

PERSPECTIVE

Scientific Evaluation of Traditional Chinese Medicine Under DSHEA: A Conundrum

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ABSTRACT

In the United States, traditional Chinese medicines (TCM) are currently sold as dietary supplements, as defined by The Dietary Supplement Health and Education Act (DSHEA). This legislation is unique to the United States and while "structure and function" claims are allowable under DSHEA, disease claims are not. The narrow definition, however, poses a challenge to designing appropriate clinical studies that can provide data for "structure and function" claim substantiation. The process of melding Chinese herbal medicines into the dietary supplement category is complex and there is a need to define a clinical trial paradigm carefully that addresses "structure and function claims" without sacrificing scientific rigor. It is frequently not recognized that TCM favours an amalgamation of several herbs to generate the putative clinical effect. Because of this historical multiherb approach, the reliance on retrospective data to support the potential health benefits of an herb extract has severe limitations. Notwithstanding the immense value of identifying the pharmacological activity of a TCM herb to a chemical suitable for pharmaceutical development, another approach to safe and efficacious herbal products is to develop a standardized herbal extract. This article highlights issues related to the latter approach and will discuss a research-based strategy that may be suitable for validating, in part, the putative health benefits of TCM.

OVERVIEW

Dietary supplement sales in the United States are booming and consumption of botanical products is expected to grow exponentially. To date, at least 3 of the top 10 selling botanical products can trace their origins to traditional Chinese medicine (TCM), namely *Ginkgo biloba*, garlic (*Allium sativum*), and *Panax ginseng* (Fig. 1). It is interesting to note that these products are indicated respectively for alertness, disease prevention, and energy – categories that garner the most interest among supplement users.

<u>Botanical</u>	<u>Growth (%)</u>	<u>1996 Rank</u>
1. St. John's Wort	24%	17
2. Ginkgo (TCM)	24%	3
3. Garlic (TCM)	24%	2
4. Ginseng (TCM)	19%	7
5. Echinacea	44%	1
6. Echinacea/Goldenseal	34%	unranked
7. Saw palmetto	23%	5

8. Bilberry	26%	12
9. Goldenseal	15%	4
10. Valerian	24%	18

FIG. 1. Top 10 herbal products in the United States in 1997.

Two major factors have influenced the increasing use of herbs or herbal extracts in the United States. First, aging baby boomers are highly motivated to identify alternative approaches to improving their quality of life. With the advent of managed healthcare and disenchantment with synthetic pharmaceutical drugs, many consumers are turning to natural remedies, especially herbs, as a solution to maintaining good health. Second, the mass media, by providing regular reports of the putative healing effects of herbs, are fueling this belief and increasing the awareness of this category by the consumer. For example, the effect of *Ginkgo biloba* on memory improvement (Bauer, 1984; Kleijnen and Knipschild, 1992; Harrer and Schulze, 1994; Chang and Chang, 1997; LeBars et al., 1997) and the antidepressive effects of St. John's wort (DeSmet et al., 1994; Martinez et al., 1994; Linde et al., 1996) had both been reported in major medical journals and propagated by the mass media. Given this heightened interest, United States' natural product manufacturers have expanded their product line to increase sales; indeed, the herbal industry, now numbering more than 1300 companies in the United States alone, is a \$2.5 billion industry, which is expected to grow at a double-digit rate annually.

Despite the popularity of botanical dietary supplements, many herbal products on the market are of low quality and suspect efficacy. The absence of product approval guidelines from federal agencies has created a commercial environment that is rife with abuse and unethical marketing of natural products. Fallacies and hyperbole associated with herbal products have included: (1) herbs being natural are implicitly safe; (2) herbs do not have side effects; (3) herbs are panacea; and (4) efficacy can be obtained over a wide range of doses. Such claims have precipitated regulatory scrutiny, which is likely to increase if solid scientific evidence is not forthcoming from dietary supplement companies. Given this scenario, well-designed clinical research of botanicals can only be viewed as essential rather than a luxury.

Against this backdrop, this article discusses, and takes into account both economic and scientific factors, a research-based strategy that may be suitable for developing TCM as dietary supplements in the next millennium. It should be stressed that the strategy is a work-in-progress and most probably will require extensive revision depending on the evolving regulatory landscape. I have also highlighted some of the differences between product development within the Dietary Supplement Health and Education Act of 1994 (DSHEA) and drug development under New Drug Application (NDA) guidelines. It should become apparent that the differences are substantive and are critical factors in defining an appropriate strategy for commercialising TCM as dietary supplements in the United States.

