Dietary supplements and functional foods: 2 sides of a coin?¹⁻³

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ABSTRACT Dietary supplements are used by more than one-half of the adult US population. In contrast to pharmaceuticals, dietary supplements may be sold in the United States with little regulation other than listing of ingredients and the potential health benefits. By contrast, herbal products in Germany are carefully regulated by the same standards as drugs, and efforts are under way to standardize their regulation in the entire European Union. Most herbal users do not inform their physicians that they are taking these supplements, and most physicians do not inquire. Although some herbal products have clinically proven benefits, it is increasingly apparent that many contain potentially toxic substances, particularly in relation to interactions with drugs. Hence, it is essential that practicing physicians develop a working knowledge of herbs—specifically, about claims for their usage and potential or proven efficacies and toxicities—and that they incorporate such knowledge into the evaluation and management of their patients. By contrast, functional foods—integral components of the diet that are understood to contribute added health benefits—are the subject of intense and widespread research in food and nutritional science. Examples include many polyphenolic substances, carotenoids, soy isoflavones, fish oils, and components of nuts that possess antioxidant and other properties that decrease the risk of vascular diseases and cancer. Practicing physicians are advised to stay abreast of these emerging findings in order to best advise their patients on the value of health-promoting diets in disease prevention. Am J Clin Nutr 2003;77(suppl):1001S–7S.

KEY WORDS Dietary supplements, herbal products, functional foods, challenges to medical practitioners

INTRODUCTION

In 1994 the US Congress enacted the Dietary Supplement Health and Education Act (DSHEA) (1). This act defines a dietary supplement as “a product (other than tobacco) that is intended to supplement the diet and 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 man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract or combination of these ingredients.” Furthermore, a dietary supplement is intended for ingestion in pill, capsule, tablet, or liquid form; is not represented for use as a conventional food or as the sole item of a meal or diet; and is labeled as a dietary supplement (1). In a recent Science forum, Zeisel (2) provided 2 additional, useful working definitions. A neutraceutical can be defined as “a diet supplement that delivers a concentrated form of a biologically active component of food in a non-food matrix to enhance health.” The US Food and Drug Administration (FDA) does not recognize the term neutraceutical. Functional foods, according to Zeisel, are not dietary supplements but rather “are consumed as part of a normal diet and deliver one or more active ingredients (that have physiologic effects and may enhance health) within the food matrix” (2).

Dietary supplements

Among his “bedside teachings,” Sir William Osler stated, “The desire to take medicines is one feature which distinguishes man, the animal, from his fellow creatures” (3), a viewpoint recently corroborated by the finding of medicinal herbs in the intestine of the 5300-y-old frozen “iceman” who was recently discovered in the Swiss Alps (4). Botanicals with medicinal properties have been used from time immemorial in all cultures and, with the introduction of ingredient assays and standards in the early 20th century, form the foundation for modern Western pharmacology (5). On the other hand, the consumption and market value of herbs and other nutritional supplements has reached astonishing proportions in the United States. According to recent FDA testimony, dietary supplements, including vitamins, were consumed by 158 million Americans in the year 2000—that is, more than half the US population (6). This compares with a 1997 survey that showed that alternative medical therapies, principally herbs, were used by 83 million people (7). In 2000, the total dietary supplement market included 32% as herbs and 38% as vitamins. The sales of dietary supplements in the United States doubled after passage of the DSHEA in 1994, to $17.1 billion in 2000, and are anticipated to continue increasing by 10% per year (5).

Although the FDA was charged with implementing stringent governmental regulations for ensuring the accurate labeling, safety, and efficacy of drugs, the food supplement industry was under no specific regulations until the Nutrition Labeling and Education Act of 1990, which permitted health claims for nutritional supplements that were restricted to several categories, including osteoporosis, hypertension, heart disease, and cancer. Spurred by intensive industry lobbying, Congress passed the DHSEA in 1994 to broaden the availability of all dietary supplements by authorizing their claims for functional specific health benefits, but not specific disease prevention or cure. The FDA established a Center for Food Safety and Applied Nutrition

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alternative therapies were fraudulent, potentially harmful because they supplanted conventional therapy, and/or a waste of time and money. Most patients derived their information from advertising or Internet sources (15).

