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COMMENTARY

Medicinal Herbs: Drugs or Dietary Supplements?

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ABSTRACT. The process of evaluating medicinal herbs is complex, and there is a need to carefully define a research strategy that addresses a solution to safe and efficacious herbal products. Notwithstanding the immense value of distilling the pharmacological activity of an herb into a chemical suitable for drug development, another approach is to develop a standardized herbal extract that yields consistent pharmacological activity. However, it frequently is forgotten that even in an extract several active ingredients contribute to the pharmacological action. Sufficient evidence exists to suggest that extracts of medicinal herbs, once isolated in their pure state, can produce pharmacological effects that differ significantly from that of the whole herb. This article discusses a research-based strategy that may be suitable for validating, in part, the putative health benefits of medicinal herbs. Additionally, the body of scientific evidence that underpins the pharmacological activity of several herbs is reviewed briefly. BIOCHEM PHARMACOL **59**;3:211–219, 2000. © 1999 Elsevier Science Inc.

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OVERVIEW

Dietary supplement sales in the United States are booming, and consumption of botanical products is expected to grow exponentially. Sales of medicinal herbs or herbal extracts are expected to exceed $4 billion annually. Two major factors have influenced the increasing use of herbs or herbal extracts in the United States. First, aging baby boomers are highly motivated to identify alternative approaches to improving their quality of life. With the advent of managed health care and the disenchantment with synthetic pharmaceutical drugs, many consumers are turning to natural remedies, especially herbs, as a solution for maintaining good health. Second, the mass media, by providing regular reports of the putative healing effects of herbs, are fueling this belief and increasing consumer awareness of this product category. For example, the effects of ginkgo on memory improvement [1–5] and the antidepressive effects of St. John's wort [6–8] have been both reported in major medical journals and propagated by the mass media. Given this heightened interest, and the inability of the world economy to absorb the rising cost of Western pharmaceuticals, there is a need to re-evaluate medicinal herbs as complementary medicines for the world population. The cost of bringing a single drug to market is now more than the gross national product of some countries. The ideal of magic bullets to treat disease is receding as it becomes clear that diseases are polymorphic in nature, and agents that often appear in the raw state in plants may not be as undesirable as once thought. It is important to note that although many of these therapies are considered alternative and/or complementary in Western countries, they are mainstream in many developing countries, where, by contrast, Western medicine is alternative.

Despite the popularity of botanical dietary supplements, many herbal medicines are not well researched in terms of their mechanisms of action, toxicity, and clinical effects. Fallacies and hyperbole associated with herbal products have included the following: (i) herbs, being natural, are implicitly safe; (ii) herbs do not have side-effects; (iii) herbs are a panacea; and (iv) efficacy can be obtained over a wide range of doses. Such claims run counter to fundamental pharmacological tenets and lessen the value of medicinal herbs in the overall strategy to prevent or treat disease. Given this state of affairs, pharmacological research on botanicals can only be viewed as essential in establishing the true value of medicinal herbs.

This article describes a research strategy that may be suitable for evaluating medicinal herbs within the context of the current regulatory environment. Several popular herbs are also described in terms of their pharmacology and putative mechanisms of action to illustrate the type of research that has been conducted.

The Dietary Supplement Health and Education Act (DSHEA)

The DSHEA defines dietary supplements in the United States as comprising plant extracts, enzymes, vitamins, minerals, and hormonal products that are available to the consumer without prescription [9]. This statutory definition is unique to the United States and occupies a regulatory position at the nexus of foods and prescription drugs [10].

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Under the DSHEA, dietary supplements may carry "structure/function" claims—claims that a product may affect the structure or functioning of the body—but not claims that they can treat, diagnose, cure, or prevent a disease. The DSHEA has established a formal definition of "dietary supplement" using several criteria listed below:

- A product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by people to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combination of these ingredients
- A substance that is intended for ingestion in pill, capsule, tablet, or liquid form
- A substance that is not represented for use as a conventional food or as the sole item of a meal or diet
- A substance that is labeled as dietary supplement
- A substance that includes products such as an approved new drug, certified antibiotic, or licensed biologic marketed as a dietary supplement or food before approval, certification, or license

Other provisions of the DSHEA include the ability to use third-party literature to help consumers to be better informed about the product as long as the literature is truthful and does not promote a specific company or brand of supplement. It should be stressed that DSHEA legislation preserves the authority of the Food and Drug Administration (FDA) to safeguard the public against an unsafe product and to remove any product from the market if the FDA deems the product to present a significant and unreasonable risk of injury.

