Botanical Medicines in Research

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DESCRIPTION
Botanicals have been used for millennia to combat illness—but why are there so few clinical trials testing the merits of this modality?

This whitepaper describes rationale for why IRBs should embrace botanical medicine protocols.

TOPICS
- The History of Botanical Medicines
- The Regulatory Landscape
- What Is Known of Efficacy and Safety
- Ethical Issues Associated With Research in Botanical Medicine
- How an IRB Should Approach Review of Botanical Medicine Protocols
History of the Use of Botanical Medicines

Plants have been used medicinally by humans for as long as humans and plants have co-existed. The Merriam Webster definition of herbal (or botanical) medicine is: “The art or practice of using herbs (plants) and herbal preparations to maintain health and to prevent, alleviate, or cure disease.”

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The use of botanical medicine falls under the broader rubric of Complementary and Alternative Medicine (CAM), or what is now referred to as Complementary and Integrative Medicine (CIM). Federal funding for research in CAM/CIM reflects (albeit as a lagging indicator) both CIM’s increasing usage in the US, and an acknowledgment that from among CIM modalities there are many with the potential to significantly expand the therapeutic armamentarium of this country’s medical system. *

But only positive results from well-designed clinical trials will allow those therapies to be identified and responsibly incorporated into standards of health care.

* In 1991 the NIH formed the Office of Alternative Medicine (OAM) with funding of $2 million and the directive to “investigate and evaluate promising unconventional medical practices”. In 1998 this office was renamed the National Center for Complementary and Alternative Medicine (NCCAM) and was renamed again in 2014 as the National Center for Complementary and Integrative Health (NCCIH). Its current budget is $124 million. https://nccih.nih.gov/
In 1993, David Eisenberg and colleagues at Harvard University published a systematic survey on the use of “unconventional medicine” in the United States. At that juncture, roughly 30 percent of survey respondents reported using CAM to treat chronic (as opposed to life-threatening) conditions. Demographically, the majority of users were well educated and relatively affluent. At the time of the initial survey, total expenditures for CAM therapies were $13.7 billion, three-quarters of which was paid out of pocket.¹

The Harvard group’s subsequent surveys have demonstrated that CAM use continues to increase: in 1998 and 2008, 40 percent of Americans used some form of CAM and expenditures were conservatively estimated to be over $21 billion; about $5 billion of this went to purchase herbal products. Furthermore, it was noted that almost 20 percent of the respondents taking prescription medications used herbal products concomitantly.²

The CDC/DHHS has conducted a National Health Interview Survey every five years since 2002. Their methodology differed between time points with respect to which modalities were included under the broad rubric of CAM, but the conclusions support Eisenberg’s. CDC data indicates that about one-third of Americans use CAM, and herbal products represent the most commonly used (20 percent of respondents) CAM therapy across all time points. In 2002 and 2007 the most frequently used herbal products were Echinacea, ginseng, ginkgo biloba, garlic, and flaxseed.³⁻⁵

It bears mention that according to the CDC reports, the use of Echinacea, garlic, ginseng, and ginkgo biloba declined between the 2007 and 2012 survey time points. This period roughly corresponds to the time during which research began to capture inconclusive efficacy and/or adverse side effects in some applications of these products.³⁻⁷ It is beyond the scope of this paper to discuss challenges in research methodology and design of natural medicine studies, but the author believes, as do Bent and others, that “...lack of efficacy does not indicate a lack of benefit, but primarily indicates a lack of conclusive studies, positive or negative, for the efficacy of most herbal products.”⁸

Given the prevalence of botanical product usage by Americans, there is a pressing need to understand whether and how these compounds work. In what disease conditions can efficacy be demonstrated? What are the safety profiles of these products? In particular, how do they interact with prescription drugs? Indeed, the second of the five strategic objectives articulated by NCCIH for 2011-2015 was to “Advance research on natural products used as complementary health practices.”⁹

As the need to validate or debunk claims of efficacy of botanical products persists, clinical research in botanical medicine will continue to be funded, and IRBs will continue to be presented with botanical medicine protocols to review. IRBs accustomed to reviewing conventional pharmaceutical/biomedical studies could reasonably want to squeeze their eyes shut and hope the protocol returns to the earth that engendered it. This paper will suggest tips for taking a bolder approach.
Regulatory Landscape

Regulatory guidance covering research in botanical products proceeds mainly from the FDA, and in particular from the Center for Drug Evaluation and Research (CDER). Historically, the appropriate scope of FDA authority over botanicals was widely debated and strongly contested by elements within the natural products industry. Those opposed to FDA oversight argued that data accumulated anecdotally over millennia of use constituted de facto evidence of safety and efficacy. The FDA and others disagreed.

