

Herbal/Botanical Medicine

Where's the Evidence?

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Healthcare professionals face significant challenges in providing evidence-based healthcare when the evidence base is limited. A prime example of this dilemma is finding the evidence base for answering patient questions about the use of herbal therapies. This article summarizes the current resources available to healthcare professionals. An example of the types of information available for selected herbal therapies for diabetes mellitus from each resource is also presented. Greater consistency in methodologies used to evaluate the safety and efficacy of herbal/botanical therapies would be helpful. The handbook published by the National Institute of Environmental Health Sciences' Office of Health Assessment and Translation, which integrates both evidence for safety and evidence for efficacy, sets the stage for future systematic reviews. The current information on herbal/botanical medication continues to be limited by the number of high-quality studies, which in turn limits the types of conclusions that can be drawn by systematic reviews. *Nutr Today*. 2015;50(4):194-206

Although herbs and herbal medicines have often been considered outside traditional Western healthcare in the past, functional medicine is increasingly being integrated into overall healthcare in the United States. Functional medicine is described in Krause's *Food and Nutrition Care Process* as "an evolving evidence-based discipline that treats the body with its mutually integrated systems as a whole, rather than as a set of isolated symptoms."¹ The Institute for Functional Medicine identifies 5 hallmarks of functional medicine practice, one of which states that "Treatments may include drugs, botanical medicines, nutritional supplements, therapeutic diets, detoxification programs, and counseling on lifestyle, exercise, or stress-management techniques."²

In 2011, the American Dietetic Association (now the Academy of Nutrition and Dietetics [AND]) Standards of Practice and

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Standards of Professional Performance for Registered Dietitians in Integrative and Functional Medicine identified professional performance indicators for evidence-based practice for the following 3 levels of practice in this area: competent practitioner, proficient practitioner, and expert practitioner.³ The Standards of Practice indicates that competent practitioners should consider evidence-based and practice-based research and protocols when ranking nutrition diagnoses in order of importance (indicators 2.2 and 2.2A), and practitioners should base their intervention plan on evidence and research.³ The Standards of Practice further specifies that dietitians should use evidence-based resources (eg, national guidelines, published research, and evidence-based libraries and databases), AND position papers, and Institute of Medicine (IOM) guidelines (indicators 3.2 and 3.2A). Proficient and expert dietitians have more comprehensive and sophisticated knowledge of the evidence and utilize these data in ranking the nutrition diagnoses and planning the intervention (indicators 2.2B, 2.2C, and 3.2B).

The companion document, the Standards of Professional Performance, also addresses evidence-based practice in standard 2 (application of research).³ Indicator 2.2 identifies the need to base practice on significant scientific principles and the best available evidence, and indicator 2.3 identifies the need to integrate the best available evidence with clinical and managerial expertise and client values for all dietitians practicing in integrative and functional medicine. Additional indicators for proficient and expert levels of practice related to the use or creation of evidence-based resources are included in standard 1 (provision of service), standard 2 (application of research), standard 3 (communication and application of knowledge), standard 4 (utilization and management of resources), standard 5 (quality in practice), and standard 6 (competence and accountability). The value of using an evidence-based approach, for example, the best available science and systematic reviews to make decisions about healthcare decisions, is clearly acknowledged. However, finding the evidence base to support treatments with herbal/botanical medicines and dietary supplements may be challenging.

Finding evidence-based resources describing effectiveness and safety of herbal therapies is challenging.

KEY QUESTIONS TO BE ANSWERED

There are 2 types of questions that need to be answered when nutrition professionals or consumers consider integrating botanical or herbal medicines and dietary supplements into their practice: (1) questions of effectiveness (Does the product work? Is it effective?) and (2) questions of safety (Is the product safe? How much is too much?).

Systematic Review Methodologies for Key Types of Questions

Questions of Effectiveness

For questions of effectiveness, the traditional systematic review protocols for evaluating medical treatment effectiveness used to create evidence-based guidelines are appropriate. Examples include reviews that are conducted by professional societies to support evidence-based guidelines, such as those available in the AND Evidence Analysis Library and the Cochrane Library. Other examples include reviews conducted by government agencies, including the National Heart Blood and Lung Institute (used by American Heart Association), the US Department of Agriculture (Nutrition Evidence Library used by the Dietary Guidelines Advisory Committees), the Agency for Health Quality Research (AHRQ Systematic Reviews used by the Office of Dietary Supplements [ODS] to set research priorities), and the US Food and Drug Administration (FDA) (Reviews of Qualified Health Claims used as the basis of decisions for health claims).

