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CLINICAL TRIALS OF TRADITIONAL HERBAL MEDICINES IN INDIA: CURRENT STATUS AND CHALLENGES

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ABSTRACT: Traditional herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain active ingredients parts of plants, or other plant materials, or combinations. Clinical trials of traditional herbal medicines are carried out with herbal preparations only after standardization and identification of markers to ensure that the substances being evaluated are always the same. It is very important to assess the direct and indirect risks associated with traditional herbal medicines. This can only be established once the safety and efficacy of herbal medicines are being proven during clinical trials. There are various concerns over the clinical trial designs in India. It has been observed that during clinical trials various problems are being observed such as Batch to batch variation, use of placebo instead of innovative product, inadequate quality control system, the inadequate requirement for the assessment of safety and efficacy for different types of herbal medicines and difficulty in quantification due to complex nature of extract. This review focuses on the current status of clinical trials of traditional herbal medicines in India, and an attempt has also been made to review the problems encountered during conduction of clinical trials and suggestions and recommendations are also provided to ensure that the clinical trials can be conducted with safety and efficacy.

INTRODUCTION: By definition, 'traditional' use of herbal medicines implies substantial historical use, and this is certainly true for many products that are available as 'traditional herbal medicines.' Ayurveda, Unani, and Siddha are the medical systems primarily practiced in India that has been known for nearly 5000 years. It includes diet and herbal remedies while emphasizing the body, mind, and spirit in disease prevention and treatment [1].

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Herbal medicine is the mainstay of about 75 - 80% of the world population, mainly in the developing countries for primary health care [2]. This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available [3]. According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times [4].

The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Many conventional drugs originated from plant sources: a century ago, most of the few effective drugs were plant-based. Examples include aspirin (willow bark), digoxin

(from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy) [5]. Clinical trials of traditional herbal medicines are carried out with herbal preparations after standardization and identification of markers to ensure that the substances being evaluated are always the same.

WHO Guidelines for Herbal Medicines: In 1992, the WHO Regional Office for the Western Pacific invited a group of experts to develop criteria and general principles to guide research work on evaluating herbal medicines [6]. This group recognized the importance of herbal medicines to the health of many people throughout the world, stating: 'A few herbal medicines have withstood scientific testing, but others are used simply for traditional reasons to protect, restore, or improve health.

Most herbal medicines still need to be studied scientifically, although the experience obtained from their traditional use over the years should not be ignored. As there is not enough evidence produced by common scientific approaches to answer questions of safety and efficacy about most of the herbal medicines now in use, the rational use and further development of herbal medicines will be supported by further appropriate scientific studies of these products, and thus the development of criteria for such studies'.

The document covered such topics as developing protocols for clinical trials using herbal medicines, evaluating herbal medicine research, guidelines for quality specifications of plant materials and preparations, and guidelines for pharmacodynamic and general pharmacological studies of herbal medicines and toxicity investigations of herbal medicines. WHO has also issued Guidelines for the Assessment of Herbal Medicines [7]. These guidelines defined the basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations and manufacturers in assessing documentation, submissions and dossiers in respect of such products.

It was recommended that such assessments take into account long-term use in the country (over at least several decades), any description in the medical and pharmaceutical literature or similar sources or documentation of knowledge on the application of herbal medicine, and marketing authorizations for similar products. Although prolonged and uneventful use of a substance usually testifies to its safety, investigation of the potential toxicity of naturally occurring substances may reveal previously unsuspected problems. It was also recommended that regulatory authorities have the authority to respond promptly to new information on toxicity by withdrawing or limiting the licenses of registered products containing suspect substances, or by reclassifying the substances to limit their use to medical prescription. The guidelines stressed the need for assessment of efficacy including the determination of pharmacological and clinical effects of the active ingredients, and labeling which includes a quantitative list of active ingredient(s), dosage, and contraindications [8].

