PHYTOMEDICINES AND GLOBAL HEALTH: AN ETHICAL ANALYSIS OF HERBAL MEDICINE

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Abstract

Governments, international agencies and corporations are increasingly investing in traditional herbal medicine research. Yet little literature addresses ethical challenges in this research. In this paper, we apply concepts in a comprehensive ethical framework for clinical research to international traditional herbal medicine research. We examine in detail three key, underappreciated dimensions of the ethical framework in which particularly difficult questions arise for international herbal medicine research: social value, scientific validity and favourable risk–benefit ratio. Significant challenges exist in determining shared concepts of social value, scientific validity and favourable risk–benefit ratio across international research collaborations. However, we argue that collaborative partnership, including democratic deliberation, offers the context and process by which many of the ethical challenges in international herbal medicine research can, and should be, resolved. By "cross-training" investigators, and investing in safety-monitoring infrastructure, the issues identified by this comprehensive framework can promote ethically sound international herbal medicine research that contributes to global health.

Keywords

Global Health, traditional herbal medicine

INTRODUCTION

Traditional herbal medicines are naturally occurring; plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices. Traditional herbal medicines are getting significant attention in global health debates. In China, traditional herbal medicine played a prominent role in the strategy to contain and treat severe acute respiratory syndrome (SARS)[1]. Eighty per cent of African populations use some form of traditional herbal medicine[2,3] and the worldwide annual market for these products approaches US$ 60 billion[2]. Many hope traditional herbal medicine research will play a critical role in global health. China, India, Nigeria, the United States of America (USA) and WHO have all made substantial research investments in traditional herbal medicines[2]. Industry has also invested millions of US dollars looking for promising medicinal herbs and novel chemical compounds[4,5]. This is still a relatively modest investment compared to the overall pharmaceutical industry; however, it raises interesting ethical questions, some of which are not faced in more conventional drug development. As attention and public funding for international traditional herbal medicine research collaborations grows, more detailed analysis of ethical issues in this research is warranted. Scant literature has addressed

selected issues such as informed consent and independent review related to traditional herbal medicine research[6,7]. Here we apply a practical, comprehensive and widely accepted ethical framework to international traditional herbal medicine research[8]. We examine in detail difficult questions related to social value, scientific validity and favourable risk–benefit ratio. We conclude with implications for future research in this area, focusing on the importance of collaborative partnership. Nongovernmental organizations may be primarily interested in preserving indigenous medical knowledge. One such organization, the Association for the Promotion of Traditional Medicine (PROMETRA), based in Dakar, Senegal, is "dedicated to preserving and restoring African traditional medicine and indigenous science"[9]. Governments in developing countries may want to use traditional herbal medicine research to expand the influence of their culture's indigenous herbal practices in the global health-care market. For instance, Nigeria's president recently established a national committee on traditional medicine with the expressed desire to boost Nigeria's market share of traditional medicine[10]. In developed countries, the "need" for this research may be to protect the public. The perceived need for the research may justifiably differ across countries, but without some basic agreement on the primary source of social value for the research it may be difficult to judge its ultimate impact. In the Africa Flower case above, before agreements to study a herbal medicine are decided, partners must fully discuss potential differences about the perceived "need" for the research through public forums or structured debates. Based on these frank discussions, partners can assess whether the social values of partner countries are sufficiently compatible to warrant a research partnership.

Balancing internal and external validity

Building a valid basis for knowledge in herbal medicine will require balancing two aspects of scientific validity: internal and external validity[11]. Internal validity means the research must reliably test hypothesized relationships between an intervention and an outcome under controlled conditions. Internally valid research will typically try to answer a focused research question that is salient within the vocabulary and methods of the scientific community at the time the research is conducted. External validity refers to the applicability of the research results to a target population outside the experimental conditions of the research study. External validity must always be weighed against the need for rigorous internally valid research. This tension between internal and external validity can be illustrated by a recent herbal medicine trial of Echinacea angustifolia extract for prevention of parainfluenza virus infection[12]. The study was conducted under rigorous experimental conditions, but many herbalists pointed out that study conditions did not sufficiently reflect how these medicines are actually used. Null treatment trial results like these prompt questions about the external validity (i.e. value and meaning) of the research. Was the herbal medicine truly ineffective, or did the experiment not reflect the herb's use in "real-world" practice? In herbal medicine there are often huge variations in the way in which the medicines are used in herbalist practice, including herb source, preparation, dose and indication. Because traditional herbal

medicine practitioners may be unregulated and their products lacking in standardization, it may be difficult to generalize the results from a formal, structured and highly monitored trial to what will happen in the widespread dissemination of the herbal medicine. Nevertheless, herbal medicine research must endeavour to achieve a balance between internal and external validity.

