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BOSWELLIC ACIDS IN ENDODONTICS: AN OVERVIEW

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ABSTRACT

Therapy of root canal may be carried out as an alternative to dental extraction on a tooth in which the nerve has been injured or has died. Management of root canal is carried out because the offending canal is infected or the pulp severely inflamed. The aim of *canalis radicis dentale* treatment is to eliminate bacteria from, and prevent their further entry to the root canal system. The method involves cleaning and removal of any remaining bacteria and nerve canal contents. Removal of any infection improves the chance of success, and irrigation of the canal with certain types of solutions during the procedure can be helpful in achieving this. Several antimicrobial irrigating solutions are available. Hypochlorite solution; e.g. NaOCl in a variety of strengths has been used by dentists for many years, but concerns have been raised about its toxicity and the occasional report of pain when higher concentrations are used. An antimicrobial; e.g. chlorhexidine has also been used in a variety of concentrations as either a solution or gel. Antibiotic and a detergent (MTAD) combination have been recently developed and are being used increasingly. Shaping the canal with hand and rotary instruments under constant irrigation to remove the inflamed and necrotic tissue, microbes/biofilms, and other debris from the root-canal space. The purpose of using instrumentation is to facilitate effective irrigation, disinfection, and filling.

KEYWORDS

Boswellic acids and *Canalis radicis dentale*.

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INTRODUCTION

Irrigation

Irrigation has a central role in endodontic treatment. While using instrumentation, the irrigants facilitate the removal of microorganisms, tissue remnants, and dentin chips from the root canal through a flushing mechanism. Irrigants assist in prevention of packing of the hard and soft tissue in the apical root canal and extrusion of infected material into the periapical area. Many used irrigating

preparations dissolve either organic or inorganic tissue in the root canal. Moreover, several irrigating solutions have antimicrobial activity and actively kill bacteria and yeasts when introduced in direct contact with the microorganisms. However, many irrigating preparations also have cytotoxic potential, and they may cause severe pain if they gain access into the periapical tissues[2].

An ideal irrigant must satisfy all or most of the positive characteristics

- Washing action (helps remove debris)
- Reduce instrument friction during preparation (lubricant)
- Facilitate dentin removal (lubricant)
- Dissolve inorganic tissue (dentin)
- Penetrate to canal periphery
- Solublized organic materials and tissues (dentin collagen, pulp tissue, biofilm)
- Kill bacteria and yeasts (also in biofilm)
- Do not Cause inflammation of vital periapical tissue, no caustic or cytotoxic effects
- Do not weaken tooth structure

Types of Current Irrigants

Nowdays, the used irrigants during cleaning and shaping can be divided into antibacterial and decalcifying agents or their combinations. They may have sodium hypochlorite (NaOCl), chlorhexidine, ethylenediaminetetraacetic acid (EDTA), and a mixture of tetracycline, an acid and a detergent (MTAD).

Sodium Hypochlorite

Hypochlorite solution (NaOCl common bleach) is the most widely used root canal irrigant. It is an antibacterial and economic lubricant that has been used in dilutions ranging from 0.5% to 5.25%. Nacent Cl in NaOCl dissolves vital and necrotic tissue by breaking down proteins into amino acids. Reducing the concentration of the preparation reduce its toxicity, antibacterial effect and ability to dissolve tissues. Increasing its volume or warming it increases its effectiveness as a root canal irrigant[3]. The major privileges of NaOCl include its ability to dissolve organic substances present in the root canal system and its affordability.

The major disadvantages of this irrigant are its cytotoxicity when injected into periradicular tissues, foul smell and taste, ability to bleach clothes and ability to cause corrosion of metal objects[4]. In addition, it does not kill all bacteria[5], nor does it remove all of the smear layer. It also alters the properties of dentin[6].

Chlorhexidine

Chlorhexidine gluconate (CHX) has been used for the past 50 years for caries prevention[7] in periodontal therapy and as an oral antiseptic mouthwash.