Ethical Considerations in Clinical Trials with Herbal Products: WHO: All of the fundamental ethical principles of human participation in research apply equally to herbal remedies and research involving these compounds. Consent must be obtained, subject selection must be equitable, risks and benefits must be weighed and must be favorable to the potential participant, and experimental design must be sound.

Concerns that particularly apply to clinical trials with herbal products include:

- Product adulteration (has it been documented) ?
- Interactions between herbal remedies and other entities (rarely understood).
- Reproductive and organ toxicity data (may be minimal).
- Prior dose-finding (likely to be incomplete).

The uncertainty in these areas must be disclosed to all concerned, particularly during the informed consent process. In many regions of the world, a strong belief that herbal medicines will be beneficial and safe may introduce bias, which can be minimized by careful attention to study design including appropriate control groups. Where

possible, the community from whom the medicine originates should be consulted during the research, and the results and benefits of the research should be shared with this community.

As in other types of research, a well trained, the ethical investigator is the best assurance of patient safety in research. Therefore, skilled clinicians should be chosen as investigators to assure prompt recognition and appropriate treatment of any observed adverse event or worsening of a pre-existing condition.

Ethics committees must apply the same vigilant attitude towards herbal studies as they do towards conventional treatment protocols [9].

Market Importance and Use of Herbal Medicines: Indian Scenario: In India, a great deal of folk knowledge exists among ordinary people about the traditional use of herbal medicines. It is difficult to quantify the market size of the traditional Indian systems since most practitioners formulate and dispense their recipes. The present annual turnover of products manufactured by large companies is estimated at approximately US $ 300 million, compared to a turnover of approximately US $ 2.5 billion for modern drugs. According to a study on the attitude of modern medicine practitioners towards Ayurvedic products, general practitioners are relatively unfamiliar with Ayurvedic products even though some are prescribed. They are willing to try an Ayurvedic product if its efficacy is scientifically proven, and would try.

Ayurvedic products if no modern medicinal remedies were available. People use self-medication for minor ailments such as a cough, cold, diarrhea and stomach problems. Patent and proprietary Ayurvedic medicines are sold over the counter in pharmacies. These products appear to represent a major share of branded traditional products in India.

Nevertheless, systems like Ayurveda still need to gain empirical support of modern medical science to make them credible and acceptable for all. An innovative research effort to define the advantages of traditional systems of medicine concerning their safety and efficacy could result in better utilization of these complementary systems of medicine [10].

In India, there are currently about 2,50,000 registered medical practitioners of the Ayurvedic system (total for all traditional systems: approximately 2,91,000), as compared to about 7,00,000 of the modern medical system. In every Indian state, about one-third of the governmental medical posts are occupied by physicians who belong to the traditional systems [11].

Legal Status of Traditional Herbal Medicines in India: In India, traditional medicines are governed by the Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of 1945. They regulate the import, manufacture, distribution, and sale of drugs and cosmetics. In 1959, the Government of India recognized the traditional Indian systems of medicine and amended the Drugs and Cosmetics Act to include drugs which are derived from traditional Indian medicine.

No products derived from traditional systems may be manufactured without a license from the State Drug Control Authorities. Patent and proprietary medicines derived from the traditional systems must contain ingredients which are mentioned in the recognized books of the above systems, as specified in the Drugs and Cosmetics Act. The government is advised by a special committee and an advisory board for Ayurvedic, Siddha, and Unani drugs. Pharmacopoeia committees have been constituted to prepare pharmacopeias for all these systems [10,11].

In 1993, an expert committee appointed by the Indian government developed guidelines for the safety and efficacy of herbal medicines which were intended to be incorporated into the Drugs and Cosmetics Act and rules. It was proposed that no new herbal medicines other than those authorized by the licensing authorities be allowed to be manufactured or marketed, except for those mentioned in and manufactured in compliance with the formulae given in the "authoritative" books for Ayurveda, Siddha, and Unani herbal medicines.