COMPLEXITY OF MEDICINAL HERBS

The putative efficacy of medicinal herbs relies on empirical or anecdotal data and tradition of use, which frequently cannot satisfy the requirements of evidence-based medicine. Thus, establishing the pharmacological basis for the actions of medicinal herbs is a constant challenge. Even when scientific data are available, it is often difficult to determine whether a consistent herbal preparation was used in various studies. Often, several herbs are mixed to achieve a pharmacological effect, thereby making it extremely difficult to attribute the effect to a particular herb. Recognition of these confounding factors by researchers will aid in generating useful data that can lead to a better understanding of the proper role of medicinal herbs in health.

DSHEA VERSUS NEW DRUG APPLICATION (NDA) DEVELOPMENT

Table 1 compares and contrasts the development of DSHEA products relative to the drug development process. It is clear that there are significant differences between the two approaches, and these differences can have an important impact on how medicinal herbs are evaluated. Whereas the manufacturing and clinical evaluation of drug substances and products is well defined by the NDA process, there are no clear regulatory guidelines for creating botanical products, an issue that is under intense current debate. The outcome of this debate is uncertain, but ultimately will have a fundamental impact on how these products will be developed, especially in the United States. In the interim, it is likely that a flexible strategy that accounts for the present environment while remaining relevant for the future is the most prudent approach. Regardless of regulatory issues, certain developmental elements are, nonetheless, essential to reduce the perception of medicinal herbs as nostrums by mainstream medicine. With significant advances in preclinical and clinical research, there are now several paths to creating a knowledge base on the composition and pharmacological properties of a specific herb. The 6S process illustrates one possible approach.

TABLE 1. Commercialization of herbs and drugs: Regulatory differences

Medicinal herbs	Drugs
FDA approval not required	FDA approval required
Mixture of active constituents	Single well-characterized chemical
Efficacy based mainly on historical and anecdotal data	Prospective Phase I-II studies
Oral dosage form	All dosage forms
No GMP guidelines	Well-established GMP guidelines
Difficult analytical methods	Well-established analytical methods
Environmental factors influence level of active constituents	Chemical synthesis

THE 6S PROCESS

The 6S process, as shown in Table 2, captures research elements that involve herb selection, source, structural analysis, herb standardization and manufacturing, and pharmacological and clinical studies. We believe that these

TABLE 2. The 6S process

Selection	Standardization
Herb informatics	Chemical profile
Unmet health need	Pharmacological profile
Sourcing	Safety
Chemotaxonomy	Historical/traditional use
Raw material analysis	Toxin analysis
	Safety studies in animals
Structure	Substantiation
Identification of active constituents	review of pre-existing data
Method validation	Prospective clinical study

elements cannot be ignored if medicinal herbs are to join the ranks of truly efficacious products. Notably, this process includes a prospective research component, and does not rely solely on historical evidence for safety and efficacy. There is an absolute acknowledgement that retrospective anecdotal data on medicinal herbs cannot be the only basis for demonstrating efficacy of botanicals. The 6S process also is intended to produce a pharmacologically consistent herbal product with different batches of raw materials.

Chemistry Features

Wide variations in chemical composition are characteristic of any botanical or natural product and require careful chemical analysis to ensure batch-to-batch consistency. Chemical assessment of raw material quality, an accurate taxonomic classification of the plant species, definition of a chemically standardized plant extract that is toxin-free, confirmation of the bioactivity of the plant extract, and stability of the final product are some of the important steps to ensuring batch consistency. To date, medicinal herbs can vary widely in terms of putative active ingredients, and the presence of toxic contaminants in the final product is often not evaluated. Unless these factors are controlled carefully, it will be difficult to compare data.