It has a broad-spectrum antibacterial action, sustained action and low toxicity[3]. Because of these properties, it has also been recommended as a potential root canal irrigant[7]. The major advantages of CHX over NaOCl are its lower cytotoxicity and lack of foul smell and bad taste. However, c.f. Sod. hypochlorite, it cannot dissolve organic substances and necrotic tissues present in the root canal system. In addition, like NaOCl, it is unable to kill all bacteria and cannot remove the smear layer[8].

Ethylene diamine tetraacetic Acid (EDTA)

Chelating agents such as ethylene diamine tetraacetic acid (EDTA), citric acid and tetracycline are used for removal of the inorganic portion of the smear layer[8]. NaOCl is an adjunct solution for removal of the remaining organic components. Irrigation with 17% EDTA for one minute followed by a final rinse with NaOCl is the most commonly recommended method to remove the smear layer[3]. Longer exposures can cause excessive removal of both peritubular and intratubular dentin. EDTA has little or no antibacterial effect[10].

MTAD

A good substitute solution to EDTA for removing the smear layer is the use of BioPure™ MTAD™ (DENTSPLY Tulsa Dental Specialties, Tulsa, Okla.), a mixture of a tetracycline isomer, an acid (citric acid) and a detergent[11]. MTAD was developed as a final rinse to disinfect the root canal system and remove the smear layer. The efficacy of MTAD to completely remove the smear layer is enhanced when a low concentration of NaOCl (1.3%) is used as an intracanal irrigant before

placing 1 ml of MTAD in a canal for 5 minutes and rinsing it with an additional 4 ml of MTAD as the final rinse[11]. It appears to be superior to CHX in antimicrobial activity[13]. In addition, it has sustained antibacterial activity, is biocompatible and enhances bond strength[3].

Types of intracanal medication

Intracanal medicaments have been used to disinfect root canals between appointments and reduce interappointment pain[14]. The disinfectants can be divided into phenolic compounds such as camphorated monochlorophenol, cresatin, aldehydes such as formocresol and glutaraldehyde, and halides, as well as other materials like calcium hydroxide [Ca(OH)2] and some antibiotics[15]. These compounds are potent antibacterial agents under laboratory test conditions, but their efficacy in clinical use is unpredictable[14]. Some of the aldehyde derivatives have been proposed to neutralize canal tissue remnants and to render them inert. These may be utilize to fix fresh tissues for histological examination, but they may not effectively fix necrotic or decomposed tissues. According to one report[16] fixed tissues are not inert and may become more toxic and antigenic after fixation. Intracanal treatments have also been used clinically to prevent post-treatment pain. Studies have shown, however, that routine use of these materials as intracanal medications has no significant effect on prevention of pain[14].

Calcium Hydroxide

Ca(OH)2 is a substance that inhibits microbial growth in canals[18]. The antibacterial effect of Ca(OH)2 is due to its alkaline pH. It also dissolves necrotic tissue remnants and bacteria and their byproducts[3]. It can be placed as a dry powder, a powder mixed with a liquid such as water, saline, glycerine or local anesthetic, or a proprietary paste supplied in a syringe[3]. Due its toxicity[20], Ca(OH)2 should be placed within the canal with the aid of a file or a needle. The presence of the material into the periapical tissues can cause tissue necrosis and pain for the patient. Calcium hydroxide can be removed from the canal by using irrigants such as saline, NaOCl, EDTA or MTAD.

Corticosteroids

Corticosteroids are anti-inflammatory agents that have been advocated as intracanal medicaments to reduce postoperative pain[21]. An animal study has shown a reduction of inflammatory cells in periapical tissues following supraperiosteal infiltration of dexamethasone into the buccal vestibule of rats[22]. There is no significant clinical evidence that suggests that they are effective in patients with very high pain levels[23]. The use of corticosteroids in patients with irreversible pulpitis and symptomatic apical periodontitis may be beneficial[21,24].