A manufacturer of a new herbal medicine must include safety data and appropriate efficacy data in the marketing authorization application. Herbal preparations are defined as natural products in which the predominant active constituents are of plant origin. A classification for herbal medicines

was proposed depending on their market availability, and the nature of the herbs:

- Category 1: already in use for more than 5 years.
- Category 2: in use for less than 5 years.
- Category 3: new medicines.

The classification of herbal medicines depends on whether they contain processed or unprocessed parts of plants and whether they contain potentially poisonous plants. Requirements for safety and efficacy vary according to the classification and market availability of the product. Depending on the nature of herbs and market availability, different requirements exist for submission of clinical trial data and toxicity data [11].

In 2001, the Central Drugs Standard Control Organisation of Directorate General of Health Services had recently issued GCP guidelines. These guidelines recommend the approach to clinical trials of herbal remedies and medicinal plants [12].

The guidelines divide the herbal products into different categories based on whether the use and formulation of the product are as per the traditional medicine literature or are not as per the traditional documentation.

- For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Drugs Controller General of India for allopathic drugs should be followed.

- When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, subacute and chronic toxicity data will have to be generated as required by the regulatory authority before it is cleared for clinical evaluation.

- An extract or a compound isolated from a plant, which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

The document also provides general guidelines on clinical trials of herbals, toxicity studies, need for standardization, and compliance with GCP in all clinical trials.

Some of the recommendations are:

- Clinical trials should be carried out with herbal preparations only after standardization and identification of markers to ensure that the substances being evaluated are always the same.

- Plants and herbal remedies should be prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization.

- For herbal remedies, Phase 1 studies must be undertaken to check Maximum tolerated dose (MTD) & Early Measurement of Drug activity.

- If there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months, toxicity studies (4-6 weeks toxicity study in 2 species) are needed for phase 2 trials.

- For Phase 3 trial toxicity studies (4-6 weeks toxicity study in 2 species) are needed.

- Ethical guidelines (patient information, informed consent, protection of vulnerable populations, *etc.*) for biomedical research should be followed.

- Clinical trials should be approved by the appropriate scientific and ethical committees of the concerned Institutes.

- Clinical trials should be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator. [11,12]

With the introduction of Drugs & Cosmetics Rule 158 B since August 2010, the requirement of proof

of effectiveness for licensing of a patent or proprietary ASU (Ayurvedic, Siddha, and Unani) medicine has necessitated the development of guidelines of Good Clinical Practice. The quality concerns of ASU products regarding their safety and therapeutic efficacy can be readdressed, if the clinical research generates quality data, acceptable to regulatory authorities for product registration or approval for marketing, especially for products based on non-classical or non-generic formulations [12,13].

In March 2013, The Department of AYUSH, Ministry of Health & Family Welfare introduced Good Clinical Practices guidelines for the conduction of clinical trials for Ayurveda, Siddha & Unani medicines. The document provides general guidelines on clinical trials of herbals, toxicity studies, need for standardization, and compliance with GCP in all clinical trials [13].

Current Challenges for Herbal Medicines: There are several regulatory concerns about research applications and commercialization of traditional herbal medicines.

Standardization of Herbal Drugs: For safe and effective use of herbal drugs, consistency in composition and biologic activity are essential requirements. However, herbal drugs frequently fail to meet this standard, as there are problems such as 1) difficulties in identification of plants, 2) genetic variability, 3) variations in growing conditions, 4) diversity in harvesting procedures and processing of extracts, and 5) the lack of information about active pharmacologic principles [14].

The use of chromatographic techniques and marker compounds for the standardization of herbal products can ensure batch-to-batch consistency; however, this does not ensure consistent pharmacologic activity or stability. The Lack of standardization of herbal drugs would be a serious problem for a researcher as the researcher would not be able to rely on commercially available herbal products for his research studies.

Quality of Herbal Preparations: If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Even in the absence of data on efficacy, quality assurance is important, as quality is a critical determinant of safety as well [15]. Adulteration of plants is a serious problem. Some of the common adulterants are botanicals, toxic metals, microorganisms, microbial toxins, pesticides, and fumigation agents. The drugs most frequently found were ephedrine, chlorpheniramine, methyltestosterone, and phenacetin; 10 to 15 percent contained lead, mercury, or arsenic.