In summary, dietary supplement usage is widespread because of successful marketing strategies and popularization by word of mouth, advertising, and Internet information sources. Although certain patient groups, such as pregnant women, tend to have lower herbal usage than the average person, others with intractable chronic and/or fatal diseases, such as Parkinson’s, arthritis, and cancer, are more likely to turn to alternative therapies, particularly herbal supplements. Most striking, physicians are unlikely to ask and unlikely to be told of their patients’ herbal habits. In view of the uncertain composition of most herbs, their potential interaction with prescription drugs, and their propensity to cause side effects, widespread herbal usage poses a potentially significant risk to the health of patients.

What should practicing physicians be concerned about regarding herbals and other dietary supplements? A lot, as summarized in a recent editorial that emphasizes the differences between conventional and nonconventional medicine (16). Before the application of science to medicine in the early 20th century, botanicals were the major source of nonsurgical therapy. Practitioners of herbal medicine had no way of knowing the concentrations or purity of their remedies, and toxicities from such medicines as foxglove, opium, and cinchona bark were common. Proving the safety and efficacy of botanicals was not feasible until the advent of chemical approaches to identifying and ensuring the purity of active ingredients and of the scientific approach of well-controlled randomized clinical trials. Nevertheless, the burgeoning dietary supplement industry, with its lack of rigorous scientific testing, threatens to inundate the public with ineffective and potentially harmful remedies. In the absence of patent opportunities for dietary supplements, manufacturers have little incentive to prove the efficacy and safety of their products.

The literature on dietary supplements is vast and rife with reports of unsuspected toxicities from unregulated dietary supplements. The issue is complicated by the variety of regulations in different countries, where a botanical product may be classified as an approved medicine, a dietary supplement, or a recreational herb (17). Most nation members of the European Union regulate vitamins and minerals as foods if provided within the accepted recommended dietary allowances, but they have no specific regulations on dietary supplements as long as no medicinal claims are made (18). Several countries have established commissions to assess the safety and efficacy of herbals. For example, Commission E of the German Federal Health Agency has published more than 300 monographs that evaluate the efficacy and safety of different herbal products according to acceptable clinical trials (19). Ongoing reports of herbal toxicities may not appear in recent book form and must be sought in the current literature. For example, it has only recently been appreciated that fulminant hepatic failure may occur during the chronic use of kava (20, 21). Understanding potential efficacies and hazards of dietary supplements is a daunting task for practitioners. For example, the Physicians’ Desk Reference for Herbal Medicines lists 80 under letter A alone in its common name index and lists more than 350 side effects for all herbals (22). The recently published Physicians’ Desk Reference for Nutritional Supplements describes more than 200 nonherbal supplements (vitamins, minerals, amino
acids, and other products) cross-referenced to more than 300 potential side effects (23). Given that herbal and nutritional supplements are taken by mouth, it is not surprising that the most common side effects relate to the gastrointestinal tract, including diarrhea, nausea, and vomiting. Because many plants have natural toxins that were developed for survival, hepatocellular damage is not uncommon after ingesting herbs, including comfrey, senna, and mixtures of ill-defined Chinese herbs (24). Additional problems arise from the presence of unregulated or unknown amounts of toxic substances within herbal preparations. For example, in a 1998 analysis of 251 Asian patent medicines performed by the California Department of Health Services, 10% were found to contain lead, 14% arsenic, and 14% mercury at potentially toxic levels (25). Others found toxic amounts of mercury in Chinese imported “herbal balls” and arsenic at levels that could result in daily accumulation of 73 mg arsenic and more than 1200 mg mercury (26). Aristolochia fangchi, or “birdwort,” used for gastrointestinal symptoms, was strongly associated with nephropathy and development of urothelial carcinoma in women attending a Belgian weight reduction clinic (27, 28). Underscoring the problem of lack of quality control, 2 case reports described the symptoms and laboratory evidence of digitalis toxicity after ingestion of plantain, an herbal ingredient of a mixture claimed to “cleanse the body,” that was contaminated with Digitalis lanata (29).