Pharmacological Features

Biological assays, including dose–response studies, to detect pharmacological activity also serve to minimize batch-to-batch variation, especially for complex herbal extracts. Although advances in chemical analytical methods have led to a better definition of the chemical nature of herbal extracts, a chemically standardized extract may not ensure consistent pharmacological activity. To mitigate this potential problem, we believe that a bioassay measuring a clinically useful activity will provide the necessary data to support a chemical standardization method. Mechanistic studies (*in vitro* or *in vivo*) identifying a potential molecular target also could guide the selection of a relevant bioassay. To the extent possible, identifying a surrogate biochemical marker that can be measured during clinical studies is an important feature of the 6S approach. For example, cholesterol, a predictive risk factor for atherosclerosis, can be measured easily, both *in vitro* and in blood samples. It also is known that the liver enzyme β-hydroxy-β-methylglutaryl-CoA reductase is the rate-limiting step in cholesterol biosynthesis, thereby providing a convenient enzyme assay for monitoring the activity of various herbal extracts. In this instance, therefore, it would be relatively straightforward to evaluate the batch-to-batch consistency of an herbal extract.

Development of herbal products can also benefit greatly from a better understanding of the bioavailability of herbal products. It is an axiom in pharmacology that orally active compounds must achieve acceptable plasma levels before they can exert a clinical effect *in vivo*. In many instances, conflicting reports about the efficacy of an herb may be due to differences in bioavailability among different versions of the same herb. The assumption that *in vitro* data can be extrapolated in their entirety to an *in vivo* milieu has led to erroneous conclusions about the effect of medicinal herbs *in vivo*. For herbal products, however, it is often difficult to conduct bioavailability studies through analytical chemistry; instead, bioassays may be more relevant in the assessment of oral bioavailability. Cellular assays, receptor assays, and other *in vitro* diagnostic assays are all useful as possible methods for assessing the level of the active components of medicinal herbs in the circulation. Coupled to chronic animal studies, determination of activity in blood can provide valuable information related to proper dosage. For example, bioavailability studies conducted with two similar ginkgo extracts showed that there were significant differences in blood levels of the active constituent, ginkgolides [11]. Whereas one ginkgo extract produced a blood level of ginkgolides that persisted for as long as 12 hr, the second ginkgo extract failed to maintain significant ginkgolide levels at 12 hr. Such bioavailability data can be very useful for establishing dose and dosing regimen.

TABLE 3. Clinical research and medicinal herbs

Research objective	Level of difficulty
Human safety	Low
Human efficacy	Moderate to high
Mechanism of action	Moderate
Clinical pharmacology	High

Clinical Features

Well-designed clinical trials that meet Good Clinical Practice guidelines [12] must be an integral part of any strategy to establish the validity of medicinal herbs as an efficacious modality. Unfortunately, clinical research on botanicals has not been driven by well-defined research objectives. As shown in Table 3, research objectives such as safety, assessment in a general population, mechanism of action, pharmacokinetics, clinical pharmacology, and efficacy endpoints have different levels of difficulty. Whereas these objectives are not mutually exclusive, the expectation that several objectives can be met in a single study is unrealistic and can complicate clinical trial design. For complex mixtures such as medicinal herbs, a design focusing on a single objective provides data of better quality than a multi-faceted clinical trial involving several clinical endpoints.

That medicinal herbs are inherently safe, especially after a concentration step, is a dangerous misconception. One could cite Ma-Huang as an example where serious side-effects have been observed [13, 14]. Currently, there is no systematic monitoring of the use of medicinal herbs by the general population. Adverse reactions associated with product use tend to be underreported. We believe that the

optimal active mechanism for gathering safety data is an open label study. As part of the clinical development strategy, the following clinical scheme is proposed:

- Human bioavailability studies to select a dose
- An initial exploratory clinical study using a surrogate biochemical marker of activity
- A placebo-controlled, double-blind clinical study confirming the effect on a surrogate marker
- A multi-center, open-label safety study

Importantly, many principles dealing with minimizing bias and maximizing precision are especially critical in the study of medicinal herbs. Robustness, a concept that addresses the sensitivity of the overall conclusions to changing assumptions, should be the ultimate goal of any clinical trials of medicinal herbs.