Chlorhexidine Gel

A 2% CHX gel has recently been advocated as an intracanal medicament. 49 It can be used alone in gel form or mixed with Ca(OH)2. When used for seven days to medicate bovine teeth[25] or human teeth[26], CHX gel provides antimicrobial activity for up to 21 days after contamination. When it is used in combination with Ca(OH)2, the antimicrobial activity of this mixture is greater than the combination of Ca(OH)2 and saline[27].

Specific aim

The main aim of an endodontic treatment is to remove the diseased tissue, eliminate bacteria from the root canal system and prevent its recontamination[28]. Irrigation is carried out to reduce the number of bacteria in the root canal system and to control the periapical disease[29]. A wide variety of synthetic antimicrobial agents have been used over the years as endodontic irrigants. Because of the increased antibiotic resistance to these antimicrobial agents, toxic and harmful side effects of few common antibacterial agents, there is a need for alternative agents which are affordable, non-toxic and effective. It has been found that natural plant extracts could be used as effective endodontic irrigants[30].

Most physicians rely on a combination of symptoms, clinical examination and laboratory indices to make a diagnosis and to assess the severity of a given disease. Symptoms and laboratory markers often measure different aspects of the disease, however, and having an objective

measurement of disease activity is important. Indices of disease activity[31] and prognostic scoring systems have, therefore, been developed. Disease activity indices often reflect the patients' general well-being and quality of life, however, rather than their intestinal inflammation, and prognostic scoring systems are often complicated to use.

Cytokines are generally excellent markers of inflammation

Cytokines, which are polypeptides secreted by leucocytes and other cells, act as modulators of immune and inflammatory responses and can be divided into inflammatory and anti-inflammatory cytokines. Inflammatory cytokines include interleukin (IL)-2, IL-6, IL-8, interferon (IFN)-c and tumour necrosis factor (TNF)-a, whilst anti-inflammatory cytokines include IL-4, IL-10 and IL-13. Inflammatory cytokines mediate and enhance inflammation, whilst anti-inflammatory cytokines generally suppress inflammation. *Cytokines are the guiding factors of inflammation* and its progression to tissue necrosis[32]. They are potential targets for new therapeutic strategies in the treatment of inflammatory and allergic diseases[33]. In addition, levels of cytokines have been correlated with the progression of bacterial infections[34].

An ideal marker of inflammation should be easy and cheap to measure, and measurements should be reproducible between laboratories and patients. Ideally, inflammatory markers should not only be able to identify individuals at risk for a disease, they should also be able to follow up on the disease activity and monitor the effect of treatment, and they should be of prognostic value in assessing morbidity or mortality rates. At the moment, no single laboratory marker has proven to be the gold standard[35].

Several inflammatory markers such as cytokines, total leukocyte count, C-reactive protein (CRP), among others, are being assessed:

C-reactive protein

CRP has been the most frequently used marker[36,37]. The methods used to measure other markers such as cytokines are, in general, inadequate for routine clinical use and these proteins have a very short half-life. The laboratory procedures to assess fibrinogen are not well established, despite the consistent population data. Total leukocyte count and globular sedimentation rate have a questionable value regarding their clinical applicability. On the other hand, there are well-established methods to measure ultrasensitive CRP (us-CRP). Additionally, this is a stable marker that has a long half-life (18 to 20 hours) and its measurement can be performed in either frozen or fresh plasma, without the need for special collection procedures[37-38].

IL-2

Acytokine secreted by CD4+ T cells, primarily acts to stimulate T-cell proliferation, activates natural killer cells and promotes B-cell function through T helper cell activation. In addition, IL-2 activates the transcription of other inflammatory cytokines and increases the cytolytic activity of natural killer cells[39].