A recent survey indicated that 30% of patients undergoing surgery use herbal medications, about twice the usage in the general US population (30), and that 70% of herbal users failed to mention their use of dietary supplements in the routine preoperative evaluation (31). Preoperative herbal use is particularly hazardous, because different herbs may influence operative survival and/or alter the metabolism and pharmacologic effects of conventional anesthesia and postoperative drugs. For example, prolonged preoperative use of the immunostimulant echinacea may result in immunosuppression with prolonged wound healing and postoperative infections (32). Ephedra, a stimulant and the source of ephedrine and methamphetamine, increases blood pressure, heart rate, and risks of arrhythmias and vasospasm, which together increase the risks of myocardial infarction and stroke (33). In 1997 the FDA issued a warning on the use of ephedra as an herbal weight loss drug because of its potential adverse stimulant effects on both the circulatory and nervous systems (34). Although garlic lowers serum cholesterol to a modest amount (35), ajone, a constituent of garlic, may potentiate platelet inhibitors and thereby increase the risk of bleeding complications of surgery (30). Ginkgo, used to enhance memory and improve peripheral vascular circulation, also has platelet-inhibiting properties that may result in intracerebral hemorrhage and subdural hematomas (36, 37). Ginseng may lower postprandial blood glucose in type II diabetic patients but can induce hypoglycemia and inhibit platelet aggregation (38, 39). Kava, used for its sedative and antianxiety properties, can interact with barbiturates and benzodiazepines, prolonging sleep and even inducing coma (40), and has recently been associated with fulminant hepatic failure requiring liver transplantation (20, 21). A 2002 FDA consumer advisory cited 25 reports of liver-related injury in kava users and advises caution on its use, particularly in individuals with known liver disease (41). St John’s wort, used to prevent depression, inhibits serotonin reuptake, which results in serotonin excess and increases the metabolic rate of many cytochrome P450 drugs, including cyclosporin, midazolam, lidocaine, and warfarin, leading to their ineffectuality in therapeutic situations (30). Valerian, used for its sedative properties, potentiates the effects of benzodiazepines and may result in withdrawal delirium (42).

The health claims and potential side effects of some of the most commonly used herbas are shown in Table 1 (19, 22, 43, 44).

### Functional Foods

In contrast to most dietary supplements, functional foods are components of the usual diet that may have special disease prevention attributes and are the topic of current traditional scientific investigation. According to the Food and Nutrition Board of the Institute of Medicine, a functional food is “any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains” (45). Unlike dietary supplements that can claim only general health benefits, functional foods may claim specific health benefits because they are considered part of the diet (46). The literature on functional foods is vast and growing exponentially, and this review can touch on only a few points that are essential for the practitioner. A recently published handbook provides excellent summaries (45).

#### Polyphenols and flavonoids

The term polyphenol encompasses simple phenols and flavonoids, which are found in fruits, vegetables, and nuts and their products, and possess important antioxidant properties. Flavonoids include proanthocyanidins, quercetin, and epicatechin, found mainly in chocolate, tea, and wine. Red wine also contains resveratrol, a nonpolyphenol antioxidant product of grape skins. The “French paradox” refers to the epidemiologic finding that the incidence of coronary heart disease was significantly lower in wine-drinking regions of France than in areas where wine was not the main alcoholic beverage (47). Subsequently, it was shown that wine phenols inhibited the oxidation of low-density lipoprotein (LDL) (48), an accepted reason for the preventive effect of polyphenols on the development of atherosclerosis. More recent studies demonstrate that the attenuation of coronary heart disease risk in wine drinkers is probably due as much to their lifestyle consumption of high amounts of polyphenol-containing fruits and vegetables as to wine (49). A 5-y prospective Dutch study of 800 elderly men found that the ingestion of flavonoids, mainly in tea, onions, and apples, was associated with significant reduction in mortality from coronary heart disease (50).