Examples of Pharmacologically Active Herbal Extracts

It is beyond the scope of this commentary to review pharmacological studies that have been conducted with medicinal herbs. Instead, this section highlights several herbs or herbal extracts that have contributed to pharmacological research while illustrating some of the principles outlined above.

Huperzia serrata

The Chinese herbal medicine Qian Ceng Ta, which is prepared from the moss *H. serrata*, has been used in China for centuries to treat fever and inflammation. The alkaloid huperzine A, isolated from *H. serrata*, is prescribed currently in China for senile dementia.

Huperzine A appears to have pharmacological properties that make it an attractive candidate for treating Alzheimer's disease. In studies using hippocampal and cerebellar cell cultures, huperzine A decreases neuronal cell death caused by high concentrations of glutamate [15]. This property may make huperzine A a potentially useful agent to reduce neuronal cell injury from strokes, epilepsy, and brain disorders. Consistent with this hypothesis, Grunwald *et al.* [16] demonstrated that huperzine can act as a prophylactic agent to prevent brain damage from nerve gas poisons. Systemic huperzine A significantly increased ACh,* NE, and DA levels [17]. Notably, the ACh increase persisted for at least 6 hr. Huperzine A can easily cross the blood–brain barrier, since both systemic and local intracerebral administration produces a dose-dependent increase of ACh, NE, and DA in rat cortex.

Based on laboratory and x-ray crystallography studies, huperzine A is several orders of magnitude more potent than tacrine as an AChE inhibitor [18]. Compared with tacrine and donepezil, huperzine A has a longer half-life, and the AChE–huperzine A complex has a slower rate of dissociation. According to Ashani *et al.* [18], huperzine A appears to be strongly specific for AChE, suggesting that it may have fewer side-effects than tacrine. The resolution of the three-dimensional structure of the huperzine A–AChE complex may provide valuable insights into strategies to synthesizing analogs with improved therapeutic properties [19].

Red Yeast Rice

The popularity of fermented foods in China was the foundation for the modern discovery of a red yeast rice extract that lowers cholesterol [20]. For several hundred years [21], red yeast rice traditionally has been prepared by fermenting non-glutinous rice with red yeast (*Monascus purpureus*). Indeed, a description of red yeast rice found in *Ben Cao Gang Mu* (*Compendium of Materia Medica*, 1578 A.D.) promotes its ability to "invigorate spleen, digestion, and promote blood circulation and resolve blood stasis." In China, it is part of the daily staple diet, and because of its flavor and color, red yeast rice is used frequently as a flavoring agent in several Chinese dishes. Examples of foods flavored by red yeast rice include roast pork, roast duck, fermented bean curd, preserved dry fish, and vegetable pork stew. Red yeast also is used widely for making Shioxing and Beni-Koji rice wine.

Recently, animal studies showed that red yeast rice prevented increases of serum total cholesterol and triglycerides in rabbits fed an atherogenic diet [22]. Importantly, lesions in the aorta and lipidosis in the livers of red yeast rice-treated rabbits were less severe than those of the control model rabbits. Similar findings were obtained in quail fed a cholesterol-rich diet.

Several clinical studies, in China and the United States, have since confirmed the cholesterol-lowering effect of red yeast rice in humans. One major randomized multicenter clinical trial involving 446 hyperlipidemic patients in China found that a red yeast rice extract reduces serum lipids [23]. Another randomized, double-blind, placebo-controlled trial involving a total of 152 patients showed a cholesterol reduction of 19.2% compared with 1.5% in the placebo group [24]. A double-blind prospectively randomized 12-week controlled trial in the United States confirmed the lipid-lowering effects of red yeast rice [25]. Serum total cholesterol decreased significantly by 16% between baseline and 12 weeks in the treatment group. There were no significant changes in dietary intake of fat, calories, or cholesterol or in body weight or liver function tests, and no serious adverse effects occurred in either the treatment or placebo-treated group.