DSHEA ACT

The DSHEA Act defines dietary supplements in the United States as comprising plant extracts, enzymes, vitamins, minerals, and hormonal products that are available to the consumer without prescription (United States Senate Report, 1994). This statutory definition is unique to the United States and occupies a regulatory position at the nexus of foods and prescription drugs (McNamara, 1995). Under DSHEA, dietary supplements may carry "structure/function" claims – claims that a product may affect the structure or

functioning of the body – but not claims that they can treat, diagnose, cure or prevent a disease. DSHEA established a formal definition of “dietary supplement” using several criteria listed below:

1. A product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combination of these ingredients.
2. Substance is intended for ingestion pill, capsule, tablet, or liquid form.
3. Substance is not represented for use as a conventional food or as the sole item of a meal or diet.
4. Substance is labelled as dietary supplement.
5. Substance includes products such as an approved new drug, certified antibiotic or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license.

Other provisions of DSHEA include the ability to use third-party literature to help consumers to be better informed about the product as long as the literature is truthful and does not promote a specific company or brand of supplement. It should be stressed that DSHEA legislation preserves the Food and Drug Administration’s (FDA’s) authority to safeguard the public against an unsafe product and to remove any product from the market if the FDA deems the product to present a significant and unreasonable risk of injury.

COMPLEXITY OF TCM

Although the marketing of TCM herbs as dietary supplements has been augmented by DSHEA, the process of melding Chinese herbal medicines into the dietary supplement category is complex and requires careful analysis. It is to be expected that TCM, a medical paradigm that relies on empirical or anecdotal data and tradition of use, cannot frequently satisfy the requirements of evidence-based medicine. Thus, identifying the relevant literature database for substantiating a “structure and function” claim allowable under DSHEA is a constant challenge, especially for manufacturers of single TCM herb. Even when clinical trial data are available for a single TCM herb, it is often difficult to glean data showing that the consumption of a particular herb provides health benefits to an otherwise healthy population. Clearly, there is a need to carefully define a clinical trial strategy that can address “structure and function claims,” and yet remain affordable in an industry that does not have the immense economic clout of pharmaceutical companies.

DSHEA vs NDA DEVELOPMENT

Figure 2 compares and contrasts the development of DSHEA products relative to the drug development process. It is clear that there are significant differences between the two approaches and these differences can have an important impact on how clinical studies are designed. While the manufacturing and clinical evaluation of drug substance and product is well defined by the NDA process, there are no clear regulatory guidelines for creating DSHEA products, an issue that is under intense current debate. The outcome of this debate is uncertain, but ultimately will have a fundamental impact on how DSHEA products will be marketed in the United States. In the interim, it is likely that each manufacturer will need to devise a flexible strategy that accounts for the present environment while remaining relevant for the future. Despite this dynamic environment,

certain developmental elements are, nonetheless, essential to reduce the perception of TCM as nostrums by mainstream medicine. While a demand for unequivocal proof of efficacy is unrealistic in the dietary supplement arena, we believe a preponderance of scientific evidence suggesting a health-promoting effect is a reasonable level of substantiation of dietary supplement claims. Over the past decade, new technologies have been developed to measure patient outcome. With these significant advances in patient research, there are now several paths to an optimal developmental strategy that can create a satisfactory level of label claims. While label claims have many legal and regulatory ramifications, their central purpose is to inform consumers about the composition and medical properties of a specific product. On this basis, we believe that the 6S Process is a strategy for developing TCM with credible claims while staying within the spirit and the law of DSHEA.

DSHEA

Dietary supplements

- Only structure/function claim
- Several active constituents

- Historical studies
- Oral dosage form
- No definitive cGMP guidelines
- Proprietary position based on know-how and process
- Preponderance of clinical evidence

NDA

Drugs

- Disease claim allowed
- Single well-characterized chemical entity
- Prospective Phase I-III studies
- All dosage forms
- Clear cGMP guidelines
- Proprietary position based on composition of matter
- Unequivocal clinical evidence

FIG. 2. Product development under the Dietary and Supplement Health and Education Act of 1994 (DSHEA) or New Drug Application (NDA).