Each of these organizations has previously published the methodologies used to evaluate the body of evidence and descriptions of how the body of research is characterized.⁴⁻⁹ The IOM also published standards for conducting comparative effectiveness systematic reviews.¹⁰ These standards include the following topics: (1) standards for initiating a systematic review (establishing a team, managing bias and conflict of interest [for the teams conducting the review and individuals providing input], gathering user and stakeholder input, formulating topics, developing a systematic review protocol, performing peer review of the protocol, and making the protocol publically available); (2) standards for finding and assessing individual studies (conducting the search for evidence, addressing potentially biased reporting of research results, screening and selecting research, documenting the search, managing the data collection, and critically appraising each study); (3) standards for synthesizing the body of evidence (evaluating the body of evidence, conducting qualitative synthesis, including quantitative analysis as appropriate, and providing meta-analysis guidance); and (4) standards for reporting systematic reviews (providing a structured report for the final report, conducting peer review of the draft report, and publishing the final report).

Questions of Safety

The methodology for systematic reviews to answer the second type of questions regarding safety must be slightly different. The IOM Food and Nutrition Board has published several documents addressing use of systematic reviews for safety. The risk assessment model used for establishing the upper intake levels for nutrients was published in 1998.¹¹ Another IOM report established a starting framework for evaluating safety of dietary supplements.¹² In 2007, the IOM convened a workshop to further elaborate on knowledge of the nutrition risk assessment process.¹³ Although the contextual focus of these reports centers on the evaluation of the safety of high levels of more traditional nutrients, many of the challenges identified also apply to herbal products. For example, topics identified as meriting more attention in the future included how to address uncertainties more explicitly and how to improve communication targeted to consumers.

Other agencies such as the National Institute of Environmental Health Sciences Office of Health Assessment and Translation (OHAT) conduct health assessments of environmental substances. In January 2015, OHAT published the *Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration*, and another update is anticipated in 2016–2017.⁶ This new handbook may be well suited to evaluating the research regarding the impact of herbal products. Although this handbook is not the same as standards for systematic reviews, the handbook identifies procedures for the following activities: formulating the problem and developing a protocol, searching for and selecting studies for inclusion, extracting data from studies, assessing internal validity of individual studies, synthesizing evidence and rate confidence in the body of evidence, translating confidence ratings into a level of evidence for health effects, and integrating evidence to develop hazard identification conclusions.

Systematic reviews addressing safety need to have different types of questions, use different types of research, and have different types of conclusions.

There are many similarities between systematic reviews to determine clinical effectiveness and those reviews focused on safety, yet there are also differences in the structure of the question (PICO [problem, intervention, comparison, outcome] versus PECO [problem, exposure, comparison, outcome]) and the types of research used (primarily human vs including human, animal, and mechanistic research).⁶

There are also 2 different types of conclusions that can be included: hazard identification conclusions or level of concern conclusions.⁶ For example, hazard identification conclusions could summarize evidence linking exposure to a health outcome from human, animal, and mechanistic research. However, level-of-concern conclusions integrate evidence from health outcome data used to reach hazard identification conclusions and information on the extent of exposure and pharmacokinetics.

Table 1 shows how the bodies of research are summarized in the various systems, including how the ratings for human and nonhuman animal studies are combined in OHAT reviews to reflect ratings for hazard identification conclusion statements.

In addition to differences in systematic review methodology, there are also considerable differences in the availability of a body of research to answer key questions related to the use of herbal or botanical medicines versus more traditional Western nutrition interventions. To date, no single comprehensive resource is available to assist healthcare professionals or consumers.

RESOURCES SUMMARIZING RESEARCH ON HERBAL/BOTANICAL MEDICINES

If a healthcare professional is providing care for a person with diabetes who is interested in herbal/botanical medicine, the professional may consult the following resources: Evidence-Based Nutrition Practice Guidelines, the Cochrane Library, ODS Fact Sheets, the Natural Medicines Comprehensive Database, and FDA Reviews of Qualified Health Claims. If the professional has the time and skills in systematic review methodology, the professional can also opt to conduct his/her own search for and identification and evaluation of the body of research. A brief description of each resource is included in the following sections, along with an example of the type of information that might be relevant to the healthcare professional providing care for clients with diabetes.

If a patient asks a practicing dietitian for his/her recommendation regarding nontraditional herbal or botanical treatments for diabetes, the dietitian is obligated to provide evidence-based information. However, the amount of time and research that would be necessary to address the patient's request may seem daunting.

