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SCOPE AND BOTTLENECKS IN CLINICAL TRIALS OF HERBAL DRUGS - PRESENT SCENARIO

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ABSTRACT

Purpose: This communication highlights the scope of clinical trials in herbal drugs and various problems being faced by herbal drug scientists, herbal drug industry in development of new herbal products that have to undergo clinical trials in all the countries to enhance global acceptance.

Social Implications: Herbal drugs have been used since ancient times as medicines for the treatment of different diseases. It is the oldest and most popular form of healthcare practice known to humanity for maintenance of health that has been practiced by the people of all the societies throughout the history of evolution. Herbal medicines are also known as "the people's medicines" because of their easy accessibility, safety, ease of availability and self medication. Particularly in countries like India, many of herbal drugs and formulations are used in different practices of treatment like Ayurveda, Siddha and Unani.

Research Implications: It is expected that more than 25% of all modern medicines are directly or indirectly derived from plants sources yet the contribution of developing countries in global herbal business is very poor due to lack of quality control and standardization measures. There is lack of common standards and appropriate methods for evaluating Traditional Medicine to ensure safety, efficacy and quality control. This indicates the importance and requirement to develop a standard operational procedure for the standardization of herbal drugs and formulations.

Original value: Quality control, quality assurance, safety and efficacy of herbal drugs are the bench mark in the evaluation protocols and that would play a major role in providing highly reliable and effective herbal drugs to attract international trade, thus generating returns.

Approach: For this study internet search engines and various documents available for drug regulatory affairs were screened. Problems faced by different scientist groups were analyzed and compiled from internet sources.

Findings: The study highlights a very good scope of clinical trials in herbal drugs. It also highlights stringent guidelines for conduct of clinical trials in herbal drugs that needs little bit relaxation by regulatory agencies.

Conclusion: The conclusion drawn from this review is that presently developing countries lack the necessary guidelines for clinical trials on Ayurvedic/natural/herbal medicines. If the WHO guidelines can be adopted in developing countries to approve clinical studies without the need for stringent safety data, clinical trials on Ayurvedic medicine can be encouraged to be at par with pharmaceutical products.

Keywords: *Clinical trials; Herbal drugs; Quality control; Standardization.*

INTRODUCTION

The origin of practice of medicine developed gradually and separately in ancient civilizations like Egypt, China, India, Greece, Persia and many other primitive civilizations. These slow and progressive developments lead to the birth of the modern pharmaceutical industry. In spite of the great advances observed in modern synthetic medicine in recent decades, plants still make an important contribution to health care[1]. In many countries herbal medicines or phytomedicines (to give them their modern European name), are even prescribed by allopathic practitioners alongside modern drugs and dispensed or supplied primarily by pharmacists. It is only in the USA among the developed countries that legislation has established herbs as 'dietary supplements' and thus removed them formally from the medical scene[2]. Use of herbal medicines for therapeutic purpose is now well-established and widely acknowledged to be safe and effective. Many drugs commonly used today in the developing countries are of herbal origin and a major chunk of all modern prescription drugs contain at least one active ingredient derived from plant material, either obtained from plant extracts or synthesized to mimic natural phytochemical. Many of the pharmaceuticals currently available to physicians have a long history of use as herbal remedies. According to the World Health Organization (WHO), more than 120 active compounds isolated from

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higher plants are widely used in modern allopathic medicine today and 80 per cent of them show a positive co-relation between their modern therapeutic use and the traditional use of the plants from which they are derived.

As per WHO data, about 80% of world's population in developing countries depends essentially on plants for health care because of being economical, easy availability and backed with long history of traditional use. Its use is also prevalent in some developed countries such as Germany, France, Italy and U.S as appropriate guidelines for registration of such medicines exists[3-5]. Herbal medicines continue to carry major market share in US pharmaceuticals and constitute a multi-billion dollar business just because of appropriate guidelines for registration (Figure 1)[6]. Approximately 1500 botanicals are sold as dietary supplements and as a result annual revenue from herbal medicines and herbal products in Western Europe reached USD 5 billion in 2003-2004 with a current market potential of about $80-250 billions in Europe and U.S.A. In China, sale of herbal products totaled US$ 14 billion in 2005 with a current market size of about USD 650 million, of which imported herbal medicines account for USD 15 million. Similarly herbal medicine revenue in Brazil was US$ 160 million in 2007. Despite such a great market potential, the contribution of developing countries in global herbal business is very poor due to lack of quality control, standardization measures evaluating traditional medicines to ensure safety, efficacy, quality control, registration procedures etc. Herbal medicines are closer to conventional drugs than other existing complementary and alternative medicine (CAM) approaches. Herbal medicines consist of many chemical constituents with complex pharmacological effects on the body. The widespread use of herbal medicines suggests, though does not assure, the safety and efficacy of these medicines. The lack of evidence in form of pharmacological and clinical data on the majority of herbal medicinal products is a major hurdle towards the integration of herbal medicines into conventional medical practices. There is often serious resistance in meeting the research requirements of legislation. Evaluation of efficacy of herbal products and applying the principles of modern medicine is a paramount issue[7].