In addition to antioxidant effects on LDL, other potentially cardioprotective effects of polyphenols include inhibition of platelet aggregation and vascular relaxation through the production of nitric oxide (51). Although polyphenols have the capacity to decrease LDL oxidation, inhibit platelet aggregation, and induce vascular relaxation, their clinical efficacy is modulated by many factors that include differences in wine and tea preparation, volatility, and absorbability. For example, green tea has a higher concentration of polyphenols than black tea, which may be affected by the method of brewing (52). Wine should be consumed in moderation only, to avoid the chronic effects of alcohol. The year 2000 Dietary Guidelines for Americans identifies moderation as no more than 1 drink per day for women and 2 drinks per day for men, where a drink constitutes 5 oz of wine (53). Although these studies support the principle that fruits and vegetables should provide the main staple of a healthy diet, varied amounts of polyphenols in different foods and effects of food preparation and absorption hinder the establishment of clear-cut dietary and clinical
<table>
<thead>
<tr>
<th>Common name</th>
<th>Formal name</th>
<th>Claim, current use</th>
<th>Possible mechanisms</th>
<th>Efficacy, clinical evidence</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh (black</td>
<td><em>Cimicifuga racemosa</em></td>
<td>Improves menopausal symptoms, premenstrual syndrome, and dysmenorrhea</td>
<td>Suppresses lutenizing hormone secretion in menopausal women; weak binding to estrogen receptors</td>
<td>Many clinical studies showed favorable results</td>
<td>Gastric discomfort</td>
</tr>
<tr>
<td>Comfrey (19, 44)</td>
<td><em>Symphytum officinale</em></td>
<td>Heals skin wounds</td>
<td>Allantoin promotes cell growth; Tannins are vaso-constrictive</td>
<td>Uncertain</td>
<td>Liver failure, death. Pyrrolizidine alkaloids are hepatotoxic when taken by mouth; may be absorbed through skin</td>
</tr>
<tr>
<td>Echinacea (cone flower) (19, 44)</td>
<td><em>Echinacea angustifolia</em></td>
<td>Stimulates immune response; promotes wound healing; treats common cold and yeast infections</td>
<td>Stimulates leukocyte mobility, phagocytosis, and T-cell functions</td>
<td>Positive clinical trials showing shortened duration of common cold but not prevention</td>
<td>Immune suppression during surgery (30)</td>
</tr>
<tr>
<td>Ephedra (ma huang) (19, 34, 44)</td>
<td><em>Ephedra sinica</em></td>
<td>Relieves nasal congestion and asthma, promotes weight loss, and enhances athletic performance</td>
<td>Active constituent is ephedrine, a sympathomimetic</td>
<td>Traditional use for 2000 years in Chinese medicine to treat bronchospasm</td>
<td>Increases blood pressure and heart rate and can cause headache, insomnia, dizziness, seizures, arrhythmias, addiction, and death (34)</td>
</tr>
<tr>
<td>Garlic (19, 44)</td>
<td><em>Allium sativum</em></td>
<td>Reduces cardiovascular risk and serves as anti-inflammatory</td>
<td>Inhibits platelet aggregation, reduces cholesterol (35), and has antioxidant properties</td>
<td>Lowers LDL cholesterol and triacylglycerols in clinical trials; antibacterial in vitro (19)</td>
<td>Can potentiate other platelet inhibitors or cause bleeding</td>
</tr>
<tr>
<td>Ginkgo (43, 44)</td>
<td><em>Ginkgo biloba</em></td>
<td>Improves memory, cognition, intermittent claudication, vertigo, tinnitus, and sexual performance</td>
<td>Promotes vasodilation, modulates neurotransmitter activity, and inhibits platelet aggregation</td>
<td>Clinical trials show that it may improve cognitive performance and memory in the morning; mixed results in Alzheimer’s disease</td>
<td>Diarrhea, nausea, vomiting; intracranial bleeding reported (30, 37)</td>
</tr>
<tr>
<td>Ginseng (43, 44)</td>
<td><em>Panax ginseng</em></td>
<td>Improves physical performance, energy level; cancer prevention; blood sugar reduction</td>
<td>Unknown; possible pharmacologic effects attributed to steroidal saponins</td>
<td>Mixed data on regulation of blood glucose and cancer prevention</td>
<td>Insomnia, diarrhea and hyperactivity</td>
</tr>
<tr>
<td>Kava-kava (19, 41, 44)</td>
<td><em>Piper methysticum</em></td>
<td>Elevates mood and relieves anxiety and menopausal symptoms</td>
<td>May interact with brain γ-aminobutyric acid receptors (19)</td>
<td>Positive clinical studies</td>
<td>Weakness, allergies, interaction with benzodiazepines (40, 41)</td>
</tr>
<tr>
<td>Saw palmetto (22, 44)</td>
<td><em>Serenoa repens</em></td>
<td>Reduces prostatic hyper-trophy, builds sexual vigor, and increases sperm production</td>
<td>Has antiandrogenic action</td>
<td>Similar to finasteride in reducing symptoms of prostatitis, but with fewer side effects</td>
<td>Feminization</td>
</tr>
<tr>
<td>St John’s wort (19, 43, 44)</td>
<td><em>Hypericum perforatum</em></td>
<td>Serves as mild to moderate antidepressive, and as antiviral</td>
<td>Inhibits serotonin, norepinephrine, and dopamine reuptake; inhibits monoamine (MAO)</td>
<td>Positive clinical trials for mild to moderate depression</td>
<td>Causes photosensitivity; may interact with benzodiazepines and warfarin (30)</td>
</tr>
<tr>
<td>Yohimbe (19, 44)</td>
<td><em>Pausinystalia yohimbe</em></td>
<td>Works as aphrodisiac and improves athletic performance</td>
<td>Dilates blood vessels of skin and mucous membranes</td>
<td>Several studies show positive value for erectile dysfunction</td>
<td>Active MAO inhibitor; may activate psychosis; increases anxiety, blood pressure, sleeplessness, tachycardia, tremor, and vomiting; ruled unsafe by US Food and Drug Administration (8)</td>
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recommendations of polyphenol-rich fruits and vegetables in the nutritional prevention of heart disease.