6S PROCESS

The 6S process, as shown in Figure 3, captures developmental elements that involve herb selection, sourcing, structural, analysis, herb standardization and manufacturing, pharmacological, and clinical studies. We believe that these elements cannot be ignored if TCM herbs are to join the ranks of truly efficacious products. Notably, this mechanism includes a prospective research component, and does not rely solely on historical evidence for the safety and efficacy of TCM. There is an absolute acknowledgement that the pre-existing body of knowledge on TCM cannot be the only basis for claim substantiation although DSHEA permits use of retrospective scientific data in support of the efficacy of botanicals. The 6S process is also intended to produce a consistent herbal product that is “near-pharmaceutical” grade and to eliminate any uncertainty related to the amount of pharmacological activity that could be achieved with different batches. Indeed, this developmental paradigm for TCM is specifically created with an eye toward establishing an effective mechanism that can separate the “wheat from the chaff” among TCM that are currently touted to provide health benefits.

Selection

- Herbinformatics
- Consumer need

Sourcing

- Chemotaxonomy
- Raw material verification

Standardization

- Chemical Profile
- Pharmacological profile

Safety

- Historical safety data
- Toxin analysis
- Animal test

Structure

- Chemistry
- Method validation

Substantiation

- Pre-existing data
- DSHEA clinical study

FIG. 3. The 6S Process.

Chemistry features

Wide variations in chemical composition are characteristic of any botanical or natural products and require careful chemical analysis to ensure batch-to-batch consistency. Chemical assessment of raw material quality, an accurate taxonomic classification of the plant species, definition of a chemically standardized plant extract that is toxin-free, confirmation of the plant extract's bioactivity, and stability of the final product are some of the important steps to ensuring batch consistency. To date, TCM herbs can vary widely in terms of putative active ingredients and the presence of toxic contaminants in the final product. Unless these factors are carefully controlled, it would be cavalier to use published scientific data as a basis for supporting a proposed health benefit.

Pharmacological features

Biological assays, including dose-response studies, to detect pharmacological activity also serve to minimize batch-to-batch variation, especially for complex herbal extracts. Although advances in chemical analytical methods have led to a better definition of the chemical nature of herbal extracts, a chemically standardized extract may be necessary but not sufficient to ensure consistent pharmacological activity. To mitigate this potential problem, we believe a bioassay measuring a clinically useful activity will provide the necessary data to support a chemical standardization method. Mechanistic studies (*in vitro* or *in vivo*) identifying a potential molecular target could also guide the selection of a relevant bioassay. To the extent possible, identifying a surrogate biochemical marker that can also be measured during clinical studies is an important feature of the 6S approach. For example, cholesterol, a predictive risk factor for atherosclerosis can be easily measured, both *in vitro* and in blood samples. It is also known that the liver enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is the rate-limiting step in cholesterol biosynthesis, thereby providing a convenient enzyme assay for monitoring the activity of various herbal extracts. In this instance, it would therefore, be relatively straightforward to evaluate the batch-to-batch consistency of an herbal extract.

Development of herbal products can also benefit greatly from a better understanding of the bioavailability of herbal products. It is an axiom in pharmacology that orally active compounds must achieve acceptable plasma levels before it can exert a clinical effect *in vivo*. In many instances, conflicting reports about the efficacy of an herb may be due to differences in bioavailability among different versions of the same herb. The assumption that *in vitro* data can be completely extrapolated to an *in vivo* milieu has led to erroneous conclusions about the effect of TCM *in vivo*. For herbal products, it is often difficult to conduct bioavailability studies through analytical chemistry. Instead, in the 6S model of TCM development, bioavailability studies are better conducted with bioassays. Cellular assay, receptor assays, and other modern *in vitro* diagnostic assays are reviewed as possible methods for assessing the level of TCM active components in circulation. Coupled to long-term animal studies, determination of activity in blood can provide valuable information related to proper dosage (Li and Wong, 1997). For example, bioavailability studies conducted with 2 similar *Ginkgo biloba* extracts showed that there were significant differences in blood levels of the active constituent, ginkgolides that

persisted for as long as 12 hours, the second *Ginkgo biloba* extract failed to maintain significant ginkgolide levels at 12 hours. Thus, for certain types of products, bioavailability data can be very useful to establish dose and dosing regimen.

