서양의 식이보충제와 기능성 식품에 대한 인식

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A Understanding of Dietary Supplements and Functional Foods in the Occident

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Abstract

Dietary supplements are used by more than one-half of the adult US population. 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 herbals-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.

Key words: Dietary supplements, Herbal products, Functional foods

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Ⅰ. 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 combinations 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 nutraceutical 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 nutraceutical. 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].

Ⅱ. 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 herbals, were used by 83 million people[7]. In 2000,the total dietary supplement market included 32% as herbals and 38% as vitamins. The sales of dietary supplements in the United States doubled after pas-sage 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(CFSAN) with responsibility for oversight of new supplemental products, including the marketing of clearly identified products declared to be of known composition and strength. New dietary supplements are reviewed by the FDA under the rubric of the same good manufacturing practice regulations that apply to conventional foods. The manufacturer is responsible for ensuring that the "supplement facts"label and ingredient lists are accurate, that the dietary ingredients are safe, and that the content matches the amount declared on the label. However, the FDA does not require accurate chemical analyses as a basis for the identification and quantification of ingredients. The label must also contain the disclaimer, "This product is not intended to diagnose, treat, cure, or prevent any disease." This policy bypasses the usual FDA procedures of requiring proof of safety from the manufacturer before approval of a drug for public consumption, and puts the post marketing burden of proving significant risk on the FDA. Supplements that were produced before1994 are assumed safe, whereas the safety of those marketed after 1994 is the responsibility of the manufacturers. The specifics of the role of the FDA in regulating dietary supplements can be found in a recently posted web site: http://www.cfsan.fda.gov/dms/ds-oview.html[8].

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 supplement . 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 non conventional medicine[9]. 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[10]. Most nation members of the European Union regulate vitamins and minerals as foods if provided within the accepted recommend ed dietary allowances, but they have no specific regulations on dietary supplements as long as no medicinal claims are made[11].

Several countries have established com-missions 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[12]. Understanding potential efficacies and hazards of dietary supplements is a daunting task for practitioners.

Ⅲ. 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"[13]. 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[14]. The literature on functional foods is vast and grow-ing exponentially, and this review can touch on only a few points that are essential for the practitioner. A recently published hand-book provides excellent summaries[13].

Ⅳ. 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 non polyphenol 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[15]. Subsequently, it was shown that wine phenols inhibited the oxidation of low-density lipoprotein(LDL)[16], an accepted reason for the preventive effect of polyphenols on the development of atherosclerosis. 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 polphenols than black tea, which may be affected by the method of brewing[17]. 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[18]. 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 recommendations of polyphenol-rich fruits and vegetables in the nutritional prevention of heart disease.

Ⅴ. Soy isoflavones

Soy isoflavones are phytoestrogens that are derived from the protein fraction of the soybean and its food products

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 iso avones 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 45g per day can lower serum cholesterol levels by 10%[19], 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. Data are mixed on whether soy isoflavones pro-mote or protect against breast cancer[20-22],and one retrospective study of 1300 non-Asian women with breast cancer history found no association of phytoestrogen use and breast cancer risk[23]. 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[24].

Ⅵ. 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[25]. Clinical studies suggest but have not yet proven that either β-carotene or lycopene is cardioprotective[26-27]. Aortic athero-sclerosis incidence was significantly inversely correlated with the intake of dietary lycopene in the Rotterdam study of 108 patients and control subjects[28].

A review of more than 30 studies concluded that there is an inverse relationship between lycopene in tomato products and the risk of cancers of the prostate, lung, and stomach[29], and one study demonstrated a 21% reduction in prostate cancer with consumption of diets high in tomato-derived lycopene[30]. A study of more than 25000 middle-aged male Finnish smokers found that the incidence of lung cancer was

increased in those receiving β-carotene supplements[31]. In large cohorts followed over time, cataract formation was reduced significantly by dietary intake of fruits and vegetables rich in lutein and zeaxanthin [32-33]. Recent data suggest a potential preventive relationship between intake of these carotenoids and risk of macular degeneration[34].

Ⅶ. 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[35-37]. The biological effects of fish oils include inhibition of hepatic synthesis and secretion of triacylglycerol and very low density lipoprotein with reduced postprandial lipemia, increased circulating high-density lipoprotein, inhibition of platelet aggregation, and prevention of cardiac arrhythmias[37]. Eicosapentaenoic acid(EPA) and its elongated product docosa-hexaenoic 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[38]. 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[39].

Ⅷ. 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[40-42]. 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[42]. Walnuts are

particularly noteworthy for having a high content of n−3 linolenic acid[42].

Ⅸ. 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 their relevance 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 some−what 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.

