



Research Journal of Pharmaceutical, Biological and Chemical Sciences

Planning of clinical evaluation for Ayurvedic medicines

Sapkale GN*, Patil SM, Karpe PP, Ulhas S Surwase

ASPM's K.T.Patil College of Pharmacy, Osmanabad 413501(MS) India

ABSTRACT

According to traditional system of medicine like ayurveda where in it is believe to that a single chemical entity may not be responsible for complete biological activity hence qualification of active constituent in crude drug may be misleading in judging the efficacy of ayurvedic medicine. In response to the growing need for enhancing the effectiveness, safety and potency of the drug therapy the clinical evaluation are carried out in order to reduce the inherent risk. Ayurvedic preparations have been successfully evaluated for treatment of bronchial asthma, rheumatoid arthritis, and ischaemic heart disease. Piperine from pipali has come out as a bioenhancer in recent clinical evaluation. Botanicals like *Withania somnifera*; *Asparagus racemosus* have exhibited significant vaccine adjuvant activity in experimental systems, which have valuable applications in immunobiological industry. Clinical trials should be conducted with appropriate controls, e.g. by using the study design. During the drug development periods, clinical studies are done in three phases. Phase-I, Phase-II, Phase-III. This review article presents an overview of Introduction, A methodology for clinical evaluation, treatment under evaluation, Efficacy and Safety Studies of clinical evaluation.

Keywords: Ayurveda, clinical evaluation, Efficacy and Safety Studies.

***Corresponding author**

Email: geeta_sapkale@rediffmail.com



INTRODUCTION

Definition

The clinical evaluation is the conformation of potency and safety of drugs on human being. [1]

Objective

According to traditional system of medicine like ayurveda where in it is believe to that a single chemical entity may not be responsible for complete biological activity hence qualification of active constituent in crude drug may be misleading in judging the efficacy of ayurvedic medicine [2]. In response to the growing need for enhancing the effectiveness, safety and potency of the drug therapy the clinical evaluation are carried out in order to reduce the inherent risk [3].

General information

Ayurveda considers that the universe is made up of combinations of the five elements (panch mahabhutas). These are akasha (ether), Vayu (air), teja (fire), aap (water) and prithvi (earth). The five elements can be seen to exist in the material universal at all scales of life and in both organic and inorganic things. In biological system, such as humans, elements are coded into three forces, which govern all life processes. These three forces (kapha, pitta and vata) are known as the three doshas or simply the tridosha. Each of the doshas is composed of one or two elements. Vata is composed of space and air, Pitta of fire, and kapha of water and earth. Vata dosha has the mobility and quickness of space and air; pitta dosha the metabolic qualities of fire; kapha dosha the stability and solidity of water and earth. The tridosha regulates every physiological and psychological process in the living organism. The interplay among them determines the qualities and conditions of the individual. A harmonious state of the three doshas creates balance and health; an imbalance, which might be an excess (vridhdhi) or deficiency (kshaya), manifests as a sign or symptom of disease [9-10].

METHODS

A methodology for clinical evaluation of existing practice, using traditional herbal medicinal formulations

A Supreme Court judgement makes open clinical trial, conducted by a mutually oriented multidisciplinary group of experts including doctors of various systems of therapy, as the legal and effective method to carry out the clinical evaluation to determine the exact role of a given traditional herbal medicinal formulation (THMF) – which includes those from Ayurveda – in ameliorating a particular disease. Blind clinical trials have a place in the second phase of