The mechanism of action of red yeast rice may be due, in part, to the presence of several monocolins. HPLC analysis shows that red yeast rice contains monocolins, which have been shown previously [26] to be potent inhibitors of β-hydroxy-β-methylglutaryl-CoA reductase, the rate-limit-

* *Abbreviations*: ACh, acetylcholine; NE, norepinephrine; DA, dopamine; AChE, acetylcholinesterase; tNOX, tumor-specific NADH oxidase; 5-HT, 5-hydroxytryptamine, serotonin; GABA, γ-aminobutyric acid; NO, nitric oxide; iNOS, inducible nitric oxide synthase; HCA, hydroxycitric acid; TNF, tumor necrosis factor; IFN-γ, interferon-γ; and IL, interleukin.

ing step in cholesterol synthesis. Other constituents such as unsaturated fatty acids (>125 mg/g of extract), including monounsaturated fatty acids and diene-, triene-, tetraene-, and pentaene-fatty acids could also be a factor in lowering blood lipids. Other less well-characterized components include proteins, amino acids, saccharides, β-sitosterol, campesterol, stigmasterol, isoflavone and its glycoside, saponin and sapogenin, and many trace elements.

Green Tea

In recent years there has been a renewed interest in tea as a possible source of free radical scavengers and in the role of tea in cancer chemoprevention [27, 28]. As with most crude extracts, tea is a complex mixture of many compounds, but generally tea contains caffeine, amino acids, protein, chlorophyll, lignin, organic acids, and polyphenols. Of these compounds, the polyphenols or tea catechins are of the most relevance for antioxidant activity [29]. Increasing evidence suggests that the therapeutic effects of green tea, including cancer prevention, are mediated by tea polyphenols. The putative anti-carcinogenic mechanisms of tea polyphenols include antioxidant activity, inhibition of nitrosation reactions, modulation of carcinogen-metabolizing enzymes, trapping of ultimate carcinogens, and inhibition of enzymes associated with cancer cell proliferation and growth [29–33]. Powerful antioxidant properties, equivalent to those of vitamin E and greater than those of vitamin C, are conferred by the multiple hydroxyl groups of the polyphenols, which are readily oxidized to give the corresponding *O*-quinones. As a result, green tea polyphenols are effective scavengers of active oxygen species such as superoxide and hydroxyl radicals. In addition, the flavonoids contain strong nucleophilic centers, which have a high affinity for metal ions. Since the generation of reactive oxygen species is catalyzed by metal ions, the metal-chelating properties of the tea polyphenols also contribute to reducing the levels of oxygen free radicals in the cell.

Green tea polyphenols can inhibit carcinogen-induced modification of DNA structure that leads to tumor formation; for example, green tea polyphenols inhibit DNA alkylation and DNA–carcinogen adduct formation [33]. It has also been suggested that the strong nucleophilic centers of tea flavonols decrease the levels of electrophilic carcinogens through the formation of flavonol–carcinogen adducts and thus inhibit tumorigenesis [34]. Finally, these potential protective effects also may be augmented by enhanced carcinogen inactivation, since administration of green tea to mice caused modest elevations in the levels of several conjugating and antioxidative enzymes [35].

A review by the International Agency for Research on Cancer examining the relationship between tea consumption and cancer incidence in humans is equivocal [36]. In general, the consumption of green tea may be beneficial in reducing tumors along the gastrointestinal tract, with the degree of protection depending on the location of cancer [37–40]. A recent large case-control study conducted in Shanghai, China, involving 2266 cancer patients and 1552 controls, suggested that green tea consumption lowered the risk of cancer of the colon, rectum, and pancreas by 18, 28, and 37%, respectively, in men and by 33, 43, and 47%, respectively, in women [37]. Previous studies by the same workers had suggested protective effects of green tea of similar magnitude against esophageal and stomach cancers [37, 38]. Other smaller studies had revealed a significantly reduced risk of colon, but not rectal, cancer and of precancerous adenomas of the colon and rectum in green tea drinkers [39, 40]. Overall, most case-control studies have revealed no clear relationship between tea consumption and the risk of pancreatic cancer, although five out of six cohort studies have reported lower risks of pancreatic cancer among tea drinkers [41]. Data from such studies often are confounded by the lack of information on the type of tea consumed (i.e. green or black), the quantity, and other dietary and life-style factors such as tobacco and alcohol use [42].