Evidence-Based Nutrition Practice Guidelines

Many of the more traditional evidence-based guidelines do not have a significant focus on or include questions or recommendations on botanical or herbal medicine therapy. The AND Evidence Analysis Library includes some questions about herbal products as nutrition therapy as part of the systematic reviews for 2 topics: oncology and estimating energy expenditure.^{16,17} Each question receives a rating that explains how strong the science is that was used to

create the conclusion statement. A conclusion statement can be worded to provide either positive or negative support of effectiveness/use of the product.

For example, if you search using the term “herbs” in the AND Nutrition Evidence Analysis Library, you will find only a few questions addressing herbs as a treatment. There are 2 questions that explore whether ginger is related to a reduction in symptoms and complications from, tolerance of, or support recovery from anticancer therapy (ie, chemotherapy or radiation).¹⁶ Both of these conclude that there is no evidence and grade the conclusion statement as grade V. There are also 17 worksheets summarizing research that includes references to herbal treatments. However, most of the worksheets address the impact of herbs on resting energy expenditure measurement.¹⁷ Searching for clinical practice guidelines that address clients with diabetes might lead you to the Evidence-Based Nutrition Practice Guidelines, where you would not find any significant information about herbal or botanical products for treatment of diabetes.¹⁸ However, the American Diabetes Association's (ADA's) *Executive Summary: Standards of Medical Care in Diabetes—2014* includes 1 statement indicating that there is insufficient evidence to support the use of cinnamon or other herbs/supplements for the treatment of diabetes and cites a C level of evidence.¹⁹

According to the ADA, results from the National Health Interview Survey showed that 22% of patients with diabetes used some type of herbal therapy. The ADA Web site also states there is currently no system to test the effectiveness of these products.²⁰

An Internet search of international Web sites for diabetes and herbal therapies may locate the diabetes community Web site in the United Kingdom, which summarizes the plant-based therapies that have been shown in some studies to have antidiabetic properties.²¹ When you evaluate the diabetes community Web site, you may find that it gives you a list of products in 2 categories: plant-based therapies that have been shown in “some” studies to have antidiabetic properties (aloe vera, bilberry extract, bitter melon, cinnamon, fenugreek, ginger, and okra) and another list of 27 additional products that have been traditionally used by native people in the regions where they grow. This list may serve as a starting point for what your patient may be hearing, and it may be a useful way to create a list of potential herbal and botanical medicines to explore; however, this list does not provide evidence-based information that you need to make practice recommendations.

Cochrane Library

The Cochrane Library is world renowned for systematic reviews addressing the efficacy of medical interventions, and it relies heavily on randomized controlled trials. The Cochrane Library includes publications of protocols as well as completed results. For example, if we search the Cochrane

TABLE 1 Summary of How the Strength of Evidence Is Characterized

| AND Evidence Analysis Library ^{14,a} | AHRQ Systematic Reviews ^{7,a} | OHAT Reviews—Levels of Evidence for Health Effects in Human Studies ^{6,a} | OHAT Reviews—Hazard Identification Conclusions ^{6,b} | Natural Medicines Comprehensive Database Effectiveness Ratings ^{15,b} | Natural Medicines Comprehensive Database Safety Ratings ^{15,b} |
|--|--|---|--|--|--|
| <p>Grade I: Good—The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of serious doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large sample sizes to have adequate statistical power</p> | <p>High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (ie, another study would not change the conclusions)</p> | <p>High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is <i>highly likely to be reflected</i> in the apparent relationship. if reflecting health effect, the level of evidence is “high.” <i>If reflecting evidence for no health effect, then there is “evidence of no health effect”</i></p> | <p>Known to be a hazard to humans—High level of evidence for health effects in human studies with any level of evidence for health effects in nonhuman animal studies</p> | <p>Effective—This product has a very high level of reliable clinical evidence supporting its use for a specific indication. Products rated “effective” are generally considered appropriate to recommend</p> | <p>Likely safe—very high level of reliable clinical evidence showing its safe use when used appropriately. Products rated “likely safe” are generally considered appropriate to recommend</p> |
| <p>Grade II: Fair—The evidence consists of results from studies of strong design answering the question addressed, but there is uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the questions addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most</p> | <p>Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains</p> | <p>Moderate confidence (+++) in the association between exposure to the substance and the outcome. The true effect <i>may be reflected</i> in the apparent relationship. <i>If evidence reflects a health effect, it is called “moderate.” If evidence reflects no health effect, it is called “inadequate.”</i></p> | <p>Presumed to be a hazard to humans—Moderate level of evidence for health effects in human studies with moderate or high evidence in nonhuman animal studies or low evidence in human studies with high level of evidence in nonhuman animal studies</p> | <p>Likely effective—This product has a very high level of reliable clinical evidence supporting its use for a specific indication. Products rated as “likely effective” are generally considered appropriate to recommend</p> | <p>Possibly safe—Some clinical evidence showing its safe use when used appropriately; however, evidence is limited by quantity, quality, or contradictory findings. Products rated “possibly safe” appear to be safe, but they do not have enough high-quality evidence to recommend them for most people</p> |