A defining moment in the debate was the passage of the Dietary Supplement Health and Education Act of 1994, colloquially referred to as DSHEA. Passed by the House and Senate and ratified by President Clinton, it amended the Federal Food, Drug, and Cosmetic Act to establish standards with respect to dietary supplements and for other purposes. Under the bill, a dietary supplement is defined as "a product (other than tobacco) intended to supplement the diet that bears or contain 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 dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients."¹⁰

Under DSHEA, a dietary supplement is not considered to be a drug and therefore is not subject to the FDA premarket approval (PMA) process normally required for a new drug to be brought to market (with caveats to be outlined below). As nutraceutical companies expanded their product lines to take advantage of growing consumer demand, many (if not most) used DSHEA to claim that clinical research designed to bolster claims of efficacy could be conducted without an Investigational New Drug application (IND). The DSHEA loophole became big enough to drive a truck through, and many products were pushed to market without adequate clinical validation or regulatory oversight, but then were marketed in a manner that conveyed a therapeutic promise.

In point of fact, DSHEA states that a dietary supplement is not considered to be a drug if the intended use for which it is marketed is only to affect the structure or function of the body, and is NOT to be used for a therapeutic purpose. By extension, a clinical investigation intended only to evaluate the dietary supplement’s effect on structure or function of the body would not require an IND. Conversely, if the clinical investigation is intended to evaluate the dietary supplement’s ability to "diagnose, cure, mitigate, treat, or prevent a disease," then it is being evaluated as a drug and the investigation would need to be conducted under an IND.

¹ The FDA defines a drug as “A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.” It also adds the following definition: “A substance (other than food) intended to affect the structure or any function of the body.” In the context of IND requirements, herbal products generally claim the “food” category. ¹¹
In its 2013 guidance document, the FDA provides these clarifications:

*However, if the clinical investigation is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease an IND is required under part 312. For example, a clinical investigation designed to study the relationship between a dietary supplement’s effect on normal structure or function in humans (e.g., guarana and maximal oxygen uptake) or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function (e.g., fiber and bowel regularity) would not need to be conducted under an IND. However, a clinical investigation designed to evaluate a dietary supplement’s ability to prevent osteoporosis or to treat chronic diarrhea or constipation would need to be conducted under an IND.¹²*

In response to comments on this guidance document, the FDA released a notice of administrative stay of action dated October 26, 2015, wherein it was announced that certain (stayed) categories of investigations would not require an IND while the stay is in effect. These categories pertain to products marketed as dietary supplements or conventional foods, and include those studies designed to evaluate whether a conventional food or dietary supplement may reduce the risk of a disease, or are intended to support a new or expanded health claim. The caveat to the stay is that the studies may not include subjects less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions.¹³

Irrespective of what a botanical product is called—food, dietary supplement, herbal or botanical product—whether or not an IND is required turns on the intent of the clinical investigation. If the compound is being evaluated as a drug (to diagnose, cure, mitigate, treat, or prevent a disease) then an IND is required. IRBs must scrutinize not only the stated intent of a research protocol, but also the specific inclusion and exclusion criteria, the outcome measures, and other elements of the proposal to evaluate the true intent of the investigation, and not rely upon the sponsor’s assurances that an IND is not necessary. If uncertainty persists, the FDA should be consulted to obtain a ruling.¹⁴ Examples at the end of this paper will elucidate the decision algorithms used by Quorum Review IRB when evaluating natural product protocols.

**What is Known of Safety and Efficacy?**

Once the IND question has been addressed, an IRB must next consider the risks and potential benefits of the proposed research. How are these best assessed? Historically, much of the evidence in support of a botanical product’s safety and effectiveness has come from anecdotal reports amassed over many centuries of use in cultures around the world. These reports, often commemorated in medical texts, should not be dismissed out of hand for lack of research-based evidence. However there are some endemic pitfalls to be aware of.
1. Botanical medicines derive from folk traditions in which plants—either the whole plant or isolated parts of it—are harvested and prepared according to learned wisdom. Botanical extracts are complex mixtures of molecular constituents that are difficult to standardize and characterize, an issue further complicated by the timing of the harvest, method of extraction, and growing conditions. The Western science paradigm of pharmaceutical development and testing of a single molecule delivered in pure form at relatively high concentrations does not fit the realities of botanical therapies.  

2. Geographic dispersion of clusters of people and (their) medicinal plants can result in the co-evolution of genetic metabolic traits such that a plant effective in one group of people may be ineffective or in fact toxic in another. An example of this is kava (piper methysticum), long (and safely) used by Native Hawaiians as a social and religious drink. Marketed as an anxiolytic and widely consumed in the United States and Europe, it was associated with many reports of severe hepatotoxicity.  

3. Systematic collection of safety data is often lacking for botanical products with a long history of use in other cultures. Fortunately, resources are available to help IRBs understand the risks and possible benefits of botanical compounds. The Cochrane Review conducts meta-analyses of literature from studies that meet standards of quality and rigor. Although their review groups are organized by disease state rather than therapeutic modality, their database is easily searchable by topic. For example, a search on the term “St. John’s wort” (hypericum perforatum) produces an analysis of 29 randomized double-blind trials including 5,489 patients with major depressive disorder. The authors’ conclusions are that hypericum is superior to placebo, similarly effective to standard antidepressants, and has fewer side effects than standard antidepressants in treating subjects with MDD.  