research when two THMFs, whose role in treating a given disease has already been confirmed, need to be compared for their efficacy. However, testing on laboratory animals prior to the human clinical trials will have to be done when the ingredients and/or vehicle of a THMF of proven value are altered to increase the latter's efficacy during the next phase of research. Compartmentalization of medical practice in India facilitates the 'natural random allocation' of patients to conduct this study. Patient selection will play a major role here. Eastern medicines, including Ayurveda, are more based on the response than the clinical parameters; with enough space for retrospective diagnosis. According to the theory of Prabhava, for a single THMF there could be more than one response with the same dosage. If the patient has the illness, response is therapeutically beneficial. Hence Ayurvedic treatment is individualized in terms of therapeutic response. Let us consider the example of Thuja, in the treatment of venereal wart. As per the existing homeopathic knowledge, thuja in the potencies used for this disease will not produce any side effects in a correctly chosen patient. Hence those patients who develop side effects will not come under the selection criteria to use this drug. Therefore patient selection should begin after patient allocation, and is likely to be a continuous process throughout the clinical evaluation. Clinical features of these patients will become the criteria for patient selection during the repetition of clinical trial using the same THMF. Diagnosis in such cases needs to be confirmed, with the investigative techniques available in modern medicine, so that drugs from different systems of therapy can be compared. The clinical data accumulated by such multicentric trials using 'standardized THMF' will define the indications for a given THMF. In Ayurveda, some diseases are given specific names and while others are described without specific names. Hence a list of indications for a given THMF does not exist in literature. Ayurveda texts are only the guidelines and much emphasis is laid on the accumulated experience of treating doctors. Evolving the criteria for patient selection, by the process of recording the experiences of Ayurvedic physicians, could answer the basic question of indications for a given THMF. This may also give a new direction to the practice of patient treatment in Ayurveda.

Background Information:

Ayurveda and traditional Chinese medicine (TCM) have many commonalities. The focus of both the systems is on the patient rather than disease. Both systems fundamentally aim to promote health and enhance the quality of life, with therapeutic strategies for treatment of specific diseases or symptoms in holistic fashion. Almost half of the botanical sources used as medicines have similarities; moreover, both systems have similar philosophies geared towards enabling classification of individuals, materials and diseases. TCM considers the human at the center of the universe as an antenna between celestial and earthly elements. Water, earth, metal, wood and fire are the five elements of the material world. The world is a single unit and its movement gives rise to yin and yang, the two main antithetic aspects. The actual meaning of the term yin and yang is 'opposites', such as the positive and the negative. However, Chinese believe that yin and yang is not absolute but relative. Consistent with the modern view of homeostasis, yin and yang are interchanged to meet the view that 'yang declines and yin rises'

or 'yang is raised to produce a decline of yin'. The four bodily humors (qi, blood, moisture and essence) and internal organ systems (zang fu) play an important role in balancing the yin and yang in human body. Proper formation, maintenance and circulation of these energies are essential for health. When the two energies fall out of harmony, disease develops. The physician takes into account this concept while treating patients. Drugs or herbs are used to correct this imbalance of yin–yang in the human body [12-13].

Details of treatment under evaluation

Treatment theory focuses on a comprehensive treatment plan (rasayana) that may combine dietary changes, herbs, meditation, breathing exercise (pranayam), Ayurvedic massage (abhyanga), yoga postures (asanas), detoxification and rejuvenation programs (panchakarma), and lifestyle changes. Thus the bulk of the responsibility for treatment rests with the patient through integrating the recommendations into their daily lifestyle. Most practitioners do not perform actual treatments or healing in the office, although some massage therapists will perform Ayurvedic massage. Typically the initial consultation is the longest, lasting from forty-five to ninety minutes. Follow-up consultations may be spaced several weeks or even months apart to monitor progress. These will usually be brief office visits involving diagnostic review and a fine tuning of the treatment regimen.

