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The Public Health Impact of Herbs and Nutritional Supplements

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Abstract

Dietary supplement use has increased exponentially in recent years despite the lack of regulatory oversight and in the face of growing safety concerns. This paper provides an overview of the public health implications and safety concerns associated with dietary supplement use, especially by cancer patients. Botanical research is actively pursued at the Memorial Sloan-Kettering Cancer Center (MSKCC) Integrative Medicine department. Work of the MSKCC Center for the Study of Botanical Immunomodulators is described, and guidelines for cancer patients' use of dietary supplements outlined. Herbs and other botanicals are complex, physiologically active agents, but little is known about most of the popular, widely available dietary supplements. Herb-drug interactions, a major concern, are exacerbated in the cancer setting. Biologically active agents may interfere with chemotherapy and other prescription medications. They may exert anti-coagulant activity at rather inconvenient times such as during surgery, and create other serious problems. Research on the bioavailability, effective dosage, safety and benefits of these complex agents is sorely needed. Oncology professionals and other healthcare providers should educate themselves and their patients about these issues. Probably the largest, continuously-updated free information resource is MSKCC's AboutHerbs website (www.mskcc.org/AboutHerbs).

Keywords

Dietary supplements; botanicals; herbal medicines; legislation/jurisprudence; cancer; product labeling

Introduction

Efficacy and safety studies of dietary supplements are limited and often methodologically poor. Probably for the preceding reasons, many studies of the same supplement yield conflicting results. Despite these problems, dietary supplement use continues to increase and is prevalent in developed countries. Ever larger numbers of adults consider themselves "regular users" (CRN, 2007).

Although herb popularity shifts from year-to-year, some remain perennial favorites, and the money spent on dietary supplements continues to increase over time (NMI, 2007). Two popular, and incorrect, beliefs tend to prevail in many countries: that herbs and other dietary supplements are safe because they are natural; and that they are effective because of long-term use, often over centuries or millennia.

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Plants were used as medicines in every human culture throughout human history. They are the source of approximately 40% of today's pharmaceutical products. Herbs and other botanicals are biologically active; hence, both the benefits and dangers of dietary supplements require appropriate attention. Professional and public education is required, especially in light of the widespread marketing that further increases their widespread use.

In this paper, we discuss the regulatory oversight background, increased popularity and effect of dietary supplements. We also highlight safety concerns, especially for cancer patients and others on prescription medication. Finally, the steps necessary to ensure safe and effective dietary supplement use are outlined using research conducted at the MSKCC Center for the Study of Botanical Immunomodulators as a model.

The Dietary Supplements Health and Education Act

The U.S Dietary Supplements Health and Education Act (DSHEA) became law in 1994. DSHEA changed the marketing and legal climate for dietary supplements and herbs, and enabled the exponential growth of product sales since that time. This Act amended previous statutes to encompass dietary supplement-specific provisions, including the definition of dietary supplements, product safety, nutritional statements and claims, ingredient and nutritional labeling, good manufacturing procedures, and the classification of 'new' dietary ingredients.

As defined by DSHEA, a dietary supplement is a product other than tobacco that is intended to supplement the diet and contains one of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients (USFDA, 1995). A dietary supplement is also ingested by mouth in pill, capsule, tablet, or liquid form. It is not intended or represented for use as a conventional food or as the sole item of a meal or diet and must be labeled as a "dietary supplement".

The safety concerns of dietary supplements are addressed in a manner similar to what has been historically done in the food industry, where the burden of safety rests on the shoulders of the manufacturers. Third party literature regarding dietary supplements is also regulated under DSHEA so that informational materials such as fact sheets and articles may be displayed in commercial retail sites as long as they are displayed separately from the product, do not contain false or misleading information, and do not promote a specific brand of supplement (USFDA, 1995). Enforcing these rules has been difficult, and the Internet presents additional challenges to the public regarding dietary supplements and advertising claims, many of which are questionable, false or misleading.

DSHEA guidelines focus on regulating the labeling of dietary supplements. Statements regarding nutrient deficiency diseases are permitted, so long as these statements disclose the prevalence of the disease in the U.S. Any claims to prevent, treat, or cure a specific disease are expressly prohibited unless these claims are approved by the FDA. The labeling may contain claims regarding supporting "structure and function" or general "well-being" as long as they are truthful and contain the following: "**This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease**."