(continues)

TABLE 1 Summary of How the Strength of Evidence Is Characterized, Continued

| AND Evidence Analysis Library ^{14,a} | AHRQ Systematic Reviews ^{7,a} | OHAT Reviews—Levels of Evidence for Health Effects in Human Studies ^{6,a} | OHAT Reviews—Hazard Identification Conclusions ^{6,b} | Natural Medicines Comprehensive Database Effectiveness Ratings ^{15,b} | Natural Medicines Comprehensive Database Safety Ratings ^{15,b} |
|---|--|--|--|--|---|
| <p>Grade III: Limited—The evidence consists of results from a limited number of studies of weak design for answering the questions addressed. Evidence from studies of strong design is either unavailable because no studies of strong design have been done or have been done are inconclusive because of lack of generalizability, bias, design flaws, or inadequate sample sizes</p> | <p>Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect</p> | <p>Low confidence (+) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship. <i>If evidence reflects a health effect, it is called "low." If it reflects no health effect, it is called "inadequate"</i></p> | <p>Suspected to be a hazard to humans—Moderate level of evidence for health effects in human studies with low or inadequate evidence in nonhuman animal studies or low or inadequate evidence in human studies with moderate level of evidence in nonhuman animal studies</p> | <p>Possibly effective—This product has some clinical evidence supporting its use for a specific indication; however, the evidence is limited by quantity, quality, or contradictory findings. Products rated as "possibly effective" might be beneficial, but they do not have enough high-quality evidence to recommend them for most people</p> | <p>Possibly unsafe—Some clinical evidence showing safety concerns or significant adverse outcomes; however, the evidence is limited by quantity, quality, or contradictory findings. People should be advised NOT to take products with a "possibly unsafe" rating</p> |
| <p>Grade IV: Expert opinion only—The support of the conclusion consists solely of the statement of informed medical commentators based on their clinical experience, unsubstantiated by the results of any research studies</p> | <p>Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion</p> | <p>Very low confidence (+) or no evidence identified in the association between exposure to the substance and the outcome. The true effect is <i>highly likely to be different</i> from the apparent relationship. <i>If evidence reflects a health effect, it is called "inadequate." If evidence reflects no health effect, it is called "inadequate"</i></p> | <p>Not classifiable as a hazard to humans—Low or inadequate evidence in both human and nonhuman animal studies</p> | <p>Possibly ineffective—This product has some clinical evidence showing ineffectiveness for a specific indication; however, the evidence is limited by quantity, quality, or contradictory findings. People should be advised NOT to take products with a "possibly ineffective" rating</p> | <p>Likely unsafe—Very high level of reliable clinical evidence showing safety concerns or significant adverse outcomes. People should be discouraged from taking products with a "likely unsafe" rating</p> |
| <p>Grade V: Not assignable—There is no evidence available that directly supports or refutes the conclusion</p> | | | <p>Not identified as a hazard to humans</p> | <p>Likely ineffective—This product has a very high level of reliable clinical evidence showing ineffectiveness for its use for a specific indication. People should be discouraged from taking products with a "likely ineffective" rating</p> | <p>Unsafe—Very high level of reliable clinical evidence showing safety concerns or significant adverse outcomes. People should be discouraged from taking products with an "unsafe" rating</p> |

(continues)

TABLE 1 Summary of How the Strength of Evidence Is Characterized, Continued

| AND Evidence Analysis Library ^{14,a} | AHRQ Systematic Reviews ^{7,a} | OHAT Reviews—Levels of Evidence for Health Effects in Human Studies ^{6,a} | OHAT Reviews—Hazard Identification Conclusions ^{6,b} | Natural Medicines Comprehensive Database Effectiveness Ratings ^{15,b} | Natural Medicines Comprehensive Database Safety Ratings ^{15,b} |
|---|--|--|---|--|---|
| | | | | <p>Ineffective—This product has a very high level of reliable clinical evidence showing ineffectiveness for its use for a specific indication. People should be discouraged from taking products with an “ineffective” rating</p> | |

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; AND, Academy of Nutrition and Dietetics; OHAT, Office of Health Assessment and Translation.

