

Review Article

Herbal medicaments in endodontics – Current guidelines for *in vivo* studies in India

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Abstract

Elimination of bacteria from infected root canal systems is a challenging task. Various techniques have been described to reduce the number of bacteria within the root canal system, which include chemomechanical instrumentation, use of various irrigants to remove or dissolve organic and inorganic debris, and to destroy bacteria. The intracanal medicament plays a key role in the success of root canal treatment. With the rise in bacterial resistance to antibiotics, there is considerable interest in the development of other classes of antimicrobials for the control of infection. Natural products are known to play an important role in human life. The use of herbal products as mouthwash has been tried and tested in the literature. However, the use of herbal intracanal medicament has been shown promising results when used under *in vitro* conditions, but *in vivo* studies are very scarce. This may be due to the limited supporting literature available to use it as intracanal medicament in patients due to the ethical concern. Hence, the purpose of this review is to highlight the current guidelines (laid by the drugs and cosmetics act as per the Gazette of India) regarding the use of herbal medicaments for the clinical trials in endodontics.

Keywords: Endodontics; guidelines; herbal products; intracanal medicaments

INTRODUCTION

The purpose of root canal therapy is to disinfect the root canal system as thoroughly as possible and to fill it in all its dimensions.^[1] This involves a process called “chemomechanical preparation,” wherein chemically active solutions are used along with the mechanical instrumentation of the root canal system.^[2]

However, it has been proved that mechanical instrumentation with antibacterial irrigation causes only 50%–70% of infected canals free of microorganisms. Hence, additional methods such as the use of intracanal medicaments are required to maximize disinfection of root canal system and kill as many bacteria as possible.^[3]

Hence, the intracanal medicament plays a key role in the success of root canal treatment. With the rise in bacterial resistance to antibiotics, there is considerable increase in the interest for the development of other classes of antimicrobials for the control of infection. Natural products are known to play an important role in human life. Various parts of the plants such as root, bark, seed, and leaves have been an important source of medicine since thousands of years. In recent years, a predominant interest has been observed in evaluating different plant extracts for their antimicrobial properties against bacteria causing dental caries and periradicular pathology. The constant increase in antibiotic-resistant strains and side effects caused by synthetic drugs has prompted the researchers to look for herbal alternatives in endodontics.^[4]

The use of herbal products as mouthwash has been extensively studied and proved in literature. Even though the use of herbal intracanal medicament has shown promising results when used under *in vitro* conditions, but *in vivo* studies are very limited.^[5,6] This may be due

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to the limited supporting literature available to use it as intracanal medicament in patients due to the ethical concern. Hence, the purpose of the present article is to highlight the current guidelines and literature regarding the use of herbal medicaments for *in vivo* clinical trials in endodontics.

PHYTOTHERAPEUTIC SUBSTANCES USED IN DENTISTRY

These are generally classified into three groups:

1. Plant products
2. Animal products
3. Mineral origin.

Herbal drugs used in dentistry can be classified based on their actions as:^[7]

1. Antimicrobial action: *Acacia nilotica* (babool), *Aloe barbadensis*, *Arctium lappa*, *Azadirachta indica* (Nimba), *Carvacrol*, *Casearia sylvestris* (Gulkhair), *Allium sativum* (Garlic), *Marticaria recutitia*, *Camellia sinensis* (Tea), *Citrus limonum* (Lemon), *Morinda citrifolia*, *Propolis*, *Psidium guajava* (Guava), *Psoralea corylifolia* (Bakuchi), *Rhus lancia* (African Sumac), *Salavadora persica* (Peelu), *Syzgium aromaticum* (Clove), *Melaleuca alternifolia*, *Curcuma longa*, and *Glycyrrhiza glabra*
2. Antiinflammatory action: *C. sylvestris*, *Marticaria recutitia*, *C. sinensis*, *M. citrifolia*, *Propolis*, *P. guajava*, *Rhus lancia*, *Salavadora persica*, and *Glycyrrhiza glabra* (Yashtimadhu)
3. Sedative and anxiolytics: *A. lappa*, *Marticaria recutitia*
4. Miscellaneous action (endodonticirrigants, medicaments and endodontic retreatment): *lappa*, *A. indica*, *C. sylvestris*, *Allium sativum*, *M. citrifolia*, *C. sinensis*, *Citrus limonum*, *Orange Oil*, *Propolis*, *Salavadora persica*, *M. alternifolia*, *Triphala*, *C. longa* (Turmeric).^[7]

The prime benefits of using herbal alternatives in dentistry are cost-effectiveness, readily available, less toxic, and lack of microbial resistance reported so far. On searching the literature, there are very few clinical trials reported to evaluate the antimicrobial efficacy and postoperative pain assessment of the herbal medicaments in endodontics.^[6,8]

CRITERIA TO INTRODUCE NEW DRUGS FOR CLINICAL TRIALS

The national policy on traditional and alternative medicine in the form of Drug and Cosmetic Act 1940 and Drug and Cosmetic Rule was introduced in 1940, which was updated in several times. The Government of India recognized the traditional Indian System of Medicine (ISM) in 1959, and updated Drug and Cosmetic Act. For different ISM, several expert committees were

formed time to time and the earliest was in 1962. In the year 1969, separate chapter related to Ayurveda, Siddha, and Unani drugs was inserted by Act 13 of 1964 in the Act, which partly similar as those for conventional pharmaceuticals. In 2006 and 2008 guideline for the evaluation and analysis of drugs under ISM was given under Drug and Cosmetic Rule 1945.^[9]