The incidence of heavy metal contamination is not known, but one study showed that 64% of samples collected in India contained significant amounts of lead (64% mercury, 41% arsenic and 9% cadmium) [16]. This can cause serious harm to patients taking such remedies and could confound the assessment of safety in a clinical trial. Quality has to be assured at all stages - herbal raw materials, processing of herbals and finished herbal medicines.

Evidence of Clinical Efficacy: Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture, some herbal medicines and some of the manual therapies [17]. Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. Even if the animal studies or anecdotal clinical experiences are promising and use of an herb is widespread, such observations cannot predict the results of well designed randomized, controlled trials.

A recent review concluded that evidence-based studies on the efficacy and safety of traditional Indian medicines are limited [18]. The data available is mostly experimental or in animals.

Most trials do not report hard efficacy endpoints and duration of observation periods is generally short. The clinical relevance of the observed effects is not always clear [19]. For instance, most Indian trials of hepatoprotective agents are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the herbal product [20].

A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts; use different plant species (*E. purpurea*,

pallida or angustifolia), different parts (herb, root, both), and might have been produced in quite different manners (hydro- or lipophilic extraction). The same name may know Even different species in the local language. Brahmi refers to *Centella asiatica* and *Bacopa monniera*.

The herbal industry is not required to conduct clinical trials, and the industry professionals argue that it would not be possible to recover the high research costs, as herbal products cannot be patented as easily as new chemical entities. Nevertheless, randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional [15].

Safety Concerns - Drug Interactions: Herbal medicines are generally considered comparably safer than synthetic drugs. While this may be probably correct, case reports show that severe side effects and relevant interactions with other drugs can occur. For instance, the herb Ephedra marketed as a dietary aid led to at least a dozen deaths, heart attacks, and strokes. Other well-known safety issues have been hepatotoxicity of kava and renal effects of aristolochic acid [21]. Besides, drug interactions of herbal drugs are of serious concern. For example, hypericum extracts can decrease the concentration of a variety of other drugs by enzyme induction.

Lack of regulatory standards regarding the efficacy and safety of herbal products did not arouse much concern in the past, as these products were often perceived as so safe that even if they were ineffective, little harm resulted [21]. However, the situation is changing now, and there is an increasing body of literature on the side effects and interactions of herbal medicines [22, 23]. Besides the direct risks of adverse effects and drug interactions there is an indirect risk that an herbal remedy without demonstrated efficacy may compromise, delay, or replace an effective form of conventional treatment [15].

Challenges in Clinical Trial: It is very difficult, impracticable or sometimes impossible to have active and control groups with identical color, smell, and taste of the herbal drug. Also, the use of placebo involves similar difficulties as the herbal study drug may exhibit a strong aroma or a specific distinguished taste and these cannot be imitated while manufacturing a placebo. An integrated approach of many herbal systems does not differentiate the disease from the patient.

This approach creates difficulties for the inclusion and exclusion criteria in a clinical trial. Administration of a study drug to a subject population of various constitutions may not yield uniform outcomes. Most often, quality control of herbal medicines is complicated and difficult. Traditional treatment processes propose different interventions at different stages of the disease in the same patient providing another variable in a clinical trial. Relevant, appropriate requirements should be established for the assessment of safety and efficacy for different categorized herbal medicines to reduce cost and expenditure.

CONCLUSION: The challenges can be overcome by applying the most recent methodologies and guidelines for clinical trials. With modern manufacturing techniques, and WHO approved, ISO certified units; drug can be manufactured by masking the strong smell, and fine coating blinds the typical colors and tastes of herbs. This facilitates blinding methods for clinical trials. Planning of scientific, clinical study design is very much essential for the success of any clinical trial which is applicable here. To obtain reliable clinical trial results for herbal medicines, double-blind experiments should be applied with enough patients selected, ideally using the standard of the clinical trial for new drug development.

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