^aRatings of the strength of evidence for the Evidence Analysis Library, AHRQ, and OHAT reflect how strong the evidence is to support the specific answer being provided. For example, in the Evidence Analysis Library, if the answer is that a herbal product does not have a desirable effect, the strength of evidence to support that could be anywhere on the continuum from grade I to grade IV. Likewise, OHAT confidence ratings for health effects can be evidence of a *health effect* or evidence of *no health effect*.

^bOther ratings are ratings that reflect the *actual effectiveness* or *safety* of the herbal product.

Database of Systematic Reviews for diabetes mellitus, we find that a protocol was published for herbal medicines for type 1 diabetes mellitus in 2008; however, the results are not yet published.²² There is an older review published with review content current as of 2004, which compared Chinese herbal medicines to hypoglycemic drugs in individuals with type 2 diabetes mellitus.²³ Sixty-nine different herbal medicines were tested in 66 randomized trials. Bushen Jiangtang Tang, Trichosanthis, Jiangtang Kang, Ketang Ling, Shenqi Jiangtang Yin, Tangzhi Xiao, Xiaoke Tang, Xiaoyao San, and Yishen Huoxue Tiaogan showed significantly better effects on blood glucose levels than selected traditional drugs. In addition, the following Chinese herbs enhanced the positive effects on blood glucose control when combined with traditional diabetes drugs: Astragalus, Buqi Zhiyin Huoxue Huayu, Danzhi Xiaoyao San, Jiagtang Fang, Jiantang Tiaozhi Tang, Jianpi Huatan Huoxue, Jinli Da, Potentilla, Qimai Dahuang Tang, Shugan Jianpi Huoxue Tang, Tianuan Jiangtang Wan, Xiaotang Ling, Xiaoyao San, Xuange Yin, Yishen Jiangtang Fang, and Zhonghui Chuanhuang. The discussion included limitations such as herbal medicines often being a combination of herbs tailored to individual patient needs, products not being tested more than once, small sample sizes, and lack of blinding methods. The authors concluded that some traditional Chinese herbal medicines have beneficial effects on blood glucose control for those with type 2 diabetes mellitus; however, none could be recommended for routine clinical use because of methodological quality and lack of repeated benefits in large high-quality trials.

Bodies of evidence for herbs were often limited by small sample sizes, lack of blinding, being only a single research trial, or herb combinations tailored for an individual patient.

ODS Fact Sheets

More than 90 different vitamins, herbs, and dietary supplements are included in the ODS Fact Sheets.²⁴ The information about the topics is provided in various formats. Some are reports from the National Toxicology Program on the safety of plant products, whereas others are reports from the National Center of Complementary and Alternative Medicine, and some are ODS systematic review reports with a table of contents that includes topics such as a description of the item, recommended intake, food sources, information about absorption and metabolism, deficiencies, controversies, interactions, and references. For example,

aloe vera includes 2 links: one links to the information from the National Center for Complementary and Alternative Medicine, and the other links to the safety assessment from the National Institute of Environmental Health Sciences.^{25,26}

The ODS has developed a free mobile app for consumers called My Dietary Supplements, which can be downloaded from <https://myds.nih.gov> but is not available in app stores. The My Dietary Supplements app provides a feature called Professional Fact Sheets, which includes 20 items; however, most of the items listed are normal vitamins and minerals with only a few nontraditional supplements (black cohosh, carnitine, ephedra, and valerian). The information provided is sound background information; however, most of the resources are not true systematic reviews. Therefore, it is unclear how/when the search for research was completed, and the characterization of the body of evidence is often unclear.

The ODS information is driven by the product name, not the disease condition, so there is no easy way to search to find out which fact sheets may discuss diabetes mellitus. If the dietitian uses the list of potential herbal products from other sources (eg, from popular Web sites or other published reports), the information related to that specific product can be reviewed. These fact sheets are usually not systematic reviews.

Natural Medicines Comprehensive Database

The Therapeutic Research Center started creating the Natural Medicines Comprehensive Database in 1990 to add to the drug information that the organization was already gathering. This database was recently combined with another resource, Natural Standards, and it is now called Natural Medicines.²⁷ The database includes detailed evidence-based monographs listing the alternative names, scientific names, safety, common use, mechanism of action, dosage, and interactions with other medications. More than 1100 monographs on different foods, supplements, vitamins, and herbs are included in the database.²⁸ A brief description of the methodology used to create the monographs is described, which indicates that the center monitors the scientific literature and updates searches every 3 to 18 months.²⁹ One of the clinical tools is the Natural Product Effectiveness Checker, which provides an effectiveness rating for the ability of natural products to treat a condition or disease. The name of the product is entered, and the search engine identifies whether effectiveness research studies are available. This service is available by subscription for either a consumer version or a more in-depth resource for health professionals.³⁰