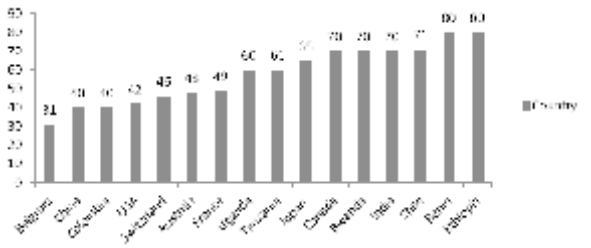

Fig. 1: *Percentage of population using complementary and alternative medicines in different countries*[6]

Keeping in view the above scenario in mind, it is necessary to develop a standard operational procedure for standardization and formulation of herbal drug that could play a major role in providing highly effective and reliable herbal drugs to attract international trade. In most of the developing countries there are no guidelines which could give a smooth drive to a clinical researcher for a clinical trial of herbal drugs. There are number of vague guidelines which are far away from the understanding of most of the researchers. Most of the industry people who want to invest in herbal drug research face a big constraint for indulging into it, just because there are not set guidelines by regulatory bodies. Due to increasing demand of herbal drugs, India is losing a lot of revenue just because of lack of set patterns guiding clinical research and herbal based product development. Being clinical researchers it is pertinent to make the scientists, physicians, post-graduate students, industry and top regulatory authorities aware about potentials and bottlenecks of clinical trials in herbal drugs so as to enable our country to come forward in clinical trials in herbal drugs and hold a significant part of revenue generated by herbal product development. Hence, the objective of this manuscript is to understand and discuss the various problems being faced by developing countries and suggest a unique approach for the preparation of SOP/guidelines for the standardization of herbal based formulations and systematic clinical trials of traditional plant based medicines to enhance global acceptance.

Scope of herbal medicine clinical trials

Traditional/Herbal products have always been an important part of the public's healthcare around the world. In recent years, world has witnessed the increasing growth in popularity of over-the-counter (OTC) health foods, nutraceuticals and medicinal products from plants or other natural sources in developed as well as developing countries. During the past decades, public interest in natural therapies, namely herbal medicine, has increased dramatically not only in developing countries but also in industrialized countries. This has renewed and rejuvenated the international trade in herbal medicine enormously and has attracted most of the pharmaceutical companies, including the multinationals[8]. This new drive of phytotherapeutic market is due to a number of factors like preference of consumers for natural therapies; concern of consumer regarding undesirable side effects of modern medicines, since millions of people all over the world have been using herbal medicines for thousands of years; some traditional/conventional therapies, where treatment paradigm is quite slow, psychologically patient finds solace in herbals; freedom and tendency towards self-medication; revival of trust and faith due to steps taken by regulatory authorities for improvement in quality, proof of efficacy and safety of herbal medicines and relatively high cost of synthetic medicines[9].

The success story of complementary medicine has also been supported by the more accentuated research efforts into their safety and effectiveness; however a lack of scientifically valid research into complementary medicine has always been a significant barrier to orthodox medicine in accepting these health care approaches[10]. Another important additional factor is the

increasing number of individuals/patients experiencing dissatisfaction with the outcome of conventional medicine as compared to complementary medicine, that most commonly have conditions associated with chronic pain (back and neck injuries, arthritis and rheumatism) or illnesses such as cancer whereas orthodox medicine deals primarily with treating the symptoms[9].

Earlier as mentioned, these herbal products/herbal preparations/OTC products may be contaminated with excessive or banned pesticides, microbial contaminants, heavy metals and chemical toxins which may be related to the source of these herbal materials, if they are grown under contaminated environment or during careless collection of these plant materials[11,12], but now recently, many international authorities and agencies, including the World Health Organization, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine (ESCOP), US Agency for Health Care Policy and Research, European Pharmacopoeia Commission, Department of AYUSH has started laying down new stringent mechanisms to induce and regulate quality control and standardization of herbal medicine. Moreover World Health Organization recently issued an operational guideline regarding these regulatory requirements needed to support clinical trials of herbal products. The evaluation of research quality in herbal medicine uses the same approach as that in the clinical trials of modern medicine, with additional components relevant for herbal products. Numerous "quality rating" systems have been developed for the evaluation of clinical research most notably the CONSORT (Consolidated Standards of Reporting Trials) group has produced a widely adopted set of reporting guidelines for Randomized Controlled Trials of herbal medicine[13,14]. So more awareness of people around the world and more result oriented actions taken by regulatory authorities towards safety, efficacy and strict regulation in interest of patients have posed a great faith in herbal drug industry. This has opened up many avenues for herbal drug industry to conduct concerted clinical trials on herbal drugs.