The label must also identify the product as a dietary supplement and contain nutritional labeling, as required in food products. For example, the label must include the name and quantity of each dietary ingredient, and if the ingredient is botanical in origin, the label must state the part of the plant from which the ingredient was derived.

Trends in dietary supplement use in the United States

In 2005, more than $4.4 billion were spent on herbs in the USA. Over $713 million were expended in mass markets, including food and grocery stores, drug stores, mass merchandise, club and convenience stores such as Wal-Mart and Costco (Ferrier et al., 2006). An additional $1.4 billion were spent in natural and health food stores, and $2.3 billion in direct sales (e.g., mail order, internet, and catalogs) (Ferrier et al., 2006). Despite an increase in total dietary supplement spending, the dollars spent on herbs in the US were essentially constant, with 2007 herb and botanical sales totaling $4.5 billion (Ferrier et al., 2006). The total spent on dietary supplements today is over $20 billion, and some estimate as high as $30 billion.

The popularity of individual herbs varies from year to year, depending in part on the recent research published, on the marketing efforts of the manufacturers, and the public media. In 2005, the most popular selling herb was garlic, with over $26 million, second was *Echinacea* with $21 million (Blumenthal et al., 2006). The dollars spent on Green Tea extracts nearly doubled from 2004–2005 (Blumenthal et al., 2006). In 2007, the most popular herbs were noni juice, garlic, mangosteen juice, green tea, saw palmetto, *Echinacea*, *Ginkgo biloba*, ginseng, milk thistle, and psyllium (NMI, 2007).

The largest increases in 2007 consumer use came from fish oil and omega-3 fatty acids, and the largest decrease in use was seen for soy (NMI, 2007). Analysis of the MSKCC "AboutHerbs" web site, which provides free, evidence-based and clinically useful information on more than 240 dietary supplements and is continually updated, indicated that graviola, juice plus, turmeric, acai berry, and reishi mushroom were the top five the most frequently searched herbs in 2008.

As the amount of money spent on dietary supplements increased, so did the percentage of regular users. According to the Council for Responsible Nutrition (CRN) in Washington DC, approximately 68% of American adults used dietary supplements in 2007 compared with 66% in 2006. Those who considered themselves to be regular users of dietary supplements increased from 46% in 2006 to 52% in 2007 (CRN, 2007).

Cancer patients also increasingly use dietary supplements; 56–73% of cancer patients regularly use multivitamins-multiminerals (Burstein et al., 1999; Grainger et al., 2008; Rock, 2007). Herbal use also increases upon cancer diagnosis (Deng & Cassileth, 2005; Molassiotis et al., 2005). The American Institute for Cancer Research (AICR) nutritional guidelines do not recommend dietary supplements for daily use, and do not recommend supplements for cancer prevention (AICR, 2007). The AICR recommendation is to meet nutritional needs through dietary sources alone and not through supplements (AICR, 2007). Additional recommendations and cautions regarding nutritional supplement use from the American Cancer Society (ACS) and the Office of Dietary Supplements (ODS) are found on their web pages. Similarly, the American Cancer Society (ACS) and the National Institute of Health Office of Dietary Supplements (ODS) do not recommend routine use of nutritional supplements. Prior to beginning any supplement, consultation with the health care provider is strongly advised. While in some instances it might be appropriate to use a low dose multivitamin supplement, in almost all instances the higher dose supplements are not advised (ACS, 2007; ODS, 2009). Vitamin D and calcium are two noted exceptions as it is often difficult to obtain the recommended daily intake of these nutrients through dietary sources alone.

Safety concerns

Since DHSEA, botanical products and dietary supplements have been available as over the counter agents and are not regulated by the Food and Drug Administration (FDA). Unlike drugs, which are single chemical structure compounds that have passed rigorous scientific and

quality assurance testing in test tube research, animal studies and human clinical trials before they are approved for public use, and then only under prescription by a physician, dietary supplements can consist of hundreds if not thousands of different chemical structures and compounds. However, no tests regarding the safety, efficacy or purity are required before dietary supplements are released for public consumption: Caveat emptor.