Ⅹ. References

1. Dietary Supplement Health and Education Act (DSHEA). 42 USC 287C-11. 1994.
2. Zeisel SH. Regulation of "nutra ceuticals." Science 1999;285:1853-5.
3. Bean WB. Sir William Osler: aphorisms from his bedside teaching and writing. Spring eld, IL: Charles C Thomas, 1968;1-164.
4. Capasso L. 5300 years ago, the Ice Man used natural laxatives and antibiotics. Lancet 1998; 352: 1864 (letter).
5. Goldman P. Herbal medicines today and the roots of modern pharmacology. Ann Intern Med 2001;

135: 594-600.
6. US Food and Drug Administration. Statement by Joseph A. Levitt before the U.S. House of Representatives Committee on Government Reform. Internet: http://www. cfsan.fda.gov/lrd/st010320.html(accessed 20 March 2001).
7. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States,1990-1997:results of a follow-up national survey. JAMA 1998; 280: 1569-75.
8. US Food and Drug Administration. Overview of dietary supplements. Internet: http://www.cfsan. fda.gov/dms/ds-oview.html (accessed 3 January 2001).
9. Angell M, Kassirer JP. Alternative medicine—the risks of untested and unregulated remedies. N Engl J Med 1998; 339: 839-41.
10. De Smet PA. Health risks of herbal remedies. Drug Safety 1995;13:81-93.
11. Mason P. Dietary supplements. 2nd ed. London: Pharmaceutical Press, 2001.
12. Blumenthal M, Goldberg A, Brinck mann J. Herbal medicine: expanded Commission E monographs. Newton, MA: Integrative Medicine Communi-cations,2000.
13. Wildman REC. Handbook of nutra-ceuticals and functional foods. Boca Raton, FL: CRC Press, 2001.
14. Ross S. Functional foods: the Food and Drug Administration perspective. Am J Clin Nutr 2000; 71(suppl)
15. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992; 339: 1523-6.
16. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet 1993; 341: 454-7.
17. Prior RL,Cao G. Antioxidant capacity and polyphenolic components of teas: implications for altering in vivo antioxidant status. Proc Soc Exp Biol Med 1999; 220: 255-61.
18. Dietary Guidelines Advisory Committ-ee. Report of the Dietary Guide-lines Advisory Committee on Dietary Guidelines for Americans. 5thed. Washington, DC: US Department of Agriculture, 2000.
19. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995; 333: 276-82.
20. Sirtori CR. Risks and benefits of soy phytoestrogens in cardiovascular diseases, cancer, climacteric symp-toms and osteoporosis. Drug Safety 2001; 24: 665-82.
21. de Lemos ML. Effects of soy phyto estrogens genistein and daidzein on breast cancer growth. Ann Pharma

cother 2001; 35: 1118-21.
22. Kurzer MS. Hormonal effects of soy in premenopausal women and men. J Nutr 2002;132:570S-3S.
23. Horn-Ross PL, John EM, Lee M, et al. Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am J Epidemiol 2001; 154:434-41.
24. Mitchell J. Phytoestrogens: involve -ment in breast and prostate cancer. In: Wildman REC, ed. Handbook of nutraceuticals and functional foods. Boca Raton, FL: CRC Press, 2001:99-111.
25. Faulks RM, Southon S. Carotenoids, metabolism and disease. In: Wildman REC, ed. Handbook of nutraceuticals and functional foods. Boca Raton, FL: CRC Press, 2001:143-56.
26. Gale CR, Ashurst HE, Powers HJ, Martyn CN. Antioxidant vitamin status and carotid atherosclerosis in the elderly. Am J Clin Nutr 2001; 74:402-8.
27. Arab L, Steck S. Lycopene and cardiovascular disease. Am J Clin Nutr 2000;71(suppl):1691S-5S; dis cussion 1696S-7S.
28. Klipstein-Grobusch K, Launer LJ, Geleijnse JM, Boeing H, Hofman A, Witteman JC. Serum carotenoids and atherosclerosis: the Rotterdam Study. Atherosclerosis 2000; 148: 49-56.
29. Giovannucci E. Tomatoes, tomato-based products, lycopene,and cancer: review of the epidemiologic litera ture. J Natl Cancer Inst 1999;91: 317-31.
30. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995;87:1767-76.
31. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study comp liance. J Natl Cancer Inst 1996;88: 1560-70.
32. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. Am J Clin Nutr 1999; 70: 509-16.
33. Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. Am J Clin Nutr 1999; 70:517-24.
34. Johnson EJ, Hammond BR, Yeum KJ, et al. Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density. Am J Clin Nutr 2000;71:

1555-62.

35. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23-8.
36. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205-9.
37. Connor WE. n-3 Fatty acids from sh and sh oil: panacea or nostrum? Am J Clin Nutr 2001;74: 15-6.
38. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary preven -tion of coronary heart disease. Lancet 1994; 343: 1454-9.
39. Volker DH, Garg ML. n-3 poly unsaturated fatty acids and rheuma -toid arthritis. In: Wildman REC, ed. Handbook of nutraceuticals and functional foods. Boca Raton, FL: CRC Press, 2001: 353-76.
40. Fraser GE, Lindsted KD, Beeson WL. Effect of risk factor values on lifetime risk of and age at rst coronary event: the Adventist Health Study. Am J Epidemiol 1995; 142: 746-58.
41. Hu FB, Stampfer MJ. Nut con sumption and risk of coronary heart disease: a review of epidemiologic evidence. Curr Atheroscler Rep 1999;1:204-9.
42. Sabate J, Radak T, Brown J. The role of nuts in cardiovascular disease prevention. In: Wildman REC, ed. Handbook of nutraceuticals and functional foods. Boca Raton, FL: CRC Press, 2001: 477-95