A mechanism whereby green tea polyphenols may exert at least some of their anti-cancer effects through a non-antioxidant mechanism has been proposed. Morré and co-workers [43–45] have shown that the enzyme tNOX is expressed specifically on the cell surface of many cancer cells. Capsaicin isolated from Cayenne peppers inhibited tNOX activity, which could be correlated with cancer cell division and growth. More recently, epigallocatechin gallate, a tea catechin, also has been shown to be a potent specific inhibitor of tNOX at nanomolar concentrations.* This finding now may explain epigallocatechin gallate-induced inhibition of the proliferation of several cancer cell lines, which has been observed in several green tea studies [46, 47].

St. John's Wort

The herb St. John's wort has been associated with a number of CNS effects [48]. For example, an extract of St. John's wort, LI 160, inhibited both 5-HT and NE uptake in a dose-dependent manner [49]. 5-HT uptake was reduced by 50%, whereas for NE, there was a 4.5-fold reduction in the apparent affinity of NE for its uptake sites. Upon removal of LI 160, uptake was restored, thereby indicating that the inhibition was not due to a toxic effect on the cells. Extracts, fractions, and constituents of St. John's wort were subjected to *in vitro* receptor binding studies [50]. A lipophilic fraction revealed relatively potent antagonism of the μ-, δ-, and κ-opioid receptors and the 5-HT_6 and 5-HT_7 receptors. Binding to the opioid and 5-HT receptors was inhibited by hypericum constituents such as the naphthodianthrones, hypericin and pseudohypericin, and the phloroglucinole hyperforin at low micromolar concentrations. The lipophilic fraction was a weak antagonist of the neurokinin-1 receptors compared with the opioid and 5-HT receptors, whereas an ethanolic extract potently

* Dr. James Morré, personal communication. Cited with permission.

inhibited $GABA_A$ binding. In addition, hypericin inhibited dopamine β-hydroxylase, which regulates the synthesis of catecholamine neurotransmitters [51]. Together, these results support the hypothesis that several active constituents of St. John's wort might contribute to its antidepressant effect.

The major naphthodianthrones in St. John's wort, hypericin, pseudohypericin, isohypericin, and emodin-anthrone, are light-sensitive. Photodynamic therapy with hypericin rapidly induces apoptosis of HeLa cells [52], and this photodynamic therapy-induced apoptosis with hypericin is related to the activation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase. It is tempting to speculate that photodynamic therapy with hypericin may be effective as part of the armamentarium to treat human tumors.

Although hypericin has been reported to have antiretroviral activity *in vitro*, a recent clinical study did not confirm this effect *in vivo*. Of the 30 patients who were studied, 16 discontinued treatment early because of toxic effects. Severe cutaneous phototoxicity was observed in 11 of 23 evaluable patients, and dose escalation could not be completed. Virologic markers and CD4 cell count did not change significantly [53].

Saw Palmetto

Saw palmetto, which is native to the southeastern portion of the United States, is an herb used for preventing benign prostatic hyperplasia. In a clinical trial that compared the efficacy of finasteride and a saw palmetto extract, both products relieved symptoms compared with the placebo [54]. Saw palmetto appears to act as a weak antiandrogen to reduce 5α-reductase, which converts testosterone to dihydrotestosterone, thus leading to the overproduction of prostatic cells and prostate enlargement. The existing literature on saw palmetto for treating benign prostatic hyperplasia is limited in terms of study duration, variability in study design, use of inconsistent preparations, and reports of outcomes. Current evidence suggests that saw palmetto probably improves urologic symptoms and flow measures. Compared with finasteride, the use of saw palmetto had fewer side-effects. Using human prostate cells, finasteride, however, was shown to be 5600 times more active than saw palmetto extract [55]. It has been argued that enzyme inhibition by saw palmetto requires the presence of free fatty acids to modulate enzyme activity. Indeed, enzyme inhibition was most pronounced in saw palmetto extracts containing free fatty acids [56]. The active constituents of saw palmetto are believed to be sterols and fatty acids [57], and a liposterolic extract significantly inhibited the conversion of testosterone to dihydrotestosterone by human foreskin fibroblasts [57]. At extremely high doses, saw palmetto inhibited androgen binding to the cytosolic receptor in the prostate [58].