There is a second feature for health professionals called the Clinical Management Series, which includes a compilation of data about natural medicine safety and effectiveness for more than 35 medical conditions.³¹ The reports are

organized to include the following: an introduction to the condition, risk factors for the condition, a table of commonly used conventional and natural medicines, a description of treatment modalities, the bottom line, and references. The bottom line includes a recommendation chart for natural medicines used for a particular condition.³² This matrix shows the combined safety ratings (likely safe, possibly safe, insufficient evidence, possibly unsafe, likely unsafe, and unsafe) and effectiveness ratings (effective, likely effective, possibly effective, insufficient evidence, possibly ineffective, likely ineffective, and ineffective). The cells are then color coded in accordance with the recommendations (green, consider recommending this product; yellow, do not recommend using this product; and red, recommend against using this product). Continuing Education Unit (CEU) courses are developed each 3 years to reflect the content in the monographs. The monographs are updated annually. The current Diabetes Mellitus CEU course is being updated to match current information in monographs.

FDA Reviews of Qualified Health Claims

The published results of reviews for health claims or qualified health claims may be another source of summaries of research on herbal or botanical products. The establishment of health claims must be firmly based on scientific knowledge and legal regulation. Efficient biomarkers related to biological response must be found. Furthermore, it is essential to analyze possible diet or drug interactions, and it is vital to conduct valid studies on humans. The decision letters are posted on the FDA Web site. The summaries reflect the state of the science reviewed by the FDA, and they conclude whether the evidence of a substance/disease relationship supporting a proposed health claim meets “significant scientific agreement.” The summaries include the following sections: (1) overview of data and eligibility for a qualified health claim (substance, disease- or health-related condition, safety review), (2) the agency’s consideration of a qualified health claim (assessment of review articles, meta-analysis and abstracts, assessment of animal and in vitro studies, assessment of the intervention studies, and assessment of relevant observational studies), (3) strength of the scientific evidence, (4) other enforcement discretion factors (qualifying level of substance), (5) the agency’s consideration of disclaimers or qualifying language, and (6) conclusions. The methodology used for the reviews is included in the *Guidance for Industry: Evidence-Based Review Systems for the Scientific Evaluation of Health Claims—Final Guidance*, which was published in January 2009.⁹ The currently posted reviews do not include any herbal therapies for diabetes mellitus.

Dietary Supplements Subset—National Library of Medicine and ODS

The ODS and the National Library of Medicine have developed a new PubMed subset called Dietary Supplements.³³

This project replaced the prior International Bibliographic Information on Dietary Supplements database. The subset is based on a search strategy provided by the ODS and is intended to assist in searches from a broad spectrum of dietary supplement literature, including botanical and herbal supplements in both human nutrition and animal models. The information includes sample searches and the search strategy used to create the database, which includes topics on chemical composition, biochemical role, clinical trials, health and adverse effects, fortification, traditional practices, cultivation of botanical products, and surveys of dietary supplement research.

If you search PubMed for the terms “diabetes mellitus,” “systematic review,” and “herbal,” you may retrieve approximately 180 citations for your perusal. Most of these are systematic reviews on an individual herbal product. However, if you review this list, you may find a systematic review conducted by Yeh et al³⁴ in 2003 that is focused on reviewing multiple herbal products as they relate to diabetes mellitus. The authors concluded that the interest in herbs and supplements will likely continue to grow and that there is merit in monitoring the scientific literature, particularly for 7 products that seemed most promising for use by persons with diabetes mellitus, including *Coccinia indica*, American ginseng, *Momordica charantia*, nopal, L-carnitine, *Gymnema sylvestre*, aloe vera, and vanadium.

Example of Herbs for Diabetes Mellitus

Although the previously described resources are available to healthcare professionals, it is a daunting task to find the appropriate information and interpret it into meaningful answers to patient/client questions. For example, a list of herbal/botanical medicines traditionally used for persons with diabetes was compiled from popular Web sites. The databases referenced were searched for 21 of the common herbs associated with treatment of diabetes mellitus. The information is summarized in Table 2.