Another excellent resource is the NCCIM website, which includes a link to the Cochrane Collaboration Complementary Medicine Reviews, as well as a section called “Herbs at a Glance,” devoted specifically to botanical products. For each herb listed in the “Herbs at a Glance” section, there is information on what the plant is and how it has been used historically; what preclinical and clinical evidence exists to support its use; information about known side effects and cautions about its usage; key references; and a link to search the scientific literature for possible herb-drug interactions.

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“There is a widely held notion that if something is ‘natural’, it must be safe or beneficial.”
Finally, an IRB might be well served to enlist an expert in botanical medicine to act as a consultant on protocols for which there are particular safety concerns. Herbalists can advise on plant phylogeny, growing and harvesting practices, and methods of extraction and manufacturing that may bear significantly on the therapeutic potential and safety profile of a plant.20-21

What Ethical Issues Are Associated with Research in Botanical Medicine?

INFORMED CONSENT

Federal regulations stipulate that the informed consent document must accurately describe reasonably anticipated risks and potential benefits.22 Yet in many cases botanical medicines have not had systematic safety or efficacy data collected, as discussed above, and are ratified primarily by historical anecdotal evidence. The informed consent document should make clear that although a product may have been in widespread use, rigorously evaluated safety and efficacy data may not be available.

MISCONCEPTIONS

A prospective research subject must analyze the information presented to them in the consent document as pertains to risks and benefits of their participation in the trial. The therapeutic misconception—the belief (irrespective of disclaiming language in the consent form) held by many research subjects that they will benefit from being in the study—weighs in favor of participation. Additionally, there is a widely held notion that if something is “natural,” it must be safe or beneficial. This misconception also weighs in favor of participation by reducing the perceived risks associated with the study. In clinical trials on botanical products, it is imperative to impress upon potential subjects that both the risks and benefits of participation are harder to anticipate than they are for interventions supported by more preliminary data.

STUDY DESIGN

When evaluating a botanical medicine proposal, IRBs (perhaps with the help of a consultant) should pay particular attention to how the medicine is prepared. As noted above, botanical products are complex molecular mixtures, and are typically dose-standardized to a particular active constituent using established analytic methodology. If a botanical compound has not been well studied, it is reasonable to require more intensive safety monitoring and perhaps a gradual dose escalation paradigm to be included in the protocol.

HERB–DRUG INTERACTIONS

One of the principal concerns about botanical medicines is their potential to interact with conventional drugs in ways that may be harmful. Botanicals and conventional drugs are common substrates for CYP450 enzymes, and their concomitant use can result in the same array of induction- or inhibition-related events as have been characterized for drug–drug interactions.23

For example, St John’s wort is known to affect the metabolism of antidepressants,
contraceptive agents, cyclosporine, digoxin, phenobarbital, and warfarin, among others. An IRB reviewing a botanical medicine protocol will take known or reasonably anticipated herb–drug interactions into account when evaluating inclusion and exclusion criteria, safety monitoring, and the risk language in the consent form.

How Should an IRB Approach Review of a Study Involving Botanical Medicine?

- Enlist a reviewer trained in botanical medicine to assess manufacturing methods and dosing
- Hold the study to reasonable standards of scientific design rigor
- Scrutinize the informed consent form carefully

Reviewing Botanical Medicine Protocols at Quorum: IND or No IND?24

The following are examples of botanical medicine protocols reviewed by Quorum. These examples demonstrate some of the questions that arise in botanical medicine research and describe how the Board handled them.

**IND or FDA letter of exemption required by Quorum**

1. A protocol submitted in which the sponsor claimed IND exemption under a “medical food” category. Sponsor language in the protocol, however, characterized the product as a substance that “improves the quality of life by changing the amount of diarrhea” in a person. The Board determined that in this case a disease is being described (gut dysfunction) and the product is intended to treat the disease. The outcome measures included QOL questionnaires as well as a comprehensive stool panel.

2. A protocol submitted in which a nutritional product designed for glucose control was studied in polycystic ovary syndrome. The outcome measures included menstrual cycle length (abnormal in PCO) as well as hormonal status, histological examinations, and blood tests related to markers that are...
known to be altered in PCO. PCO is clearly a disease, and the intended use was deemed to be treatment.

3. (Not a botanical product, but included for illustration.) A protocol submitted in which the sponsor stated that a fish oil supplement was not intended to be labelled as “treatment.” However, the primary objective was stated as “clinical improvement,” and the outcome measures involved blood tests and assessments of biochemical markers and functional markers of specific physiological processes related to chronic inflammation. The Board determined that a chronic inflammatory condition met the criteria for a disease and that the intention was to develop a treatment.

**IND or FDA letter of exemption NOT required by Quorum**

1. A protocol submitted to evaluate the effect of a botanical product on joint health, including general pain and mobility. The primary outcome measure was a timed walk test. Because there was no mention of specific diseases (e.g. OA or RA) and no clinical endpoints measured (such as CRP, sedimentation rate, or imaging) the Board determined this satisfied the “structure or function” criteria and did not meet the criteria of treating disease. The Board did not require an IND.
References

11. Drugs @ FDA Glossary of Terms http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm
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