The Value of Plants Used in Traditional Medicine for Drug Discovery

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In this review we describe and discuss several approaches to selecting higher plants as candidates for drug discovery 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).
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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 semi-synthesis 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, Δ1-tetrahydrocannabinol, morphine, taxol, podophylotoxin, 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 screening plants for bioactivity, including (a) the paradigm of selecting plants as candidates for drug discovery, (b) the indigenous drug and its potential biologic activity, (c) the ethnomedical use of a plant and the plant’s biologic activity, and (d) the history of a drug and its potential for developing new leads.

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/bufadienolides, alkaloids, triterpenes, flavonoids, isothiocyanates, iridoids, etc. (17)) have been used in the past and are...
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 (35–37). 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, antifungal, antiparasitic, antitumor, cardiovascular, 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 multi-component 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                     | Antidysenteric        | Fraxinus rhynchophylla Hance |
| Agrimohol                      | Anti-inflammatory     | Agrimonia eupatoria L. |
| Ajmalicine                     | Anti-inflammatory     | Rauvolfia serpenina (L.) Benth ex. Kurz |
| Allyl isothiocyanate           | Rubefacient           | Brassica nigra (L.) Koch |
| Androgapholide                 | Bacillary dysentery   | Andrographis paniculatae Nees |
| Antioxidane                    | Anticholinergic       | Anisiodus turgidus (Maxim.) Pascher |
| Arnoidine                      | Anticholinergic       | Anisiodus turgidus (Maxim.) Pascher |
| Arecoline                      | Antihelmintic         | Areca catechu L. |
| Asiaticoside                   | Antitussive           | Centella asiatica (L.) Urban |
| Atropine                       | Anticholinergic       | Atropa belladonna L. |
| Berberine                      | Bacillary dysentery   | Berberis vulgaris L. |
| Bengenin                       | Antitussive           | Ardisia japonica Bl. |
| Bromelain                      | Anti-inflammatory, proteolytic agent | Ananas comosus (L.) Merrill |
| Caffeine                       | CNS stimulant         | Canmelia sinensis (L.) Kurzne |
| (+)-Catechin                   | Haemostatic           | Potentilla fragilis Ehrh. |
| Chymopapain                    | Proteolytic; mucolytic | Canica papaya L. |
| Coccine                        | Local anaesthetic     | Erythroxylum coca Lamk. |
| Codeline                       | Analgesic; antitussive| Papaver somniferum L. |
| Colchicine                     | Antitumor agent; antigen | Colechicum amonium L. |
| Convoluclton                   | Cardiotonic           | Convolvania majalis L. |
| Curcumine                      | Choleretic            | Curcuma longa L. |
| Cynarin                        | Choleretic            | Cynara sclyomus L. |
| Daffron                        | Laxative              | Caxia spp. |
| Deserpine                      | Antihypertensive; tranquilizer | Rauvolfia caesicae L. |
| Deslanoide                     | Cardiotonic           | Digitalis lanata Ehrh. |
| Digitalin                      | Cardiotonic           | Digitalis purpurea L. |
| Digitoxin                      | Cardiotonic           | Digitalis purpurea L. |
| Digoxin                        | Cardiotonic           | Digitalis lanata Ehrh. |
| Emetine                        | Amoebicide; emetic    | Opheliais (pecucauenha (Brotero) A. Richard |
| Ephedrine                      | Sympathomimetic       | Ephedra sinica Staph. |
| Etioposide                     | Antitumour agent      | Podophyllum pertatum L. |
| Gilarin                        | Cardiotonic           | Digitalis purpurea L. |
| Glucaracin                    | Amoebicide            | Simarouba glauca DC. |
| Glycyhrizin                    | Sweetener             | Glycyrhiza glabra L. |
| Gossypol                       | Male contraceptive    | Gossypium spp. |
| Hemsleyadin                   | Bacillary dysentery   | Helmsleya ambilis Diels |
| Hydrastine                     | Hemostatic; astringent| Hydrastis canadensis L. |
| Hyoscitamine                  | Anticholinergic       | Hyscamus niger L. |
| Kainic Acid                    | Ascordicte            | Digenea simplex (Wulf.) Agardh |
| Kewain                        | Tranquilizer          | Piper methysticum Forst. f. |
| Khaellin                      | Bronchodilator        | Ammi visnaga (L.) Lamk. |
| Latanoidsides A, B, C          | Cardiotonic           | Digitalis lanata Ehrh. |
| Lobeline                      | Smoking dependent; respiratory stimulant | Lobelia inflata L. |
| Monocrotaline                 | Antitumor agent       | Cotolilia sessiflora L. |
| Morphine                       | Analgesic             | Papaver somniforium L. |
| Neosandrapholide              | Bacillary dysentery   | Andrographis paniculatae Nees |
| Nocolinic                     | Antitussive           | Papaver somniferum L. |
| Ouabain                       | Cardiotonic           | Strophantus gratus BAIL. |
| Papain                        | Prototoxic; mucolytic | Canica papaya L. |
| Phylloducin                   | Sweetener             | Hydrangea macrophylla (Thurb.) DC |
| Physostigmime                 | Cholinesterase inhibitor | Physostigma venenousum BAIL. |
| Picrotoxin                     | Analeptic             | Anamita cocculus (L.) W. & A. |
| Pilocarpine                   | Parasympathomimetic   | Pilocarpus jaborandi Holmes |
| Podophylloctin                | Condylomata acuminata | Podophyllum pertatum L. |
| Photovertains A & B           | Antihypertensive      | Veratum album L. |
| Pseudophedrine                | Sympathomimetic       | Ephedra sinica Staph. |
| Pseudophedrine, nor-Quinme     | Sympathomimetic       | Ephedra sinica Staph. |
| Quinocilic Acid               | Antihypertensive      | Cinchona ledgeriana Moens ex. Trimen |
| Rescinnamine                  | Antihypertensive; tranquilizer | Quisqualis indica L. |
| Reserpine                     | Antihypertensive      | Rauvolfia serpenina (L.) Benth ex. Kurz |
| Rhimotoxin                    | Antihypertensive      | Rauvolfia serpenina (L.) Benth ex. Kurz |
| Roritone                      | Antitussive           | Rhododendron molle G. Don |
| Rotenone                      | Fluside               | Ronppa indica (L.) Hochl. |
| Rutainne                      | Analgesic; sedative   | Lonchocarpus ricou (Aubl.) DC. |
| Salicine                      | Analgesic             | Stephania sincra Diels |
| Santinin                      | Ascorbicde            | Salix alba 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 herbas (47); review articles (usually involving surveys of medicinal plants by geographic region or ethnic culture) (48-60); 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 vivo, in vitro, or in humans) to identify plants having both types of activity for a given effect—e.g., anticancer, antiabietic, 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, saccharatus, 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).

**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 reports reporting isolation of these compounds from their respective plants. This was done to determine whether the chemical claims 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 ED50 of 19.04 mg/kg (i.g.). Morphine showed an ED50 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 ED50 of this compound was 6.98 mg/kg (i.g.). The plant was isobutylamide, affinin (spilanthol) (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, eczolic, 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 biological 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 yuechuhkene (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 anti-diabetic agents, which resulted in the discovery of several patented compounds: cryptolepine (82–84), maprouneacin (85), 3β,30-dihydroxylupen-20(29)-en-2-one (86), harungarfin (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
Environmental Health Perspectives • VOLUME 109 | SUPPLEMENT 1 | March 2001

The value of plants used in traditional medicine for drug discovery

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 cromoglycate), 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 ethnomedicinally 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 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 pay-off 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...
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).

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