

Suggested guidelines for articles about botanical dietary supplements^{1,2}

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ABSTRACT Recently, *The American Journal of Clinical Nutrition* (*AJCN*) began reviewing articles about dietary supplements. The purpose of this commentary is to provide guidelines to authors and reviewers for articles on one category of supplement ingredients, botanicals. The botanicals in the studies published by the *AJCN* tend to fall into 1 of 2 groups: 1) plants as foods containing nonessential bioactive constituents that may provide health benefits beyond basic nutrition, and 2) plants as herbs, specifically those used as phytomedicines. Research in these areas is relevant to clinical nutrition, but both topics represent relatively new territory to many *AJCN* reviewers, readers, and contributors. Although studies of botanicals are unique in many respects, the research should be evaluated with the same basic criteria applied to other types of investigations. For example, a study cannot be evaluated or replicated unless the test materials are properly identified and characterized. Investigators must provide an accurate and complete description of the botanical test material regardless of whether it is a finished product, commercial ingredient, extract, or single chemical constituent. For herbal preparations, investigators are advised to follow the criteria used by researchers in the field of pharmacognosy. Finally, the quality of research related to botanical dietary supplements would be improved and cross-study comparisons facilitated if standard reference materials and certified methods of analysis were more broadly available. *Am J Clin Nutr* 2002;75:8–10.

INTRODUCTION

Consumer use of dietary supplements has increased dramatically since 1994 when the US Congress passed the Dietary Supplement Health and Education Act (DSHEA; 1). Estimates vary, but ≈40–50% of adults in the United States are reported to use dietary supplements (2–5). Some individuals take supplements such as essential vitamins and minerals as insurance against poor eating habits. Others regard supplements such as herbal products as a self-care option for health maintenance, disease prevention, and treatment. Although supplement use is widespread, the science base supporting the clinical efficacy and safety of dietary supplements is highly variable in terms of both quantity and quality. The *AJCN* recently began reviewing for publication articles about dietary supplements (6). The purpose of this commentary is to provide guidelines for the evaluation and submission of articles related to one category of supplement ingredients, botanicals.

ARTICLE GUIDELINES

Although a legal definition of dietary supplements exists, the task of identifying dietary supplement research is not always straightforward. According to the DSHEA (1), dietary supplements, including botanicals, are not intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals. Although the DSHEA stipulates that supplements are not intended for uses related to disease, supplement ingredients and finished products nonetheless are commonly used by consumers and are studied by researchers with exactly these goals in mind. The *AJCN* is clear on this issue and does not automatically reject studies of a botanical ingredient or product if the intended use is disease-related. Although the *AJCN* has dealt with the issue of intended use, the form of ingredient delivery also should be considered, given its clinical relevance. Dietary supplements, as defined by the DSHEA, are intended for ingestion in the form of a capsule, powder, soft gel, or gelcap but are not to be represented for use as conventional foods. Many plant-derived supplement ingredients, however, are frequently added to foods (eg, plant sterols or stanol esters are added to margarine for cholesterol reduction), blurring the once bright lines between foods, supplements, and drugs (7).

Currently, studies of botanicals submitted to the *AJCN* tend to fall into 1 of 2 groups: 1) studies of plants as foods containing nonessential bioactive constituents (eg, flavonoids such as quercetin) that may provide health benefits beyond basic nutrition, and 2) studies of plants as herbs, specifically those used as phytomedicines (eg, *Panax ginseng*). The *AJCN* considers for review articles about both of these topics. Although studies of some botanical preparations present unique challenges, clinical research on botanicals should be evaluated with the same criteria used in other types of investigations. Researchers should formulate a research question and test a clearly stated hypothesis by using an appropriate study design and corresponding methods of statistical analysis. The study population and criteria for selection

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should be described. The study methods used should be provided in sufficient detail to permit replication of the study.