Frequently, there were gaps in information in which either the herbal/botanical medicines were not included in the resource, or diabetes was not specifically mentioned (shown in gray in Table 2); in other cases, the various resources do not agree in their conclusions. Nearly 50% of the time, the resource being searched did not specifically address the herb for diabetes. The only consistency found among the 21 herbal/botanical medicines evaluated was that the 2 mentioned by Yeh et al³⁴ as having potential (*C indica* and *M charantia*) were *not* included in all 5 of these resources. Six of the herbs were listed as possibly effective in 2 or more resources without contradictory evidence in the other resources (American ginseng, blond psyllium, agaricus mushroom, glucomannan, prickly pear cactus, white mulberry). Usually, this consistency was due to the products not being addressed in the other 3 resources. Other products may have been included in multiple re-

sources but were described differently. For example, Asian ginseng (*Panax ginseng*) was included in 4 of the resources, and the descriptions included contradictory types of information: (1) some studies show it may lower blood glucose, (2) possibly effective, (3) insufficient evidence, and (4) not shown to be effective. Even different resources using the same database sometimes differed in their descriptions. For example, Natural Medicines included 2 resources that evaluated guar gum for persons with diabetes. The recommendation chart for professionals listed guar gum as possibly effective/likely safe, whereas the resource for consumers listed it as having insufficient evidence.

Herbs are often referred to by common names as well as by actual botanical names depending on the resource. Healthcare professionals do not automatically know all of the names that refer to the same product. For example, ginseng can refer to American ginseng or panax (Asian) ginseng—different plants with different active ingredient composition and effectiveness. This is further compounded by the lack of regulation to require that the herbal active ingredients be present at specified amounts in products being sold. Although USP (US Pharmacopeial Convention) provides standards of identity, strength, quality, and purity of products, it is a voluntary process for herbal/botanical products. It is often not clear in research studies what the active ingredient of interest is, what the content of the herb being tested actually is, and how these data would compare to products currently on the market in the United States.

Most of these resources that summarize information about use of herbal/botanical medicines are not true systematic reviews; therefore, it is difficult to determine the parameters used to search, identify, and evaluate the research. Some resources include the dates they were updated. The terms used to summarize the bodies of research vary between resources, as discussed previously and shown in Table 1.

SUMMARY

Healthcare professionals are caught between knowing that the standard of care when using herbal/botanical medicines is “evidence based” and also knowing that the evidence base is very difficult to find and is very weak. The systematic reviews that are the hallmark of evidence-based healthcare can only be as good as the body of research to be evaluated. The body of research for herbal/botanical medicines is often limited to 1 or 2 very small studies on a given herb, and often these studies have methodological limitations. Although there has been a concerted effort to build the research base for herbal/botanical medicines, we are still a long way from having the research that tests and replicates the results for thousands of herbal/botanical products. In addition to focusing on continuing to build high-quality original research, integrated and functional medicine would

TABLE 2 Example of Application of Resources for Herbal Products of Interest With Diabetes Mellitus

| Source (Herbal/ Dietary Supplement) | Herbal and Natural Therapies (www.diabetes.co.uk) ²¹ | ODS Fact Sheets ²⁴ | Recommendation Chart for Natural Medicines Used for Diabetes, Natural Medicines in Clinical Management of Diabetes ³² | Natural Product Effectiveness Checker Results, Natural Medicines Comprehensive Database, Consumer Version (Diabetes) ³⁰ | Diabetes and Dietary Supplements ^{5,55} |
|--|---|--|--|--|---|
| Aloe vera | Shown in some studies to have antidiabetic properties | People with diabetes who use glucose-lowering medication should be cautious if also taking aloe by mouth because preliminary studies suggest that aloe may lower blood glucose levels. ^{25,26} | Not addressed specifically ^a | Insufficient evidence | Not proven to be effective |
| Bilberry extract | Shown in some studies to have antidiabetic properties | The potential use of bilberry for diabetes is mentioned; however, the ODS concludes that there is "not enough scientific evidence" to support its use. ³⁶ | Not addressed specifically | Not addressed specifically ^a | Not addressed specifically ^a |
| Bitter melon | Shown in some studies to have antidiabetic properties | Not included as a fact sheet ^a | Insufficient evidence of effectiveness/possibly safe ^b | Insufficient evidence | Not proven to be effective |
| Cassia cinnamon | Shown in some studies to have antidiabetic properties | Diabetes is included in a list of traditional uses; the ODS concludes that high-quality clinical evidence in humans is generally lacking to support use for any medical condition and specifically mentions 5 clinical trials that do not appear to show an effect on factors related to diabetes and heart disease. ³⁷ | Insufficient evidence of effectiveness/likely safe | Insufficient evidence | Some risks, but no clear benefits of cinnamon |

(continues)