Dietary supplements and botanical products are presumed to be safe, and are freely available without prescription to all. The DHSEA Act specifically removed FDA or other regulatory agency review for sales of these agents. However, the FDA reserves the right to remove a product from the market after it is shown to be unsafe or harmful, such as in the case of ephedra-containing dietary supplements (Haller, 2000). In the past year, the FDA has become increasingly active in pursuing false claims and documented dangers associated with some dietary supplements.

The DHSEA assumption of safety, as well as efficacy, is not always founded, and the widespread marketing and use of herbs and other dietary supplements may be problematic for cancer patients and others on prescription medication. MSKCC guidelines request no herbal remedies or other supplements during receipt of cancer treatment. USDA-level vitamins, calcium and vitamin D are exceptions under a patient's specific clinical circumstances.

In addition, there is no requirement that the content inside the bottle matches the dietary supplement label. The United States Pharmacopeia (USP) is a non-governmental, not-for-profit health organization that provides independent testing of over-the-counter, botanical and nutritional supplements. USP verifies product integrity, purity and potency; products that meet the USP standards for quality control have the USP symbol on their label. Participation in the USP verification process is voluntary, and unfortunately very few companies participate in this program. An important distinction between the FDA drug approval process and the USP verification review is that USP does not test for efficacy or safety, only for ingredient verification: Does what's inside match what the label says.

Why consumers use botanical dietary supplements

Botanical supplements are purchased for many reasons, predominant among them to enhance immune function. A popular marketing statement for numerous dietary supplements and botanical products is that they "boost" the immune system (Swisher et al., 2002). Many of the most popular herbs sold in the United States, including *Echinacea*, cranberry, ginseng, milk thistle, *Astragalus*, and the medicinal mushrooms, are taken for their purported immune system effects. Many such products are advertised on the Internet; over 2.3 million hits were produced when the search term "immune herbs" was used. The abundant marketing of these products contributes to faulty public assumptions about herbs and other botanicals.

Another major reason for dietary supplement purchase is to treat menopausal symptoms (Powell et al., 2002; Swisher et al., 2002). In previous decades, estrogen replacement therapy was used for this purpose, but data from studies such as the Women's Health Initiative uncovered major detrimental effects (Lyytinen et al., 2009; Rossouw et al., 2002). In response to the major safety issues raised by large clinical trials of estrogen therapy, many herbal products were marketed for menopausal symptoms.

More recently, celebrity-promoted "bio-identical hormones" emerged as a top-selling supplement. These hormones are not derived synthetically or from animal sources such as the conjugated estrogens, and are marketed as safer alternatives to estrogen. What is not mentioned is that bio-identical hormones have physiologic effects similar or identical to estrogen; their effects are mediated through similar receptors and pathways and therefore carry a similar risk-

benefit profile as estrogen. Moreover, studies have not been conducted to determine the safety and efficacy of "bio-identical hormones."

Faulty assumptions

Two widespread faulty assumptions are that "natural" equals safe, and that long-term use connotes effectiveness. Unfortunately, neither of these assumptions is correct. Because a product comes from a plant does not mean that it is safe or beneficial. Consider Socrates and hemlock; castor bean and rosary pea (http://www.ansci.cornell.edu/plants/other.html). Similarly, the fact that botanical products or herbs remain in use for many years and even for millennia does not mean that they are effective. Most of the herbs and botanicals used in traditional cultures have not been subjected to rigorous scientific study to evaluate their efficacy.

Many cancer chemotherapeutic agents are derived from plants, including the *Vinca* alkaloids from the Madagascar rosy periwinkle (the traditional long-term use of periwinkle was to treat diabetes, for which modern scientific evaluation indicated no benefit, but it is the source of vincristine and vinblastine, two important chemotherapeutic agents), and paclitaxel derived from the *Taxus baccata* evergreen tree.