Ginkgo biloba

G. *biloba* has gained worldwide interest as an herbal extract to treat dementia and claudication. In Germany, where most of the research has been conducted, the federal health authorities concluded that treatment with a ginkgo extract is safe and effective for the above-mentioned indications. A recently published study in the United States corroborated the efficacy of ginkgo in treating mild dementia [5]. The ginkgo extract was found to stabilize and in some cases improve cognition and social functioning in patients with mild to moderate dementia.

The mechanism of the pharmacological effects of ginkgo is poorly understood. Current research would suggest that the flavonoid glycosides and terpene lactones (ginkgolides) in ginkgo could act as free radical scavengers, comparable to other antioxidants such as vitamins C and E. The ginkgolides in G. *biloba* originally were shown to antagonize platelet-activating factor, an endogenous mediator of inflammation produced by a variety of inflammatory cells, which may improve cardiovascular blood flow [59, 60]. A G. *biloba* extract (EGb 761) prevented the ischemia-induced impairment of Na,K-ATPase activity and expression, and reduced the contents of fatty acids and malondialdehyde, an index of lipoperoxidation, in the ischemic cortex in the mouse [61]. It should be noted that effective doses were substantially higher than the recommended human dose. Bilobalide, a constituent of G. *biloba* extract, possesses anticonvulsant activity, and the mechanism of its anticonvulsant action involves modulation of GABA-related neuronal transmission [62]. GABA levels, glutamic acid decarboxylase activity, and glutamic acid decarboxylase in the hippocampus of mice treated with bilobalide were significantly higher than those in controls. However, there were no significant differences in glutamate levels or the number and the dissociation constants of $GABA_A$ receptors in the hippocampus between control and bilobalide-treated mice. These results suggest that the anticonvulsant effect of bilobalide is due to elevation of GABA levels, possibly through potentiation of glutamic acid decarboxylase activity and enhancement of glutamic acid decarboxylase. Another possible mechanism suggested by recent studies is the modulation of NO production [63, 64]. Extracts from the leaves of G. *biloba* have been reported to be effective at increasing vascular relaxation. A ginkgo extract relaxed the basilar artery, partly through an endothelium-dependent mechanism. Relaxation induced by transmural nerve stimulation was enhanced significantly in both endothelium-intact and -denuded basilar arteries. Enhanced transmural nerve stimulation-induced relaxations were abolished by L-arginine. G. *biloba* also inhibited NO synthesis induced by lipopolysaccharide plus IFN-γ in the mouse macrophage cell line RAW 264.7 [64]. The iNOS enzyme activity of cytosolic preparations from activated RAW 264.7 cells was inhibited, and reverse transcription–polymerase chain reaction analysis revealed that the expression of iNOS mRNA in activated macrophages was

suppressed. Thus, G. *biloba* may inhibit NO production at the gene level.

Echinacea

Echinacea has been purported to modulate the immune response, especially that associated with viral infections. Several polysaccharides in Echinacea activated macrophages to produce cytokines. Macrophages in the presence of Echinacea produced significantly higher levels of IL-1, TNFα, IL-6, and IL-10 than unstimulated cells [65]. The levels of the cytokines IL-1α, IL-1β, IL-2, IL-6, TNFα, and IFN-γ in culture supernatants of stimulated whole blood cells derived from 23 tumor patients also have been evaluated [66]. In the blood cell cultures of all patients, a rather wide range of cytokine levels was found. After therapy with Echinacea complex, no significant alteration in the production of the cytokines could be seen in comparison with the controls, and also the leukocyte populations remained constant.