Ayurvedic preparations have been successfully evaluated for treatment of bronchial asthma [14-15], rheumatoid arthritis [16], ischaemic heart disease [17-18]. Piperine from pipali has come out as a bioenhancer in recent clinical evaluation [19-20]. Botanicals like *Withania somnifera*,^[21] *Asparagus racemos* [22] have exhibited significant vaccine adjuvant activity in experimental systems, which have valuable applications in immunobiological industry. An IND application of Lupin Ltd. is in process and a US patent has been granted for development of herbal-based antipsoriatic composition containing *Argemone Mexicana* [23]. Standardized fraction of guggulipid from *Commiphora wightii* developed by CDRI has been marketed (Guglip[®], Cipla Ltd) for treating hyperlipidemia and atherosclerosis [24]. RRL Jammu has commercialized *Boswellia serrata* gum resin as NSAID (Non-Steroidal Anti-Inflammatory Drug) (Sallaki[®] Gufic). It is also hypolipidemic. E.g. Treatment of *Epilepsy* in Ayurveda.

Definition

In most Ayurvedic texts, epilepsy has been mentioned as Apasmara or Apasmrti, and has been described as one of the earliest eight diseases known (Diagnosed) that can be controlled only with medical therapies and can sometimes be incurable and remain uncontrolled.^[25]

Clinical Description, Classification and etiology

It is classified as

Prodromal symptoms and signs (purvarupa):- Contraction of eyebrows, constant irregular movement of eyes, hearing of such sounds as are non-existent, excessive discharge of saliva and nasal excreta, disinclination of abdomen, body aches, transient blackout, giddiness, profuse sweating, increased thirst, fainting, hallucination, falling and insomnia [25].

Rupa:-

It is divided into four types according to the dominant *dosa* (humour) involved in its pathogenesis:

Vataja

Pittaja

Kaphaja

Sannipataja

In Ayurveda, three basic factors have been implicated for the etiology of epilepsy.

- [a] Endogenous factors (genetic, congenital, constitutional, enzymatic disturbances and idiopathic)
- [b] Exogenous factors (intake of unwholesome and unhygienic foods, aggravation of vata dosa due to trauma, worm and other environmental factors).
- [c] Psychological factors (excessive worry, grief, fear, passion, anger, anxiety and excitement).

The aggravated *dosa* spreads throughout the body through the nerves (*dhamanis*) leading to manifestation of the epileptic fit in the form of shaking jerks or convulsions (*akshepaka*) or episodes of brief unconsciousness without shaking (*apatantraka*) [25].

Clinical examination and diagnosis

A comprehensive evaluation of the patient (*rogi pariksha*) precedes the disease diagnosis (*roga pariksa*). Ayurveda emphasize on a detailed history of the patient for a correct diagnosis.

Treatment of Epilepsy

Various treatment modalities that include strong elimination and alleviation therapies, depending upon specific requirements are mentioned as being useful for epilepsy patients. When epilepsy is associated with extrinsic factors, then *mantras* (hymns) have been recommended. The physicians advised to first take steps for the awakening of heart channels and mind blocked by *dosas* (humors) by drastic emesis (*Vatika Apasmara*), enema (*Paittika Apasmara*) and purgatives (*Slaismika Apasmara*). Drug formulations have been recommended only after the patient has been cleansed by all means and consoled well [26]. A wide variety of *ghrtas* (purified butters) have been recommended for internal use. One of the most important

among these is *Maha Panca Gavya Ghrta*. Use of mixtures of *ghrta* and *taila* (oil) cooked with drugs has also been mentioned.

Oils cooked with different herbal and animal products have been recommended for anointing the body of the patient. Even *nasyas* (nasal applications) have been recommended. The use of a wide variety of *anjanas* (collyriums) and *anjana vartikas* (collyriu sticks) to bring the patient to senses has also been mentioned. A variety of Ayurvedic medicines for epilepsy available in the Indian market include: *Asvagandhadyarishta*, *Bali Tail*, *Brahmi ghruta*, *chandanadi tail*, *Chaturmukha rasa*, *haratala bhasma*, *Kalyanaka ghruta*, *Kumaryasava*, *Mahakalayanaka ghruta*, *Mahamrutyunjaya rasa*, *Rajata bhasma*, *saarasvatarishta*, *sarpagandha vati*, *Svarna bhasma*, *Svarnamakshika bhasma*, *Vaatakulantaka rasa*, and *Yogendra rasa* [25]. The modes of administration of drugs for epilepsy recommended in Ayurveda include external applications, internal use, application in the eyes and nose. The only first-aid measure recommended in epilepsy is blood-letting (*Siravedha*) from the veins of the temples. Cauterization of both the parietal bones with needles (*Soocivedha*) has also been mentioned [26].