Major Problems and Challenges with Clinical Trials of herbal drugs

Due to the fact that plants cannot be patented, minimal research has been carried out for their role as medicinal agents. In USA the process of demonstrating drug safety and efficacy of a new pharmaceutical product takes approximately 15 years and costs an estimated USD 2.5 billion and only few research companies are willing to fully invest the time and money necessary to satisfy the FDA requirements. The regulatory requirements for proof of safety and efficacy generally make it uneconomical for the private industry to conduct costly clinical trials on herbal medicine. If, however, the regulatory requirements regarding safety and efficacy can be made a bit relaxed, private companies might pursue research more easily for safety and quality control of herbal medicine. So a considerable amount of public fund might still however be required to confirm the validity of herbal remedies, because pharmaceutical companies would earn meager incentive to develop a herbal product that might displace or replace a patented drug[15]. So it is very important to generate more data to assess the efficacy than to assess safety of herbal medicine and, for proof of efficacy, the clinical trial has become the gold standard to majority of population. It is a fact that unless a proper study has been conducted on human subjects, no pertinent and appropriate conclusion on its efficacy and or safety can be drawn. Further, the infrastructure for alternative and herbal medicine research is largely nonexistent in developing countries that add fuel to the fire[16]. Ayurvedic Herbal Medicinal Products (HMPs) are widely marketed as dietary supplements in different countries. These HMPs falls under the Dietary Supplement Health and Education Act (DSHEA), and it is not mandatory to narrate the safety or efficacy of HMPs. These HMPs escape the stringent quality control laid by Drugs and Cosmetics Act 1940. For example, in Ayurvedic HMPs various illnesses like status *epilepticus*, fatal infant encephalopathy, congenital paralysis, sensory neural deafness, and foetal developmental delay have been reported due to Lead toxicity. These morbidities have been confirmed in USA and other countries, commonly known case of heavy metals associated with Ayurvedic HMPs in 65 adults and children[17-18]. In addition to that there are a number of other factors that cause hindrance in clinical trials of herbal drugs.

1. ***Herbal preparations with isolated compounds:***
   Quite often the herbal preparations are poly herbal in nature. Problems cascade when the process standardization involves multiple plant extracts. Another area to be addressed in the standardization of the compounds using bioactive markers. Also, while conducting pharmacokinetic studies for Ayurvedic formulation in phase I, it is difficult to determine the active molecule[19].

2. ***Lack of adequate safety data:***
   In traditional practice most herbal medicines are introduced to humans without any toxicity investigation. Hence their embryo toxic, genotoxicity, teratogenicity, reproductive toxicity and carcinogenicity remain unrecognized. For example embryotoxic effects of 'Pippalyadi vati' (traditional contraceptives consisting of *Embelia ribes, Piper longum* and Borax)[20,21]. Safety profile of herbal drug interaction is unknown with other medicinal products, food and other substances like alcohol, caffeine, tobacco or nicotine or with diet. Some serious herb-drug interactions includes: a) Bleeding- co administration of *Ginkgo biloba*, garlic dong quai or danshen is combined with warfarin; b) Serotonin syndrome- when St. Johns' wort is combined with serotonin- reuptake inhibitors; and c) Induction of mania in depressed patients - when *Panax ginseng* is mixed with antidepressants[22].

3. ***Chemical composition of herbal preparation:*** Chemical composition of raw herb material also varied by environmental factors like geographical locations, climatic conditions, pollutants, harvesting strategy, and collection methods etc. greatly alter the chemical contents of herbal raw material thereby make the standardization steps difficult which jeopardize product quality[23].

4. ***Selection of dosage regimen***: The Ayurvedic principle "prakriti" is determined at the time of conception and can be defined as a "psychosomatic constitution" of an individual. Thus, raising a challenge in determining which drug should be prescribed to the same population of patients. Ayurvedic system of medicine also believes individualistic treatment. Therefore, herbal study drug administered to a subject population with various constitutions may not yield uniform outcomes. This imposes another challenge in selection of dosage regimen. Extractive value should be used in calculating dosage regimen keeping in consideration whether crude drug or extract is used[24].