Clinical features

While historical anecdotal data can be extremely useful in the selection of a botanical extract for product development, new clinical trials that would meet Good Clinical Practice (GCP) guidelines (Spilker, 1996) must be an integral part of any strategy to establish the validity of TCM as an efficacious modality. Unfortunately, clinical research of botanicals has not been driven by well-defined research objectives. As shown in Figure 4, research objectives such as safety, assessment in a general population, mechanism of action, pharmacokinetic, clinical pharmacology, and efficacy end points have different levels of difficulty. While not mutually exclusive, the expectation that several objectives can be met in a single study is unrealistic and can complicate clinical trial design. For TCM products we believe a design focusing on a single objective provides better quality data than a multifaceted clinical trial involving several clinical end points. An exemplary well-designed clinical trial of TCM product is the recent publication of the effect of a Chinese herbal medicine on irritable bowel syndrome (Bensoussan et al., 1998). In this study, a Chinese herbal medicine was shown by strict criteria to ameliorate the symptoms of irritable bowel disease. It should be noted, however, that this study used a mixture of 21 powdered herbs. Although the percentage of each herb in the mixture was documented, it is not known whether the individual herbs were standardized, making it difficult to assess batch-to-batch consistency.

That TCM are inherently safe, especially after a concentration step, is a dangerous assumption. One could cite Ma Huang as an example where serious side effects had been observed (Nadir et al., 1996; Powell et al., 1998).

Currently, there is no systematic monitoring of the use of TCM by the general population. The onus is, instead, on the company to have a surveillance system that demonstrates a commitment for assuring the safe use of its products although most surveillance systems are passive in nature and possess certain limitations. For example, adverse reports associated with product use tend to be underreported because most consumers do not recognize a product-related effect. At best, a report will have missing critical information. We believe that the optimal active mechanism for gathering safety data is an open-label study together with a long-term commitment to establishing a reporting link between the company and its customers.

As part of the clinical development strategy, we have therefore adopted the following clinical scheme:

- Human bioavailability studies to select dose;
- An initial exploratory clinical study using a surrogate biochemical marker of activity;
- A placebo-controlled, double-blind randomised clinical study confirming effect on surrogate marker;
- Multicenter, open-label safety study.

Importantly, many principles dealing with minimizing bias and maximizing precision are especially critical in the study of TCM. The term “bias” describes the systematic tendency of any factors associated with the design, conduct, analysis, and interpretation

of the results of clinical trials to make the estimate of a treatment effect deviate from its true value. Robustness, a concept that addresses the sensitivity of the overall conclusions to changing assumptions, should be the ultimate goal of any clinical trials of TCM.

Research objective

- Human safety
- Mechanism of action
- Clinical pharmacology
- Efficacy in General Population

Level of difficulty

- Low
- Moderate to high
- High
- High

Red yeast rice: a case study

The above percents are illustrated by the development of red yeast rice, a TCM that is currently available to American consumers as a dietary supplement. For centuries, the Chinese diet, especially that of Chinese people of lower income, frequently includes fermented foods to make the diet more palatable (Hesseltin, 1983). This constant search for more fermented foods was the foundation for the modern discovery of a red yeast rice extract as a natural food that lowers cholesterol (Li et al., 1998).

Red yeast rice, for more than a thousand years (Sung, 1966), is traditionally prepared by fermenting non glutinous rice with red yeast (*Monascus purpureus* Went yeast), red wine, natural juice of Polygonum grass and alum water. Indeed, a description of red yeast rice found in “Ben Cao Gang Mu” (Compendium of Materia Medica, 1578, AD_ refers to its ability to “invigorate spleen, digestion, and to promoting blood circulation and resolving blood stasis.” In China, it is part of the daily staple diet, and because of its flavour, aromatic fragrance, colour, and health-promoting properties, red yeast is frequently used as a flavouring agent in several Chinese dishes. Examples of foods flavoured by red yeast rice include roast pork, roast duck, fermented bean curd, preserved dry fish, and fermented bean curd, preserved dry fish, and vegetable port stew. Red yeast is also used widely for making Shioxing and Beni-Koji rice in china is comparable to that of grain-based products in the United States.

Recently, several clinical studies were conducted with red yeast rice in China and the United States. One major randomised multicenter clinical trial involving 446 hyperlipidemic patients found that a red yeast rice extract reduced serum total cholesterol levels by 23.0%, reduced triglycerides by 36.5%, reduced low-density lipoprotein (LDL)-cholesterol by 28.5%, and increased high-density lipoprotein (HDL)-cholesterol levels by 19.6% (Want et al., 1997). Another randomised, double-blind, placebo-controlled trial involving a total of 152 patients and using a more concentrated form of red yeast rice showed a cholesterol reduction of 19.2% compared to 1.5% in the placebo group (Shen et al., 1996). Triglycerides and LDL-cholesterol levels were reduced by 36.1% and 27.1%, respectively. In a third clinical trial of 58 hyperlipidemic patients, levels of serum total cholesterol, triglycerides, and LDL-Cholesterol were reduced by an average of 11.7%, 16.9%, and 11.7%, respectively; HDL-cholesterol was increased by an average of 6.7% (Qin et al., unpublished data).