Eligibility Criteria

Phase-I:-normal volunteer

Phase-II and Phase-III:-in case of these phases patients are selected as per the treatment regimen.

e.g. for the study of the vijaysar (*Pterocarpus marsupium*) in diabetic patients used [5].

Sample Size

The sample size is calculated by considering the difference in the magnitude of effect expected between the treatment [4].

Study Design

One group- all patients receiving single treatment

Multiple group- different groups of patients receiving different treatments

Parallel group- same groups of patients receiving different treatments one after another[4]

A multicentric study by the Indian Council of Medical Research (ICMR) showed promising results that a preparation from *Pterocarpus marsupium* was effective in reducing levels of blood glucose and glycosylated haemoglobin in patients with non-insulin-dependent diabetes mellitus [27]. Analysis of most frequently used plant based therapies in Ayurvedic system revealed that 43% of them have been tested on humans while 62% have been the subject of one or more animal studies. Among these drugs having sufficient clinical data are guggul, brahmi, ashwagandha, amlaki, guduchi, kutki, shatavari and shunthi [28]

Pharmacopoeia of India (1996)[29] covers few botanical monographs like clove, guggul, opium, mentha, senna, and ashwagandha. The Ayurvedic Pharmacopoeia of India gives monographs for 258 different Ayurvedic drugs. The standards mentioned are quite inadequate to build quality of the botanical materials [30]. Indian Drug Manufacturers Association has published Indian Herbal Pharmacopoeia (2002) [31] with 52 monographs on widely used medicinal plants growing in India where scientific data have been incorporated.

Dosage Schedule

Ancient texts describe the wide dose range for a particular drugs and the ayurvedic physician has to choose the perfect dose depending upon various factors enlisted under Dashavidha pratiksha [4].

Efficacy and Safety Studies

Clinical trials should be conducted with appropriate controls, e.g. by using the study design. During the drug development periods, clinical studies are done in three phases.

Phase-I in this phase the 20-60 healthy volunteers are included

Phase-II in this phase generally 100-200 patients are included.

Phase-III in this phase clinical trials are usually conducted in 600-1000 patients at multiple medical centers [6].

Safety is the main concern when considering herbal preparations. Ayurvedic herbs are potent, and some contain constituents, which could be potentially toxic if taken in large amounts or over a long period of time. For this reason, the supervision of a trained practitioner is recommended and encouraged. Contraindications to the use of Ayurveda include traumatic injuries, acute pain, advanced disease stages, and those requiring surgery. Sweet flag, vacha, (*Acorcus calamus*) is presently classified as an unsafe herb for internal usage by the FDA. Amlaki (amla, *Emblica officinalis*) should be avoided at bed time to prevent harmful effects on teeth. Pippali (*piper longum*) used in asthma should be avoided and should be consumed with milk. Ayurvedic preparations can often change the bioavailability of allopathic drugs so a medical professional should be consulted before combined use. It is important not to self-diagnosis, but rather to work with a qualified Ayurvedic practitioner who can assess individual contraindications of Ayurvedic treatments.

End Points

These are decided on the basis of the expected effect of the investigational drugs.

E.g. At the end of the study of an ant diabetic drug we expect that the glycosylated hemoglobin at the end of one month's treatment will fall by at least 0.5% [4].

Documentation

Case record form is a tool for collecting study data specified in the clinical study and is necessary to capture relevant data and is facilitate efficient and complete data processing analysis and reporting [7].