5. ***Drug delivery/administration platforms:*** Quiet frequently, herbal formulations are loaded with a vehicle e.g. honey, warm water, juice of herbs etc. Therefore, compatibility between the herbal formulation and the drug delivery platform is another challenge and not much explored area.

6. ***Storage conditions and adulteration:*** Conditions under which herbal medicines are stored, significantly alter their bioavailability properties. These alterations result in loss of their activity and also cause variation in microbial contamination in different batches. Good Manufacturing Practices are generally not followed during manufacturing of herbal products to keep a check on adulteration and substitution. Thus there are reported issues with safety and quality of herbal medicines. e.g. toxic herbs, contamination with microorganism, heavy metals and other contaminants (pesticides).

7. ***Difficulty in double-blind randomized clinical trials:*** The randomized clinical trials (RCT) on herbal medicine may be quite difficult to conduct because it needs large volunteer groups, is of long duration and requires expensive healthcare services. Moreover, one major problem that exists is that the funds for such trials, is usually not readily available[25,26]. Other problems in conducting randomized controlled trials on herbal medicine include the following:

7.1) Patient selection: A clearly defined treatment and indication are perquisite for clinical trials. The study subjects inclusion criteria could be based on modern medicine practice or diagnosis made per the herbal medicine practice. However, some variation in disease criteria is quiet possible in some cases. In addition, a greater challenge is to develop similar complexicity and variability in the study and control groups on the grounds of diagnosis based on herbal medicine practice. For example, a homogenous osteoarthritis group could result in various diagnostic types with each requiring unique treatment when evaluate by traditional and complementary Medicine. Quite often standardized approach is considered, which treats the average syndrome, which is inappropriate. This approach not only simplifies the treatment strategy but also maintains the blinding and prevents treatment confusion in different groups. The drawback is the generation of pseudo negative results in suboptimal patient [27].

***7.2) Patient motivation*:** In herbal medicine practice, patient involvement in centric in treatment outcome patient performance greatly influence the motivation to comply with treatment regimen. Thus there is a direct relationship between patient motivation and treatment outcome during patient recruitment factors like informed consent procedure and subjects expectation could significantly impact outcome. In addition treatment complexicity and contextual factor influence the patient's participation and thus alter treatment outcome[28-33].

7.3) Sample size: The effect of size needs to be addressed while analyzing the sample size during the conduct of powered studies. It is reported that only 0.6% RCTs conducted prior sample size calculation when evaluated in 167 studies[32]. Moreover, RCTs must address sample size to comply with CONSORT statement for the purpose of publication. It is observed that there is a wide variation in the effect size and variation between previously reported studies. Therefore, the investigator must conduct a pilot study with a predetermined test formulation to adequately address sample size. A role of investigator and statistician is very important in determining sample size in trial [34-35].

***7.4) Comparative placebo of herbal drugs*:** During the conduct of active comparator trials, the major consideration is the selection of the comparator drug. Whether it should be a herbal product or a modern medicine needs consideration. It is very difficult, impracticable or sometimes impossible to have active and control groups with identical color, odor and taste of same traditional/herbal medicines. Therefore, the synthesis of placebo involves difficulties as the herbal study drug may exhibit its strong aroma, a specific distinguished taste and hence these cannot be exactly imitated while manufacturing a placebo, for example, evaluation of complex natural products having a peculiar odor, taste such as ginger, have place a challenge in selection of matching controls. Therefore, a control intervention being odorless might raise suspicion while

a peculiar odor might exaggerate some potential outcome. There are reports with herbal placebos with matching odor as of the investigational herb. The comparative herbal placebo use in evaluation of herbal drugs also raises ethical issues as it is unethical to assign a placebo to unaware patients instead of using an available effective therapy [36-37].

***7.5) Herbal decoction*:** Herbal preparations at home could incorporate ingredients, this pose a difficulty in control selection. For example In European clinical trial in children and adults with moderate to serve eczema and refractory wide spread atopic, it was required to prepare decoction at home which were difficult and also involved problems with unpalatable nature of decoction. The results of these trials showed evidence of efficacy in these placebo control trials. Regardless of challenge involved in preparation of decoction at home. Therefore, construction of matching placebo for an active herbal product is practically possible. In addition, serious consideration should be made during selection of herbal product or alternatively a modern as an active comparator[38-39].

