants to treat snake bite in northern Papua New Guinea. Toxicon 38:299–302 (2000).
57. Merzouki A, Ed-derfoufi F, Mesa JM. Contribution to the knowledge of Rifian traditional medicine. II: Folk medicine in Ksar Lakbir District. Fitoterapia 71:278–307 (2000).
58. Natarajan B, Paulsen BS, Pushpangadan P. An ethnopharmacological study from the Coimbatore district, Tamil Nadu, India: traditional knowledge compared with modern biological science. Pharm Biol 37:378–390 (1999).
59. Natarajan B, Paulsen BS. An ethnopharmacological study from Thane District, Maharashtra, India: traditional knowledge compared with modern biological science. Pharm Biol 38:139–151 (2000).
60. Natarajan B, Paulsen BS, Korneliussen V. An ethnopharmacological study from Kulu District, Himachal Pradesh, India: traditional knowledge compared with modern biological science. Pharm Biol 38:129–138 (2000).
61. Ndubani P, Hojer B. Traditional healers and the treatment of sexually transmitted illnesses in rural Zambia. J Ethnopharmacol 67:15–25 (1999).
62. Diallo D, Hveem B, Mahmoud MA, Berge G, Paulsen BS, Maiga A. An ethnobotanical study of herbal drugs of Gourma district, Mali. Pharm Biol 37:80–91 (1999).
63. Cortella AR, Pochettino ML. Plants employed for hypotensive infusions in urban areas of Argentina. Pharm Biol 37:97–104 (1999).
64. Coe FJ, Anderson GJ. Ethnobotany of the Sumu (Ulwa) of southeastern Nicaragua and the comparisons with Miskitu plant lore. Econ Bot 53:363–386 (1999).
65. Chuakul W. Medicinal plants in Khao Kho district, Phetchabun Province, Thailand. Pharm Biol 38:61–67 (2000).
66. Bonet MA, Parada M, Selga A, Valles J. Studies on pharmaceutical ethnobotany in the regions of L'Alt Emporda and Les Guilleries (Catalonia, Iberian Peninsula). J Ethnopharmacol 68:145–168 (1999).
67. Von Reis S. Arnold Arboretum, Harvard University, Gray Herbarium. Drugs and foods from little-known plants; notes in Harvard University herbaria. Cambridge, MA:Harvard University Press, 1973.
68. Soejarto DD, Farnsworth NR. Tropical rain forests: potential source of new drugs? Perspect Biol Med 32:244–256 (1989).
69. Farnsworth NR. NAPRALERT Database. Chicago:University of Illiniois-Chicago.
70. Loub WD, Farnsworth NR, Soejarto DD, Quinn ML. NAPRALERT: computer handling of natural product research data. J Chem Inf Comput Sci 25:99–103 (1985).
71. Farnsworth NR, Loub WD, Soejarto DD, Cordell GA, Quinn ML, Mulholland K. Computer services for research on plants for fertility regulation. Korean J Pharmacogn 12:98–110 (1981).
72. Duke JA. Database of Biologically Active Phytochemicals and Their Activities. Boca Raton, FL:CRC Press, 1992.
73. Duke JA. Database of Phytochemical Constituents of GRAS Herbs and Other Economic Plants. Boca Raton, FL:CRC Press, 1992.
74. Hussain RA, Kinghorn AD, Soejarto DD. Sweetening agents of plant origin: literature search for candidate sweet plants. Econ Bot 42:267–283 (1988).
75. Soejarto DD, Kinghorn AD, Farnsworth NR. Potential sweetening agents of plant origin. III: Organoleptic evaluation of Stevia leaf herbarium samples for sweetness. J Nat Prod 45:590–599 (1982).
76. Ogura M, Cordell GA, Quinn ML, Leon C, Benoit PS, Soejarto DD, Farnsworth NR. Ethnopharmacologic studies. I: Rapid solution to a problem—oral use of *Heliopsis longipes*—by means of a multidisciplinary approach. J Ethnopharmacol 5:215–219 (1982).
77. Spieler JM. World Health Organization, the Special Programme of Research, Development and Research Training in Human Reproduction Task Force on Indigenous Plants for Fertility Regulation. Korean J Pharmacogn 12:94–97 (1981).
78. Kong YC, Cheng KF, Cambie RC, Waterman PG. Yuehchukene: a novel indole alkaloid with anti-implantation activity. J Chem Soc Chem Commun 2:47–48 (1985).
79. Oubre AY, Carlson TJ, King SR, Reaven GM. From plant to patient: an ethnomedical approach to the identification of new drugs for the treatment of NIDDM. Diabetologia 40:614–617 (1997).