IL-6

Displays multiple biological effects and acts as a major mediator of the host response following tissue injury and infection as well as inflammation. It increases the levels of acute-phase proteins, C-reactive protein, serum amyloid A and fibrinogen[40]. IL-6 causes up-regulation of adhesion molecules and induces angiogenesis leading to increase in vascular permeability and inflammatory oedema.

IL-8

Is a potent chemokine with strong chemoattractive activity for neutrophils. In addition to recruiting neutrophils, IL-8 stimulates neutrophils to a higher state of activation. It is rapidly synthesized at local sites of inflammation where it fulfils its function of recruiting and activating acute inflammatory cells[41].

TNF-a

Is a prominent inflammatory mediator and absolutely central in initiating the cascade of inflammatory reactions of the immune system including induction of cytokine production, activation and expression of adhesion molecules and stimulation of cell proliferation. It coordinates the early host response to injury and thus represents an important point of regulation in inflammatory diseases[42].

IL-10

Is a key anti-inflammatory cytokine. It is the main inhibitor of cytokine synthesis and macrophage activity. It also inhibits the production of the proinflammatory cytokines like TNF-a, IL-1b and IL-6 in various cell types[43]. IL-10 production increases during inflammatory processes exerting an immunomodulatory role[44].

IFN-c

Is a predominant cytokine in immune responses, with strong inflammatory properties. It plays crucial roles in both innate and adaptive immunity as well as in inflammation. It is the main trigger for production and release of reactive oxygen species from macrophages such as reactive oxygen intermediates and reactive nitrogen intermediates. These powerful oxidants bestow macrophages with cytostatic or cytotoxic activity against bacteria, viruses, fungi, protozoa, helminths and tumour cells[45].

Measure of inflammatory markers

In biomedical research, enzyme-linked immunosorbant assay (ELISA) is the most commonly used method for measuring concentrations of inflammatory markers, especially low-abundance markers such as cytokines[46]. ELISA uses an antibody "sandwich," with one antibody to specifically detect the cytokine or receptor of interest that is fixed to a plastic well, while the second antibody is linked to an enzyme that acts as an amplification factor to enable colorimetric or chemiluminescent detection and quantitation.

However, there are documented methodological limitations that coincide with using ELISA to quantify inflammatory marker concentrations. First, for very low-abundance markers (e.g., tumor necrosis factor-alpha [TNF-α]), the ELISA can require a relatively large volume of serum for analysis (e.g., 200uL), and many studies fall short of the required threshold. Second, the cost of individual ELISAs for each of several markers can add up and be prohibitive for researchers who lack the adequate funds to conduct such measurements.

Recently, multiplex arrays, which have the ability to estimate levels of several inflammatory markers in one assay, have been developed. Compared to traditional ELISAs, they require smaller sample volume and are less expensive and more time efficient[46]. The most widely used multiplex array for measuring inflammatory markers is based on flow cytometry technology. Flow cytometric multiplex arrays use microscopic beads with several predefined colors; beads of each color are coated with antibodies specific for one cytokine, which form the capture site for that specific cytokine. The beads can then be mixed together in "panels" in which each of the differently colored bead sets represents a different cytokine, and a single serum or plasma sample is added to the "panel" of beads. Subsequently, fluorescence or streptavidin labeled detection antibodies attach to the cytokine of interest on each the differently colored bead sets. The flow cytometer uses the color of the beads to keep track of which cytokine is being measured, and fluorescent signals are used to estimate the amount of cytokine detected.

Multiplex arrays using chemiluminescence or electrochemiluminescence technology have also been developed for measuring inflammatory marker concentrations. Although the technology offers great promise, more studies are needed to evaluate the performance of multiplex assays relative to accepted ELISAs and address or confirm some of the putative limitations. For example, complications may arise because of the different range in concentrations of various antigens being assayed together; there also may be discordance between serum and plasma measurements[47] and greater sensitivity to high levels of circulating proteins in serum or plasma samples. Finally, quality control of multiplexed assays is considerably more complicated[48] and manufacturers have found it more difficult to maintain constancy in sensitivity and specificity when preparing multiplexed reagents[49].

