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Use of natural substitutes as an intracanal medicament in the endodontics-An update for *in vivo* studies

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The success of root canal treatment depends on the elimination of bacteria by chemo-mechanical instrumentation and use of various irrigants to remove or dissolve organic and inorganic debris.The intracanal medicament also has an important role in the outcome 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. Use of Herbal intracanal medicament has been shown promising results when used under *in vitro* conditions, but very limited clinical trials reported due to the ethical concern. Hence, this review highlights 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.

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Introduction

The main goal of endodontic therapy is to disinfect the root canal system and to fill it in all its dimensions[1]. This involves the use of chemically active solutions along with 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 the root canal system and kill as many bacteria as possible[3].

The intracanal medicament plays a key role in the success of root canal treatment. With the rise in bacterial resistance to antibiotics, there is a considerable increase in the interest in the development of other classes of antimicrobials for the control of infection. In the search for novel irrigants and intracanal medicaments with good biocompatibility and antimicrobial activity, researchers have explored several potential agents of natural origin. Evaluation of antimicrobial activity of neem, propolis, turmeric, liquorice, grape seed extracts, Triphala, Green tea polyphenols (GTP) has shown good results as compared to that of sodium hypochlorite as root canal irrigants[4-6]. India has a rich source of medicinal plants that are widely distributed throughout the country[7].

Even though the use of herbal intracanal medicament has been shown promising results when used under *in vitro* conditions[8-11], but *in vivo* studies are very limited[12,13]. This may be due to the scarce literature available to use it as intracanal medicament under *in vivo* conditions due to the ethical concern. Hence, the goal of the present paper is to focus on the current guidelines and literature regarding the use of herbal medicaments for *in vivo* clinical trials in Endodontics.

Natural substitutes used in dentistry

These are generally classified into three groups, namely plant products, animal products, and mineral origin[14]. In dentistry, they are used as antimicrobial agents, anti-inflammatory agents and sedative & anxiolytics.

The miscellaneous uses include endodontic irrigants, medicaments. Herbal extracts have been used in dentistry for reducing inflammation[15], as antimicrobial plaque agents[16], for preventing the release of histamine and asantiseptics[17], antioxidants[18], antimicrobials[8], antifungals[19], antibacterials[7], antivirals and analgesics[12].

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The prime benefits of using herbal alternatives in dentistry are cost‐ effectiveness, readily available, less toxic and lack of microbial resistance reported so far. Even though the results of *in vitro* studies appear promising, there are very few studies reported to evaluate clinical efficacy and safety factor[12-13].

The Drugs & Cosmetics Act, 1940 and Rules 1945 have entrusted various responsibilities to central & state regulators for the regulation of drugs and cosmetics. It envisages uniform implementation of the provisions of the Act & Rules made thereunder for ensuring the safety, rights, and well being of the patients by regulating the drugs and cosmetics.

Central Drugs Standard Control Organisation (CDSCO)

The CDSCO is responsible for approval and regulation of New Drugs and Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act. Under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India is the National Regulatory Authority (NRA) of India. Its headquarter is located at FDA Bhawan, New Delhi, and also has six zonal offices, four sub zonal offices, thirteen Port offices and seven laboratories spread across the country[20].

The Drugs Controller General of India (DCGI)

DCGI is an official of the CDSCO who is the final regulatory authority for the approval of clinical trials in the country. His ambit also extends to 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[20].

Academic clinical trial

All clinical trials need to have approval from the Institutional Ethical Committee. No permission for conducting an academic clinical trial is required for any drug from the Central Licencing Authority where,— (i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and (ii) the clinical trial referred to in clause (i) has been initiated after prior approval by the Ethics Committee for a clinical trial; and (iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority; and (iv) the observations of such clinical trial are not used for promotional purposes[21].

Clinical Trials Registry of India (CTRI)

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[21]. 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 papers that have interventional studies not registered with a Clinical Trials Registry[22].

The current guidelines for use of herbal medicaments in a clinical trial

Indian Government has already recognized *Ayurveda* to be practised as the official system of medicine. In India, rules for practice and education of *Ayurveda* have been laid in 1970 by the Indian Medicine Central Act whereas herbal medicines of *Ayurveda* are governed by Drugs and Cosmetics Act 1940 (Chapter IV A)[23]. The Gazette of India on 30 Nov 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 bio-active or phyto-chemical 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"[24].

Herbal products

In Indian regulations, herbal drugs are regulated under the Drug and Cosmetic Act 1940 and Rules 1945, where regulatory provisions for Ayurveda, Unani, Siddha medicine are clearly laid down. Department of AYUSH is the regulatory authority and mandate that any manufacture or marketing of herbal drugs have to be done after obtaining manufacturing license, as applicable. There are two major classes of Herbal products[25].

Classical *Ayurveda* drugs

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 approval from the Institutional Ethical Committee of the research institute or university.

Patent or proprietary medicine

Patent or proprietary medicine makes use of ingredients referred in the formulations of authoritative texts but with intellectual intervention, innovation or invention to manufacture products different from the classical medicine[26].

Conclusion

The herbal products today symbolize safety in contrast to the synthetics that are regarded as unsafe to humans and the environment. Hence, to avoid antibiotic abuse as well as the development of microbial resistance, the researchers in dentistry can utilize the integration of Ayurvedic and other Indian traditional medicine in clinical practice, especially in endodontics. Proper monitoring of these medicaments periodic revisions of the regulations needs to be done to avoid irrational use, quality control and standardization issues to promotethe use of herbal medicaments in Endodontics.

Conflict of interest

Nil.

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