Studies of botanicals are often difficult to evaluate because the test material is not adequately described. As is true with any research study, it is not possible to review an article or interpret the literature without adequate knowledge of what was studied. Requirements for identification and characterization of test materials are not unique to botanical research; however, as noted by Tyler (8), many clinical researchers apparently still do not appreciate that commercial dietary supplement products and ingredients are not required to conform to official specifications. Therefore, it is ultimately the responsibility of researchers to provide an accurate and complete description of the test material regardless of whether it is a finished product, commercial ingredient, newly formulated extract, or single active compound. When trade names of botanical products are used in research, the manufacturer's name and location should be provided.

The *AJCN* regularly publishes research focused on nonnutrient bioactive constituents derived from plants used as foods. Many of the phytochemicals studied (eg, soy isoflavones, pro-cyanidins, and carotenoids) are available as ingredients in dietary supplements and may, therefore, fall under the broad umbrella of dietary supplement research. Studies of isolated phytochemicals or a related family of compounds (eg, epigallocatechin gallate compared with a group of catechins) typically include quantitative determinations of the isolated chemicals, and references to the methods of analysis used are given. Alternatively, detailed descriptions of new or modified methods are provided.


The *AJCN* has not established criteria for the identification and characterization of more chemically complex botanical preparations, such as crude plant parts, powders, or extracts. Experts in the field of pharmacognosy, however, have proposed rigorous requirements (9). The journal *Phytomedicine* (10) provides guidelines for reporting clinical studies of botanicals. First and foremost, the source material must be properly identified. "Plants used to prepare test materials must be properly identified with correct botanical (Latin) names (with authorities), and plant parts used (10)." Misidentification of a botanical can have serious consequences; clinical effects, whether positive, null, or adverse, will be attributed to the wrong plant.

Botanical dietary supplements and phytomedicines can occur in several forms, but extracts are the most common type of preparation. As noted in *Phytomedicine* (10), the method of extraction must be described and the ratio of crude plant to plant extract in test preparations must be provided. Research cannot be replicated without this information. Chemical fingerprints of plant extracts (usually determined by HPLC or liquid chromatography-mass spectrometry) are informative and provide both qualitative and quantitative information. Plants have characteristic chemical profiles of secondary metabolites. These chemical fingerprints can be used to identify the source material and provide an indication of purity. Unexpected peaks, for example, may indicate contamination or adulteration.

Researchers strive to standardize botanical extracts to provide specific concentrations of marker compounds. These marker compounds are not necessarily the active constituents of the botanical preparation. If a marker is not linked to bioactivity or a therapeutic effect, it functions primarily as an index of product consistency and quality control. Unlike single-entity synthetic

drugs, the active ingredients of most botanicals are either unknown or not definitively resolved. Absent the identification of the active ingredients in a botanical extract, it is difficult but not impossible to ensure a consistent biological effect.

It is not clear how much oversight a journal should exercise with respect to the safety of test materials used in clinical studies. Presumably, safety issues are addressed before the research is conducted. Much has been said and written about the safety of dietary supplements (11–14). Although manufacturers of dietary supplements are not required to obtain premarket safety approval from the Food and Drug Administration, they are nonetheless ultimately responsible for the safety of their products. In turn, researchers are responsible for meeting safety standards in clinical studies of any commercial product, ingredient, extract, or isolated constituent. Proper identification and characterization of test materials along with rigorous quality control will address some but not all safety concerns. Several concepts of safety assessment relevant to botanical dietary supplements have been suggested (13, 14), but these proposals are beyond the scope of this commentary. In brief, indications of use and historical exposures at relevant dosages should be considered. A clinical study to test the efficacy of a prune extract for the treatment of constipation would probably require limited safety evaluation. Common sense dictates that safety requirements would be different if the goal of the research were to study the effect of high doses of a chemically modified plant constituent on cancer risk in an otherwise healthy population.

In summary, studies of botanical dietary supplements and ingredients are relevant to clinical nutrition. The standards for research evaluation should not be modified simply because the test material is a botanical or other dietary supplement. If botanicals used in clinical studies are not accurately identified and characterized, the resulting data will be of limited value. Standardization of test materials remains one of the most challenging aspects of clinical research on botanicals. The quality of botanical research in general would improve if standard reference materials and certified methods of analysis for marker and active compounds were available. 

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