80. Ubillas R, Jolad SD, Bruening RC, Kernan MR, King SR, Sesin DF, Barrett M, Stoddart CA, Flaster T, Kuo J, et al. SP-303, an antiviral oligomeric proanthocyanidin from the latex of *Croton lechleri* (sangre de drago). Phytomedicine 1:77–106 (1994).
81. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. Clin Infect Dis 30:908–914 (2000).
82. Bierer DE, Dubenko LG, Zhang P, Lu Q, Imbach PA, Garofalo AW, Phuan PW, Fort DM, Litvak J, Gerber RE, et al. Antihyperglycemic activities of cryptolepine analogues: an ethnobotanical lead structure isolated from *Cryptolepis sanguinolenta*. J Med Chem 41:2754–2764 (1998).
83. Bierer DE, Fort DM, Mendez CD, Luo J, Imbach PA, Dubenko LG, Jolad SD, Gerber RE, Litvak J, Lu Q, et al. Ethnobotanical-directed discovery of the antihyperglycemic properties of cryptolepine: its isolation from *Cryptolepis sanguinolenta*, synthesis, and *in vitro* and *in vivo* activities. J Med Chem 41:894–901 (1998).
84. Luo J, Fort DM, Carlson TJ, Noamesi BK, nii-Amon-Kotei D, King SR, Tsai J, Quan J, Hobensack C, Lapresca P, et al. *Cryptolepis sanguinolenta*: an ethnobotanical approach to drug discovery and the isolation of a potentially useful new antihyperglycaemic agent. Diabet Med 15:367–374 (1998).
85. Carney JR, Krenisky JM, Williamson RT, Luo J, Carlson TJ, Hsu VL, Moswa JL. Maprouneacin, a new daphnane diterpenoid with potent antihyperglycemic activity from *Maprounea africana*. J Nat Prod 62:345–347 (1999).
86. Inman WD, Reed MJ. Triterpenoid compound for the treatment of diabetes. In: U.S. Patent. South San Francisco, CA:Shaman Pharmaceuticals, 1997;8.
87. Inman WD, Luo J. Hypoglycemic agents from *Harungan* or *Vismia* spp. WO 98 25,639. In: U.S. Patent. South San Francisco, CA:Shaman Pharmaceuticals, 1998.
88. Luo J, Cheung J, Yevich EM, Clark JP, Tsai J, Lapresca P, Ubillas RP, Fort DM, Carlson TJ, Hector RF, et al. Novel terpenoid-type quinones isolated from *Pycnanthus angolensis* of potential utility in the treatment of type 2 diabetes. J Pharmacol Exp Ther 288:529–534 (1999).
89. Luo J, Chuang T, Cheung J, Quan J, Tsai J, Sullivan C, Hector RF, Reed MJ, Meszaros K, King SR, et al. Masoprocol (nordihydroguaiaretic acid): a new antihyperglycemic agent isolated from the creosote bush (*Larrea tridentata*). Eur J Pharmacol 346:77–79 (1998).
90. Sneader W. Drug Discovery: The Evolution of Modern Medicines. New York:Wiley, 1985.
91. Artuso A. Drugs of Natural Origin: Economic and Policy Aspects of Discovery, Development, and Marketing. New York: Pharmaceutical Products Press, 1997.
92. Reid WV, World Resources Institute, Instituto Nacional de Biodiversidad (Costa Rica), Rainforest Alliance, African Centre for Technology Studies. Biodiversity Prospecting: Using Genetic Resources for Sustainable Development. New York:World Resources Institute, 1993.
93. Baker JT, Borris RP, Carte B, Cordell GA, Soejarto DD, Cragg GM, Gupta MP, Iwu MM, Madulid DR, Tyler VE. Natural product drug discovery and development: new perspectives on international collaboration. J Nat Prod 58:1325–1357 (1995).
94. Soejarto DD. Logistics and politics in plant development. In: Human Medicinal Agents from Plants. ACS symposium series, 534 (Kinghorn AD, Balandrin MF, eds). Washington, DC:American Chemical Society, 1993;96–111.
95. King SR, Carlson TJ, Moran K. Biological diversity, indigenous knowledge, drug discovery and intellectual property rights: creating reciprocity and maintaining relationships. J Ethnopharmacol 51:45–57 (1996).
96. Indigena FS, Kothari B. Rights to the benefits of research: compensating indigenous peoples for their intellectual contribution. Human Organization 56:127–137 (1997).
97. Soejarto DD. Biodiversity prospecting and benefit-sharing: perspectives from the field. J Ethnopharmacol 51:1–15 (1996).
98. Santayana G. The Life of Reason. New York: Scribner, 1922.