Both alcoholic and aqueous extracts of Echinacea have been reported to inhibit influenza, Herpes, and vesicular viruses *in vitro* [67]. Viracea, a blend of benzalkonium chloride and phytochemicals derived from *Echinacea purpurea*, was tested against 40 strains of herpes simplex virus. The extract was reported to have antiviral activity against both acyclovir-resistant and acyclovir-sensitive herpes simplex virus. *In vivo*, glycoprotein-rich fractions of *E. purpurea,* when given i.v. to mice, induce the release of cytokines (IL-1 and TNF). In carbon clearance and granulocyte assays, Echinacea-treated mice have shown greater phagocytic activity. While immunostimulatory constituents of Echinacea remain uncertain, lipophilic alkylamides and cichoric acid are currently believed to play major roles.

In a meta-analysis, Melchart *et al.* [68] analyzed five placebo-controlled randomized studies investigating the immunomodulatory activity of preparations containing extracts of Echinacea in healthy volunteers. A total of 134 healthy volunteers between 18 and 40 years of age were studied. The primary outcome measure for immunomodulatory activity was the relative phagocytic activity of polymorphonuclear neutrophils. The secondary outcome measure was the number of leukocytes in peripheral venous blood. In two studies, the phagocytic activity of polymorphonuclear neutrophils was enhanced significantly compared with placebo, whereas in the other studies no significant effects were observed. Leukocyte number was not influenced significantly in any study. Whether different preparations of Echinacea account for this discrepancy is not known.

Recently, the efficacy of two extracts of Echinacea for preventing upper respiratory tract infections was studied [69]. Three hundred and two volunteers without acute illness at the time of enrollment were treated with an ethanolic extract from *E. purpurea* roots, *E. angustifolia* roots, or placebo, for 12 weeks. The time until occurrence of the first upper respiratory tract infection was 66 days in the *E. angustifolia* group, 69 days in the *E. purpurea* group, and 65 days in the placebo group. The infection rate was 36.7% in the placebo group, 32.0% in the *E. angustifolia* treatment group, and 29.3% in the *E. purpurea* treatment group. In this study a prophylactic effect of the investigated Echinacea extracts, therefore, could not be shown. Participants in the treatment groups, however, believed that they had more benefit from the medication than those in the placebo group.

Garcinia cambogia

Because of limited success in the pharmacological management of weight, the use of herbal weight loss products has gained popularity. An herb-derived compound, HCA, isolated from extracts of related plants native to India, mainly G. *cambogia* and G. *indica*, has been shown to be a potent competitive inhibitor of the extramitochondrial ATP–citrate lyase [70]. In animals, HCA not only inhibited the actions of citrate cleavage enzyme and suppressed *de novo* fatty acid synthesis but also increased rates of hepatic glycogen synthesis, suppressed food intake, and decreased body weight gains [71]. Despite these intriguing findings, clinical studies have been equivocal in demonstrating an effect in obese individuals. Recently, in a well-controlled clinical trial of 135 patients, HCA was not effective in inducing weight loss, suggesting that it is often difficult to extrapolate animal data to the human condition [72].

FUTURE DIRECTIONS

It is the opinion of this author that until medicinal herbs are standardized and properly controlled in their extraction and manufacture, it is unlikely that the pharmacology of medicinal herbs will yield meaningful data. While Western medicine has advanced rapidly over the last 100 years, the implications of technology, and its costs, have led to a "grassroots" movement to restore some of the traditional concepts of preventive care to a comprehensive public health and fitness program. Herbal medicine in one form or another is being promoted as an alternative road to wellness. It is, however, presumptuous, and even counterproductive, to suggest that either herbal products or Western drugs in purified form are superior in their own right and mutually exclusive. The limitations of each must be acknowledged, and it would be more realistic by far to suggest that if there was ever a field of research suited for an epochal meeting of East and West, it is the field of herbal medicine. The intuitive approach of a 5000-year-old science surely can contribute to a better understanding of the human condition, and help regain the human element of modern medicine. Pharmacological research is central in metamorphosing medicinal herbs into viable products in the West.

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