A double-blind prospectively randomised 12-week controlled trial confirmed the lipid lowering effects of red yeast rice (Heber et al., 198). Healthy subjects (46 men, 37 women) with hyperlipidemia (total cholesterol 204 to 338 mg/dL, triglycerides 55 to 246 mg/dL, and HDL cholesterol 39 to 95 mg/dL) were evaluated in this study. Red yeast

rice at the dose of 2.4g per day or placebo capsules were randomly administered to subjects after eating an American Heart Association diet providing 30% of calories from fat, less than 10% saturated fat and less than 300 mg of dietary cholesterol. Serum total cholesterol decreased significantly by 16% between baseline and 12 weeks in the treatment group from 250 ± 30 mg/dL to 210 ± 31 mg/dL ($p < .001$). LDL cholesterol decreased by 22% from 173 ± 27 mg/dL to 135 ± 27 mg/dL ($p < 0.001$). Serum triglycerides were reduced by 7% with treatment changing from 133 ± 48 mg/dL to 124 ± 44 mg/dL. HDL cholesterol did not change significantly with treatment from 50 ± 13 at baseline to 50 ± 14 mg/dL at 12 weeks. Subjects assigned to placebo had no significant changes in cholesterol, LDL cholesterol, triglycerides or HDL cholesterol levels. There were no significant changes in dietary intake of fat, calories or cholesterol, body weight, or liver function tests or serious adverse effects in either the treatment or placebo-treated group. Recently, an identical red yeast rice formulation produced a similar cholesterol-lowering effect in a multicenter study of 187 dyslipidemic patients (unpublished observations).

The mechanism of action has not been definitively established. However, high-performance liquid chromatography (HPLC) analysis shows that red yeast rice contains monacolins (>5mg per g extract). This is of relevance since it has been shown previously (Endo, 1979) that monacolins are potent inhibitors of HMG-CoA reductase, which is the rate limiting step in cholesterol synthesis. Red yeast rice's unsaturated fatty acids (>125 mg/g extract), including mono unsaturated fatty acids diene-fatty, triene-fatty, tetraene-fatty, and pentaene-fatty acids could also be a factor in lowering blood lipids. Other less well-characterized components include proteins, amino acids, saccharides, β-sitosterol, campesterol, stigmasterol, isoflavone and its glycoside, saponin and saponin, and many trace elements.

Future Directions

For TCM to thrive and prosper in the United States environment there must be a convergence of 3 forces. First, the FDA, despite the vagaries of DSHEA, can assist the industry to define the most appropriate juxtaposition of DSHEA products in the spectrum of health-related products. It is the opinion of the author that until the FDA recognizes TCM products as potentially valuable additions to wellness, it is unlikely that TCM products will enter mainstream medicine with ease.

Second, the TCM industry must commit to quality products and should wean itself from marketing products based on hyperbole and spurious data. Without a significant improvement in the marketing aspect, the medical community will continue to view the industry's products with suspicion. The proposed research and development model as described above may be a mechanism that could reduce the perception problem. Obviously, one can contrive a different strategy based on other beliefs and resources available to each company.

Third, consumers who have a vested interest in TCM must reward companies that conduct research in this area. Such consumer support will be a powerful incentive for more companies to subscribe to the proposition that only well-conducted research can validate the value of TCM as safe and effective products. Because of their buying power, American consumers may be the most influential force to generate better research of TCM.

While Western medicine has advanced rapidly over the last 100 years, the implications of technology, and its costs, have led to a “grass-roots” movement to restore some of the traditional concepts of preventive care to a comprehensive public health and fitness program. Herbal medicine in one form or another is being promoted as an alternative road to wellness. It is, however, presumptuous, and even counterproductive, to suggest that either herbal products or Western drugs in its purified form, are superior in their own right and mutually exclusive. The limitations of each must be acknowledged and it would be more realistic by far to suggest that if there was ever a field of research suited for an epochal meeting of East and West, it is the field of herbal medicine. The empirical approach of 5000-year-old science can surely contribute to a better understanding of the human condition, and help regain the human element of modern medicine. Herein lies the central challenge of metamorphosing TCM into viable products in the West.

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