Chemotherapy agents are very powerful and require close monitoring of blood counts throughout administration to assess side effects. Unlike prescription drugs, botanical agents, herbs, and herbal extracts are not pure compounds. They should be understood as unrefined pharmaceuticals, requiring extreme caution, especially for those using prescription medications. The chemical complexity of botanical agents often produces unpredictable physiologic effects. For example, herb-drug interactions, affecting the metabolism, excretion, or distribution of prescription medications may occur. Specifically, herbs may have an anticoagulant effect, which can interfere with coumadin or other blood thinning agents, or cause prolonged bleeding during surgical procedures (Kumar et al., 2005).

In addition to those on prescription medications, cancer patients specifically face negative complications from simultaneous cancer treatment and dietary supplement use. For example, the hormonal effects of many plants are precluded for certain breast cancer patients, and herb-drug interactions are not uncommon (Liu et al., 2005). Soy and flax, two popular botanical phytoestrogens, or estrogen-like plants, are good examples. The soy isoflavone, genistein, interferes with the effectiveness of tamoxifen (Ju 2002) and letrozole (Ju 2008) in animal models of breast cancer. Thus, patients with hormone-sensitive cancers such as breast or prostate cancer should avoid using phytoestrogens as they may induce tumor growth or interfere with anticancer therapies. In addition, components of green tea, specifically epigallocatechin gallate (EGCG), interfere with bortezomibactivity in both in vitro and in vivo studies (Golden et al., 2009).

Two issues relate to the common aforementioned use of dietary supplements to enhance immune function. First, their ability to enhance immune function is not always documented. Second, the immune system is complex, and while boosting some constituents may be beneficial, increasing others could have the opposite effect. People with autoimmune diseases or those who are receiving immunosuppression medications and who also use an herb that boosts immune system may face serious complications and unwanted clinical effects. *Astragalus* extracts have been shown in animal models to reverse cyclophosphamide-induced immunosuppression (Chu et al., 1988). For an organ transplant recipient, or for patients receiving immunosuppressant medication for autoimmune disease, botanicals that boost immune function may cause organ rejection or a flare of their autoimmune disease. Thus, ingestion of certain dietary supplements may not only interfere with prescription medications,

but may also greatly complicate the medical management of chronic diseases and endanger patients' lives.

In addition to the safety issues highlighted above, there are many concerns regarding the quality and purity of botanical dietary supplements. Further, ingredients listed on the label often are not in accord with the actual contents of the bottle or capsule. Although DSHEA has added a stipulation of good manufacturing processes for large companies, concerns remain regarding contamination, toxicity, standardization, and stability of the botanical over time and under various storage conditions, such as high heat or humidity.

The MSKCC Center for the Study of Botanical Immunomodulators

The Memorial Sloan-Kettering Cancer Center for the Study of Botanical Immunomodulators was initially funded in 2005 through the National Institute of Health (NIH), National Center for Complementary and Alternative Medicine (NCCAM), and Office of Dietary Supplements (ODS). The MSKCC Botanical Research Center is one of six Botanical Research Centers funded by NIH and ODS. Each Botanical Research Center has a theme; the MSKCC center focuses on assessing botanicals thought to affect immune function. It also focuses on issues of major public health relevance and brings high-quality science to the study of botanicals.

Just as pharmaceutical agents appropriately undergo rigorous sequential analyses from test tube to animal model research to clinical trials, dietary supplements also must be thoroughly assessed at a high scientific level. The complex nature of these agents, their pharmacokinetics, active constituents and bioavailability are studied, as is determining the most effective dosage for human study and the conduct of clinical trials.

The goals of MSKCC's Botanical Research Center are to 1) determine the composition of a select group of botanicals, 2) analyze those botanicals through pharmacokinetic and bioavailability studies, and 3) develop procedures to analyze these botanicals in clinical trials. To avoid the many complications associated with analyzing the immune modulation capacity of botanicals by oral administration, a set of botanicals were initially analyzed for immune adjuvant activity in an *in vivo* animal model (Ragupathi et al., 2008).

Core botanicals were originally selected for further study based upon their prevalence of use, as well as on research suggesting their immune activity. These included *Astragalus*, H-48 (an extract composed of 10 herbs), Turmeric, medicinal mushrooms Maitake and Coriolus, and *Echinacea*. Multiple preparations and extracts from these agents were analyzed (Ragupathi et al., 2008), following authentication analyses and investigational new drug (IND) approval. This further ensured the quality and safety of targeted botanicals. *Astragalus* and the two medicinal mushroom extracts exhibited the most important adjuvant activity.