Before the drug product can be approved for import or manufacturing and marketing in the country, the demonstration of safety and efficacy of the drug product for use in humans is essential. The Rules 122A, 122B and 122D, 122 DA, 122DAA, 122E of Drugs and Cosmetics Rules and Appendix I, IA and VI of Schedule Y, describe the information/data required for the approval of clinical trial and/or to import or manufacture of new drug for marketing in the country. However, the requirements for the approval of clinical trials and new drugs may vary depending on the nature of new drugs.^[10] In India, new drugs launched elsewhere are subjected to clinical trials alone and on local patients (typical of Phase 3 trials). The requirement for local clinical trials is based on the claims that ethnicity and environmental factors can influence the efficacy and safety of drugs.^[11] For any new drug development, the applicant has to obtain license from State Licensing Authority in Form-29 based on NOC obtained from CDSCO. Clinical trials are required to be carried out right from Phase I for new drug substances discovered in India.

Phase I clinical trials should be performed by the researchers trained in clinical pharmacology with the facilities to closely monitor. At least two participants should be used on each dose at one or two centers. Phase II clinical trials have to be carried out on 10-12 participants at each dose. These studies should usually be carried out at 3-4 centers by clinicians dedicated on the specified therapeutic areas and having required the facilities to conduct the investigations for efficacy and safety.^[10] Phase III data should be obtained on at least 100 patients distributed over 3-4 centers primarily to confirm the efficacy and safety of the drug.

If the drug is a new drug substance discovered in India and not marketed in any other country, Phase III data should generally be obtained on at least 500 patients distributed over 10-15 centres. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s).^[10]

The Drugs Controller General of India (DCGI) is an official of the CDSCO who is the final regulatory authority for the approval of clinical trials in the country. His ambit, in addition, also extends to the inspections of trial sites, inspections of sponsors of clinical research and manufacturing facilities in the country, oversight of the Central Drugs Testing

Laboratory (Mumbai) and the Regional Drugs Testing Laboratory as also heading the Indian Pharmacopeia Commission among various other roles, responsibilities, and functions. DCGI monitors the quality of manufacturing, marketing, import, and distribution of drugs in India. It monitors any dispute regarding the quality of drugs and maintains uniformity in the enforcement of the Drugs and Cosmetics Act. All the research institutes conducting research are under the direct supervision of DCGI.^[12]

The Indian Council of Medical Research is the apex body that governs the formulation, coordination, and promotion of biomedical research. It receives funding from the Ministry of Health and Family Welfare and the Department of Health Research, Government of India.^[12]

Registration of Ethics Committees that approve studies (Rule 122DD):

- Investigators and Administrators of Academics Institutes should ensure that their Institutional Ethics Committees (IECs) are registered with the central licensing authority and the registration renewed at the end of 3 years. This is mandatory for Regulatory Clinical Trials.^[13]

APPROVAL FROM INSTITUTIONAL ETHICS COMMITTEE

- All clinical trials need to have approval from the IEC
- A recent regulatory change with respect to investigator initiated studies is that academicians who carry out trials with “new drugs” no longer need approval from the DCGI for conducting the clinical trial and approval from IEC should be taken. This is provided that these studies are not intended for generating data to make a regulatory submission.^[14]
- In case the IEC feels that there could be a potential overlap between the academic and regulatory purposes of the trial, they should notify the office of the DCGI. If the IEC does not hear from the DCGI within 30 days, it should be presumed that no permission is needed from the licensing authority.^[14]

REGISTRATION OF THE CLINICAL TRIAL WITH THE CLINICAL TRIALS REGISTRY OF INDIA

The CTRI is a free, online portal that allows both investigator initiated and regulatory studies to be registered. It is recommended that all studies are registered at a public portal. However, for Regulatory Clinical Trials, registration in CTRI is mandatory from June 2009.^[15]

- Registration must be done before the first participant is enrolled
- Registration is important from a publication standpoint, as editors of many Biomedical Journals will not accept

articles that have interventional studies not registered with a Clinical Trials Registry.^[16]

WHAT ARE THE CURRENT GUIDELINES FOR USE OF HERBAL MEDICAMENTS IN A CLINICAL TRIAL?

The Gazette of India in November 30, 2015, in a notification by the Ministry of health and Family welfare has made following amendment in the Drugs and Cosmetics Rules, 1945, namely:

“In rule 2 of the Drugs and Cosmetics Rules, 1945 (hereinafter referred to as the said rules), after clause (ea) the following clause shall be inserted, namely :—“(eb). “Phytopharmaceutical drug” includes purified and standardized fraction with defined minimum four bioactive or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route.”^[17]

In Indian regulations, the major classes of herbal products are:

- a. Classical Ayurveda drugs as mentioned in the authoritative books of Ayurveda system, which are manufactured and named in accordance with the formulations described in the authoritative texts. These classes of herbal medicaments do not require the approval from the DCGI for conducting the clinical trial. However, a clinical trial registration should be done after obtaining the approval from the Institutional Ethical Committee of the research institute or university
- b. Patent or Proprietary medicine makes the use of ingredients referred in the formulations of authoritative texts but with intellectual intervention, innovation, or invention to manufacture the products different from the classical medicine.^[18]

Hence, the researchers in dentistry can utilize the integration of Ayurvedic and other Indian traditional medicine in clinical practice, especially in endodontics which will help to avoid the antibiotic abuse as well as the development of microbial resistance to antibiotics. Although efforts are needed to overcome barriers such as irrational use, quality control, and standardization issues, proper monitoring and periodic revision of regulations are absolute necessary to promote herbal formulation in endodontics.

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Conflicts of interest

There are no conflicts of interest.

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