RESULTS

The research is conducted at all times by competent and qualified persons who act with total integrity and impartiality and who have been made aware of, and are mindful of, the ethical consideration to be born in mind in respect of such research of experiment. The precaution and risk minimization [5].

It is mandatory that all proposals on clinical research involving human subjects should be cleared by an appropriately constituted International Ethical Committee (IEC), also referred to as Institutional Review Board (IRB) in many countries. Safeguard the welfare and the rights of the participants. The Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the ethics of the approval programmers till the same are completed.

Natural products extracts of therapeutic relevance are of paramount importance as reservoirs of structural and chemical diversity. A recent review on national pharmacopoeias from several countries reveals at least 120 distinct chemical substances from different plants that have utility as lifesaving drugs [32]. This has been achieved through chemical and pharmacological screening of only 6% of the total plant species. Untapped, hidden wealth in the flora needs to be unearthed and explored to cure diseases like AIDS, cancer, diabetes, etc. Recently, NIH has started extensive research for anti-inflammatory compounds from turmeric, ginger and boswellia with the aid of Ayurvedic knowledge. Screening of different plants for novel anticancer compounds is also in progress with reference experiential data from traditional systems [33]. Botanical immunodrugs from traditional medicine can provide newer opportunities to bioprospect diverse and synergistic chemical moieties, which in combination might act on multiple targets and improve the therapeutic spectrum [34].

India has progressive research institutes like Central Drug Research Institute (CDRI), Central Institute of Medicinal and Aromatic Plants and National Botanical Research Institute at Lucknow, Regional Research Laboratories (RRL), at Jammu, Bhubaneshwar and Jorhat, National Chemical Laboratory at Pune, which routinely undertake research on medicinal plants. Most of them are involved in standardizing the herbal medicines and isolating active compounds. Few selected crops have been taken for improvement yet there is a need for research on quality planting materials for farmers, conservation of endangered species and to prevent exploitation

of the natural resources. Reserpine (antihypertensive from rauwolfia) is an extremely valuable contribution from Ayurvedic systems. Curcumin [35] (anti-inflammatory from turmeric), withaferin A [36] (anti-inflammatory from ashwagandha), kutkoside [37] (hepatoprotective from kutki), andrographolide [38] (hepatoprotective from andrographis) and vasicine [39] (bronchodilator and expectorant from vasaka) are chemical entities with attractive scaffolds for drug discovery.

Planning for the Clinical Evaluation of Ayurvedic Antirheumatic drug

Sameerapannag and Pimpalli Churna

Level of study:- O.P.D/I.P.D.

Design of Study:-Single Blind Study/Double Blind Study.

Centre for the Study:- -----

Number of Groups:-Single/multiple/parallel.

Schedule of Therapy:- Contain Dosing of drugs.

Duration of Study:- for antirheumatic study duration is Six weeks.

Criteria for Diagnosis:- Consists of following points-

Morning Stiffness.

Arthritis of hand Joints.

Symmetrical arthritis.

Rheumatoid nodules.

Radiological changes.

Criteria for Assessment:-

Clinical Parameters:-

Morning Stiffness.

Pain on rest.

Pain on motion.

Swelling.

Tenderness.

Muscle power.

Restricted movement.

Subcutaneous nodules.

Laboratory Parameters: -

Erythrocyte Sedimentation Rate.

Rheumatoid arthritis test.

DISCUSSION

Practitioners of modern medicine and ancient medicine like Ayurveda should join hands with researchers to understand the scientific basis of Ayurvedic therapies using the current scientific principles and technologies. Modern and Ancient medicine systems should be combined to plan effective health-care delivery systems for better epilepsy care. Ayurvedic



therapies could be scientifically tested and then used at least as add-on therapies like the new anti-epileptic drugs (AEDs). Ayurvedic and other ancient therapies could form the basis of the future “New AEDs”.

ACKNOWLEDGEMENTS

Authors are thankful to Principal, all staff members & management of ASPM's K.T.Patil College of Pharmacy, Osmanabad for providing needful.

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