**Soy isoflavones**

Soy isoflavones are phytoestrogens that are derived from the protein fraction of the soybean and its food products (eg, soy milk, soy flour, tofu, miso), include genistein and daidzein, and possess estrogenic properties because of the similarities of their chemical structures to estrogenic compounds. Clinical trials identified the potential efficacy of soy isoflavones in the prevention of coronary heart disease, osteoporosis, and breast and prostate cancer. A meta-analysis of 37 clinical studies suggested that soy protein up to 45 g per day can lower serum cholesterol levels by 10% (54), but the long-term effects of soy on cardiac risk are unknown. Because phytoestrogens compete with estrogen for binding to estrogen receptors, their use could have beneficial effects in preventing osteoporosis and sex hormone–mediated malignancy, such as breast and prostate cancer. The clinical data are mixed and inconclusive on the effect of soy isoflavones on bone turnover and bone density (55). Data are mixed on whether soy isoflavones promote or protect against breast cancer (56–58), and one retrospective study of 1300 non-Asian women with breast cancer history found no association of phytoestrogen use and breast cancer risk (59). Although prostate cancer rates are lower in Eastern cultures where soy products play a major role in the diet, and although genistein inhibits the growth of prostate cancer cells, clinical studies to date have failed to demonstrate positive effects of dietary soy products on reducing the risk of prostate cancer (60).

**Carotenoids**

There are several plant-derived carotenoids in the human diet, of which β-carotene, α-carotene, lutein, zeaxanthin, and lycopene appear to have the most significance for health. Being lipid soluble, carotenoids are absorbed with fats and circulate bound to different lipoproteins. β-carotene is a limited precursor of vitamin A, and excessive amounts of β-carotene lead to reversible carotenemia but not to vitamin A toxicity. The principal biological effects of carotenoids relate to their antioxidant properties, which form the basis of potential protection against lipid peroxidation, atherogenesis, DNA oxidation, and cancer (61). Clinical studies suggest but have not yet proven that either β-carotene or lycopene is cardioprotective (62, 63). Aortic atherosclerosis incidence was significantly inversely correlated with the intake of dietary lycopene in the Rotterdam study of 108 patients and control subjects (64). A review of more than 30 studies concluded that there is an inverse relationship between lycopene in tomato products and the risk of prostate cancer (60).