TABLE 2 Example of Application of Resources for Herbal Products of Interest With Diabetes Mellitus, Continued

| Source (Herbal/ Dietary Supplement) | Herbal and Natural Therapies (www.diabetes.co.uk) ²¹ | ODS Fact Sheets ²⁴ | Recommendation Chart for Natural Medicines Used for Diabetes, Natural Medicines in Clinical Management of Diabetes ³² | Natural Product Effectiveness Checker Results, Natural Comprehensive Database, Consumer Version (Diabetes) ³⁰ | Diabetes and Dietary Supplements ³⁵ |
|--|---|--|--|---|---|
| Fenugreek | Shown in some studies to have antidiabetic properties | A few small studies found that fenugreek may help lower blood sugar levels in people with diabetes ³⁸ | Possibly effective/likely safe | Possibly effective | Not proven to be effective |
| Ginger | Shown in some studies to have antidiabetic properties | Diabetes is not mentioned ³⁹ | Not addressed specifically | Not addressed specifically | Not addressed specifically |
| <i>Coccinia indica</i> | Not addressed specifically ^a | Not included as a fact sheet | Not addressed specifically | Not addressed specifically | Not addressed specifically |
| American ginseng | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Both Asian and American ginseng "may" help control glucose levels; not enough evidence to support use |
| <i>Momordica charantia</i> | Not addressed specifically | Not included as a fact sheet | Not addressed specifically | Not addressed specifically | Not addressed specifically |
| L-Carnitine | Not addressed specifically | Not included as a fact sheet | Not addressed specifically | Insufficient evidence | Not addressed specifically |
| <i>Gymnema sylvestre</i> | Not addressed specifically | Not included as a fact sheet | Insufficient evidence of effectiveness/possibly safe | Insufficient evidence | Not proven to be effective |
| Vanadium | Not addressed specifically | Not included as a fact sheet | Insufficient evidence of effectiveness/likely safe | Insufficient evidence | No "strong" evidence for improved blood sugar in type 2 diabetes mellitus |
| Blond psyllium | Not addressed specifically | Not included as a fact sheet | Possibly effective/likely safe | Possibly effective | Not addressed specifically |
| Guar gum | Not addressed specifically | Not included as a fact sheet | Possibly effective/likely safe | Insufficient evidence | Not addressed specifically |
| Agaricus mushroom | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Not addressed specifically |

(continues)

TABLE 2 Example of Application of Resources for Herbal Products of Interest With Diabetes Mellitus, Continued

| Source (Herbal/ Dietary Supplement) | Herbal and Natural Therapies (www.diabetes.co.uk) ²¹ | ODS Fact Sheets ²⁴ | Recommendation Chart for Natural Medicines Used for Diabetes, Natural Medicines in Clinical Management of Diabetes ³² | Natural Product Effectiveness Checker Results, Natural Medicines Comprehensive Database, Consumer Version (Diabetes) ³⁰ | Diabetes and Dietary Supplements ³⁵ |
|--|---|---|--|--|--|
| α -Lipoic acid | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Studies show that it did not prevent diabetes macula edema or improve cholesterol or insulin response, and α -lipoic acid can cause gastrointestinal problems |
| Glucomannan | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Not addressed specifically |
| Panax ginseng (Asian ginseng) | Not addressed specifically | Some studies show that Asian ginseng may lower blood glucose; evidence is preliminary, and more research is needed on treating insulin resistance ⁴⁰ | Insufficient evidence/ possibly safe | Insufficient evidence | Not shown to be effective |
| Prickly pear cactus (nopal) | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Not shown to be effective |
| White mulberry | Not addressed specifically | Not included as a fact sheet | Possibly effective/possibly safe | Possibly effective | Not specifically addressed |
| Milk thistle (Silymarin or silybinin or Silybin) | Not addressed specifically | Lowering blood sugar levels is listed as an adverse effect ⁴¹ | Not addressed specifically | Possibly effective | Not shown to be effective |

Abbreviation: ODS, Office of Dietary Supplements.

^aShaded on this chart to identify gaps in resources where no specific information was included.

^bCoded as yellow on Recommendation Chart for Natural Medicines Used for Diabetes meaning "don't recommend using this product."

greatly benefit from agreement among the various stakeholders on common methodology for describing the body of research and collaborative approaches to publishing and summarizing systematic reviews that address the effective use of herbal medicines and products in patient care. The OHAT handbook and the Natural Medicines Clinical Management Series address both effectiveness and safety in well-described methodologies and could guide future systematic review publications and resources.^{6,31}

Agreement on methodology for publishing systematic reviews of herbal products addressing both effectiveness and safety by disease condition would be tremendously helpful.

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