Inclusion and exclusion criteria

To ensure that research results are externally valid, the inclusion and exclusion criteria for research participation should fit with existing diagnostic categories in the target population specified by the research question. However, conceptualizations of health and illness can vary across medical systems and populations, making agreement on valid inclusion and exclusion criteria for international herbal medicine research collaborations more difficult to achieve. During the SARS epidemic, traditional Chinese medicine (TCM) practitioners involved in the care of SARS patients characterized patients based on nosological categories derived from TCM including "deficiency of chi and yin" as well as "stagnation of pathogenic phlegm"[13]. Designing clinical trials using these kinds of TCM categories as inclusion criteria would require significant additional effort and biomedical flexibility to implement. If one wanted to test whether TCM works for populations in south-east Asia affected by a SARS-like illness, adapting the science to include traditional diagnostic categories may be critical for its ultimate external validity. If American researchers want to test a herb's effects on heart failure, they might use the New York Heart Association classification as part of the inclusion/exclusion criteria. However, this classification makes little sense from a TCM perspective, in which heart failure may be viewed primarily as either a heart yang chi deficiency or a kidney yang deficiency[14]. TCM practitioners may prefer to categorize patients based on pulses, tongue examination, and other elements of traditional diagnosis. Investigators have simultaneously used both biomedical entry criteria and stratified for TCM diagnosis[15]. Such an approach is scientifically ideal because of its ability to maximize the external validity of results.

Determining research design

While it is generally agreed that all human subjects research must maintain valid study designs, questions arise about the characteristics of a valid research design. Two extreme positions are often defended. At one extreme, some researchers trained in biomedical methods of clinical investigation argue that the only valid source of knowledge regarding clinical efficacy must come from one type of research design, the randomized double blind, placebo-controlled trial. They argue that any deviations from this gold standard of scientific validity amount to worthless science.

At the other extreme, critics of biomedical research conducted on traditional medicines charge that attempts to evaluate traditional therapies with biomedical methodologies may fail to generate true knowledge, since that knowledge itself depends on a scientific vocabulary that only makes sense from within the concepts of

biomedicine. They worry that “standard notions of ... experimental design criteria represent an imperialistic ‘western’ mode of thinking”[16]. Research on herbal medicines should typically employ experimental research designs such as the RCT. Even if research tools (including the RCT) are imperfect[17], they are thus far the best methods we have for furthering our knowledge[18]. Consider how RCT designs could be implemented in TCM, in which treatments are individualized to patients, often incorporating several, or even dozens, of herbs in a customized preparation. Despite these complexities, investigators have successfully adapted double-blind RCT designs to complex individually tailored Chinese herbs. Bensoussan et al.[19] conducted a three-arm trial in which they tested the comparative clinical efficacy of standard complex herbal medicines, customized therapy and placebo[19]. Standard and customized therapy were comparably beneficial as compared to placebo. In other instances, cluster RCTs can allow for practitioner variability, while still rigorously testing the efficacy of a therapeutic approach. In cross-cultural settings, researchers cannot merely adopt alternative designs in an ad hoc manner, but must reflect on and refine their research question, and find a design that best answers the research question within the given cultural context. In recent years, growing attention has been paid to a group of additional important ethical issues surrounding publication bias, financial conflicts of interest, and clinical trial registries. In the arena of traditional herbal medicine, these same issues apply, and when cross-cultural differences exist in the definitions of valid science, as is the case in traditional herbal medicine research, these questions compound. For instance, until recently, there was a tendency to see only positive studies published in China. It is, therefore, critically important to the long-term scientific credibility of international traditional herbal medicine research that, at the outset, partners agree about the standards of scientific conduct, the disclosure of financial relationships, registration of clinical trials, and adequate reporting of trial results.

Improving science through collaborative partnership

How can international collaborative herbal medicine trials achieve the ethical requirements outlined above? Collaborative partnership, the first requirement for international research ethics, provides both the rationale and the context for achieving appropriate application of the other ethical requirements. Partners in these collaborations must share vocabulary for all the requirements, especially for social value, scientific validity, and favourable risk–benefit ratio. How can agreed-upon language be achieved? As illustrated here, these challenges are significant. In the case presented earlier, investigators should have reservations about implementing a large-scale clinical trial for Africa Flower. Nevertheless, the local interest in this substance may be valid and deserve some additional preliminary investigation. Collaborative partnership displays a commitment by all parties in international research agreements to work together for common language and goals.

CONCLUSION

To achieve collaborative partnership, parties can engage in structured methods of democratic deliberation to devise shared language and concepts for research. These

methods have been used to bring different parties together in a safe and collegial process of decision-making[20]. Over time, collaborations could "cross-train" basic and clinical investigators to more fully appreciate the concepts and practices of the traditional herbal medicine traditions, and developing host countries would need to develop the basic literacy, knowledge and skills among traditional medicine practitioners so that they see the value of rigorous clinical research. With a sustained investment like this, it will become increasingly possible to conduct sound international scientific investigation on traditional herbal medicine. Furthermore, sustainable collaborative research partnerships would benefit from robust and independent adverse-event reporting systems for herbal medicines so that the risk–benefit ratio for herbal medicine research can be more clearly defined. Ethical challenges in international traditional herbal medicine call for a comprehensive framework. Addressing these challenges requires collaborative partnership that implements sound research designs. So envisioned, international herbal medicine research can contribute to global health.

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