**Fish oils**

Dietary fish oils appear as n–3 polyunsaturated fatty acids mainly in cold water fish, compared with n–6 polyunsaturates mainly from plants and saturated fatty acids from animal sources. Diets in which cold water fish such as mackerel, salmon, halibut, and trout are the main staple are associated with reduced incidence of coronary heart disease but increased risk of hemorrhage. Studies of susceptible men from Holland, Japan, and the United States showed that sudden death from coronary artery disease is reduced by half when 1–2 fish meals are consumed weekly (71–73). The biological effects of fish oils include inhibition of hepatic synthesis and secretion of triglyceride and very low density lipoprotein with reduced postprandial lipemia, increased circulating high-density lipoprotein, inhibition of platelet aggregation, and prevention of cardiac arrhythmias (73). Eicosapentaenoic acid (EPA) and its elongated product docosahexaenoic acid are the predominant fatty acids in fish, whereas α-linolenic acid, the precursor of EPA, is found in canola, flaxseed, and walnut oils. A Mediterranean diet rich in these oils was found to reduce cardiac deaths by 70% in France (74). By virtue of anti-inflammatory properties and effects on cell membranes, fish oils are also thought to have a beneficial effect in the treatment of rheumatoid arthritis, although conclusive clinical studies are lacking (75).

**Nuts**

Although nuts are relatively high in fat, most of this fat is in the mono- or polyunsaturated form. Beneficial nuts include almonds, Brazil nuts, peanuts, walnuts, pistachios, and pecans. Three large prospective studies demonstrated that the consumption of 1–4 servings of nuts per week was associated with about a 40% reduction in risk of coronary heart disease, even after adjusting for conventional risk factors such as hypertension, smoking, diabetes, and hyperlipidemia (76–78). The purported beneficial effects of nuts include improvement of serum lipid profiles with a predicted 16% reduction in LDL cholesterol and presence of relatively high amounts of the nitric oxide precursor arginine, dietary fiber, and antioxidant vitamin E (78). Walnuts are particularly noteworthy for having a high content of n–3 linolenic acid (78).

**Probiotics and prebiotics**

Probiotics can be defined as “live microbial food supplements which benefit the host by improving the intestinal microbial form” (79). As such, probiotics can be consumed as either a functional food, such as a fermented milk product, or a supplement if provided separately in capsule or pill form. The rationale for probiotics is to improve intestinal immune tolerance to beneficial proteins and to maintain a normal immune intestinal barrier and permeability to exogenous foreign antigens (80). Intestinal organisms constitute the greatest cell population of the body, existing in 500 different species. Provision of normal human organisms that resist acid and bile destruction and adhere to the gut mucosa triggers a healthy immune response. The most beneficial organisms include those of the *Lactobacillus* and *Bifidobacterium* genera. Whereas controlled clinical trials are ongoing, beneficial effects have been reported in the treatment of food allergies, acute infant diarrheas, traveler’s diarrhea, antibiotic-associated colitis, and, potentially, inflammatory bowel disease (81). Prebiotics are “non-digestible food ingredients that selectively stimulate the growth of a limited number of bacteria in the colon” (82). More specifically, prebiotics are short-length carbohydrates, such as fructooligosaccharides, that resist digestion or are fermented in the colon to produce short-chain fatty acids, such as acetate, butyrate, and propionate, which have positive
effects on colonic cell growth and stability, generate many of the same bacteria as provided in probiotics, and may promote improved bowel habit but also increased flatus (83).

SUMMARY AND CONCLUSIONS

There are striking differences between dietary supplements and functional foods. Whereas dietary supplements, herbs in particular, are considered time-tested but are in most cases scientifically unproven, functional foods are components of the normal human diet that are increasingly shown by rigorous science to be inherently valuable for maintaining human health. Whereas herbal sales skyrocket and feed false public perception of the irrelevance of science to health, the era of functional foods promises to propel nutritional science to the forefront of preventive medicine for the most common diseases of humans. Together, this new era of nutrition presents imposing challenges to practitioners of medicine. It is incumbent on them to become fluent in the knowledge of commonly used herbals, including recognition of their potential benefits, side effects, and life-threatening effects when combined with certain drugs. Although advice-seeking patients typically have rudimentary knowledge of the ingredients and rationales for the herbs they ingest, physicians must be in a position of knowledge to maintain their patients’ confidence as a prerequisite to providing credible counsel. Furthermore, because most patients are curious and somewhat knowledgeable about their diets, physicians must establish a basic knowledge of conventional functional foods, which is viewed increasingly as an adjunct to sound medical advice. These are heady days for nutritional scientists as newer understandings of food and health promise to bring clinical nutrition to the forefront of clinical medicine. Practitioners must become nutritionally educated and oriented if they are to maintain their patients’ confidence and stay abreast of this aspect of continuously evolving modern medicine.

REFERENCES