7.6) Minimizing therapist and protocol variability (Occupational Standardization): A member of psychotherapy studies have elucidated the outcome of a treatment is directly related to the experience of therapist[40]. Therefore, while performing trial on herbal medicine, the training of therapist becomes a key consideration. Thus the importance of occupational standardization has been realized[41]. A treatment in compliance with approved SOP is quiet essential. This practice is a cause of concern to the holistic practitioners, as they encounter difficulty and are uncomfortable with the provided standard care[42]. Each therapist should treat similar number of patients. If the number permits the results of two therapists can be compared. This is because the practitioners intend to deliver their best practice and hence violate protocols. This variability in therapist practice could be controlled by providing instructions manual with details of procedures.

***7.7) Endpoint for evaluation of outcomes*:** Objective end points are required to reproduce the reliability of a treatment. However, herbal clinical practice utilize observations which are obsolete and over subjective in view of modern medicine practices. Thus, a method to objectively assess the subjective signs must be addressed. In herbal practice record outcomes in terms of healing, ability to cope and energy balance. The modern medicine practice monitor treatment outcome as improvement in quality of life (QoL). Reciprocally herbal practice do not evaluate treatment outcome as relief in symptoms, cure or survival. This pose a challenge to develop clinically relevant, detailed and a measurable outcome of a diverse population[43,44].

***7.8) Assessing the effects of individual differences*:** Herbal medicine practice is individual centric and cannot be standardized as a treatment while conducting RCT in large groups. Other potential variables are the expectations and trust toward the herbal medicine. In addition, another challenge is the baseline evaluation of various psychological factors like personality and mood. However, these factors controls also serve as prognostic variables to assess whether the randomization resulted in comparable groups. The variations in the treatment efficiency of the groups could be assessed with an aid from visual analog scale (VAS), which measure the treatment outcome variation by considering detailed information of treatment before the randomization[45]. Other issue, probably not relevant to herbal medicine practice but in CAM are the justification about the start and duration of effects in the absence of preliminary studies, and about the appropriate time for follow up. The availability of many herbal products outside medical settings like dietary supplements also result in drop in and sample contamination. Hence, a vigilance on consumption of herbal products other than protocol specific should be done.

***7.9) Methodological shortcomings*:** The history of herbs based therapy discloses the shortcoming in methodologies which jeopardize the efficacy and safety measures of the study. When compared with modern medical practice, there are reported indications of double standards in the way the herbal clinical trials are conducted. Moreover, principles of modern medicines are practiced while studying herbs, e.g. St. John's Wort clinical trial in treatment for depression [46-49].

DISCUSSION

Herbal drugs have been part of life since time immemorial however due to some quality related issues it has faced a lot of criticism worldwide. The discrepancy is not with the Indian system of Medicine; rather the lacunae are at the level of transformation of a raw drug into a final product (i.e. processing and production). Another important factor for loss of faith of public in herbal drugs is due to vested interest of the manufacturers by pressing substandard and low quality products in the consumer market and cash the booming herbal interest of people. Herbal drug market is also facing a lot of lobbying by allopathic drug manufacturers due to an anticipated danger to its existence too. Despite this scenario herbal drug market is booming and having a very big scope for clinical trials in future. This review emphasizes that addressing standardization issue is vital and needs broader consideration. Some of the environment related factors can be controlled by implementing standard operating procedures (SOP) leading to Good Agricultural Practices (GAPs), Good Laboratory Practices (GLPs), Good Supply Practices (GSPs) and Good Manufacturing Practices (GMPs) for producing these medicinal products from herbal or

natural sources. The public's belief that herbal and natural products are safer than synthetic medicines can only be ascertained by imposing regulatory standards on these products that should be manufactured using the Good Practices[50]. Ayurvedic medicine started and came in practice at times of limited access to technologically variable norms of standardization. Standardization of Ayurvedic botanicals and medicines is seriously required. However, it is bit difficult to readily apply the typical modern pharmaceutical Pharmacopoeial standards. At the same time the concept of active markers in the process of standardization needs a flexible approach in favor of the complex nature of these herbal materials.

CONCLUSION

A uniform research policy in herbal medicines is need of the hour. The goals of these suggestions are to facilitate the scientific evaluation and the eventual integration of traditional medicine into the national healthcare system, critically assisting an eventual rational use of traditional medicine through development of technical guidelines and international standards. The conclusion drawn from this review is that presently developing countries lack the necessary guidelines for clinical trials on Ayurvedic/natural/herbal medicines. If the WHO guidelines can be adopted in developing countries to approve clinical studies without the need for stringent safety data, clinical trials on Ayurvedic medicine can be encouraged to be at par with pharmaceutical products.

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