Because the medical mushrooms most effectively induced immune response, including immune adjuvant activity (Ragupathi et al., 2008) hematopoietic stem cell proliferation (Lin 2007), and stem cell transplantation (Lin 2009), a dose escalation trial of the Maitake extract was conducted. This clinical trial was geared to determine the appropriate dosage and analyze toxicity in cancer patients and is detailed below (Deng et al., 2009).

Standard pharmaceutical study endpoints include toxicity and maximum tolerated dose, but with botanical agents, the maximum *tolerated* dose is not always the most *effective* dose. Thus, in early phase clinical trials, immune biomarkers such as immunophenotyping, intracellular cytokine production, circulating cytokine levels, and neutrophil and monocyte respiratory burst were assessed at each dosage level. In this phase I/II trial with breast cancer patients, increasing oral doses of the extract were administered. Peripheral blood was collected and studied. Changes in immunological biomarkers were seen. No dose-related toxicity was observed.

The most effective dose in terms of influence on immune function varied depending on the immunological parameter (i.e., for some parameters 5–7 mg/kg/day was optimal, whereas 10 mg/kg/day was optimal for others). Non-monotonic dose responses are common for botanicals. Therefore, the use of the standard maximum tolerated dose (MTD) as an endpoint for botanicals research is not ideal. Importantly, this study suggests that botanicals such as Maitake may both stimulate and represses particular aspects of immune function.

A clinical trial to determine whether this medicinal mushroom extract improves neutrophil function in patients with myelodysplastic syndrome (MDS) is underway. Plans to pursue research on Maitake and other medicinal mushroom extracts with collaborators in the U.S. and China are in development.

Conclusions

The prevalence of dietary supplement use in healthy individuals as well as cancer patients has increased exponentially. Because dietary supplements often contain a mixture of biologically active chemical compounds, numerous health risks have been associated with their use. Moreover, most dietary supplements have been studied only in preclinical trials, and limited data exist on their safety and efficacy in human clinical trials. Patients, especially those taking prescription medications, should be counseled on possible side effects as well as herb-drug interactions associated with dietary supplement use. Cancer patients undergoing chemotherapy and/or radiation therapy, or potentially face surgery, should refrain from taking botanical and nutritional supplements during receipt of cancer therapy due to the high probability of adverse events and herb-drug interactions. All dietary supplement use should be discussed with the patient's oncologist or pharmacist before initiating concurrent herb-drug use to assess the risk/benefit ratio and to determine which, if any supplements are appropriate for that individual. Additional research will uncover valuable information on the benefits and necessary precautions of botanical supplements.

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Table 1

Herb Sales 2005 in Food, Drug and Mass market retailers only

Common Name	$ Sales 2005	%Change 2004–2005
Garlic	26 244 200	−3.28
Echinacea	21 114 160	−11.21
Saw Palmetto	19 252 980	−5.42
Ginkgo	16 553 030	−14.54
Cranberry	15 839 160	16.97
Soy	14 497 100	−17.12
Ginseng	11 444 550	−6.19
Black Cohosh	9 736 738	−19.05
St. John’s Wort	9 035 399	−1.34
Milk Thistle	8 312 867	6.77
Green Tea	5 648 459	93.89
Evening Primrose Oil	5 303 904	−13.00

Table 2

Most popular AboutHerbs Website (http://www.mskcc.org/aboutherbs) hits in 2008

Herb	Number of hits in 2008
Graviola	20 550
Juice Plus	12 776
Turmeric	9 099
Acai Berry	8 237
Reishi Mushroom	8 228
Ashwagandha	7 678
Zyflamend	7 234
Astragalus	7 213
Milk Thistle	6 382
Boswellia	5 928
Omega-3	5 907
Red Yeast Rice	5 700
Rhodiola	5 509
Wheat Germ Extract	5 118
Coenzyme Q10	5 086
Quercitin	5 052
St. John’s Wort	4 981
Evening Primrose Oil	4 930
Lycium	4 788
Green Tea	4 768