In summary, inflammatory marker measurement using ELISA remains the standard assay for epidemiological studies. Future research should consider whether multiplex arrays can be used as a

practical alternative to ELISA for the measurement of inflammatory markers.

Boswellic Acid as anti-inflammatory

It appears that of Boswellic Acid is directly or indirectly involved in the inhibition of inflammation induced factors and/or pathways such as histamine, prostaglandins, leukotriene, 5-lipooxygenase, human leukocyte elastase, cyto-kines, a-tumor necrosis factor (TNF), and free oxygen radicals. The anti-inflammatory activity is mainly attributed to Keto boswellic acid and Acetyl keto boswellic acid[50-54].

However, few studies have investigated the exact role and specific anti-inflammatory effects of these substances[55]. Recently, the inhibitory effects of of Boswellic Acid on microsomal prostaglan- din E synthase-1 and serine protease cathepsin G have been established[56].

double blind, randomized, placebo controlled study reported reduced pain and improved physical functionality after 90 days' treatment with 5-Loxin: a commercial of Boswellic Acid extract (250 mg per day) in seventy-five patients with osteoarthritis[57]. These reports indicate the potential of Boswellic Acid in treating inflammatory diseases and suggest the value of further investigations to establish it as an herbal alternative to synthetic non-steroidal anti-inflammatory drugs (NSAIDs).

Boswellic Acids belong to pentacyclic triterpene compounds extracted from the trunks of various Boswellia species trees[58]. The genus Boswellia belongs to the family Burseraceae and more than 600 species are widespread in all tropical regions[59].

For thousands of years gum resin from the Boswellia serrata tree has been valued in diverse parts of the world. In eastern countries, it is known as "salai guggal" and in western countries it is known as "frankincense". Traditional ayurvedic medicine called for the gum to be used in the treatment of various inflammatory conditions of the skin, eye and gums, as well as respiratory disorders such as asthma, bronchitis, and laryngitis[60]. And still today, medical practitioners in India use boswellia to treat arthritis, pain and respiratory ailments[61].

Recent research[62-63] in Germany and India has shown that the pentacyclic triterpenoids present in Boswellia inhibit human leukocyte elastase and also block production of proinflammatory leukotrienes by inhibiting 5-lipoxygenase. Two of the compounds in the series, acetyl-11-keto-boswellic acid and 11-keto-boswellic acid, have been shown to be the most potent of the triterpenoids.

Using Frankincense (Boswellia sacra) Chewing Gum on the Microbial Contents of Buccal/Oral Cavity, Taif, KSA proved that Frankincense (Boswellia sacra) application can lead to remarkable decrease in inflammatory indices in comparison to drug therapy. It's a safe and low cost herbal medicine, may be feasibly applied to improve inflammation based disease of gingival as an adjunct to the conventional mechanical therapy[64].

Common uses of boswellic acid

Traditional uses

Ayurveda (Indian traditional medicine practice) describes boswellia as an active ingredient in decoctions used for the treatment of gastrointestinal diseases such as diarrhea, constipation, flatulence and vomiting. It has also been stated that the extract is useful in the treatment of respiratory complications including cough, cold, hoarseness, bronchitis, asthma and dyspnea[65].

Anti-inflammatory

In treatment of inflammatory diseases such as rheumatoid arthritis, osteoarthritis, ileitis, colitis, Crohn's disease and bronchial asthma[65].

Anti-diabetic

The pathophysiology of diabetes (type 1) indicates that a chronic inflammatory state subsequently causes insulin deficiency-induced cell death. Shehata *et al*., 2011 investigated the antidiabetic properties of *Boswellia serrata* in animals with induced diabetes (type 1)[66].

Anticancer

The anticancer activity of BA has been reported in numerous studies. The cytostatic, anti-apoptotic, and anti-tumor properties of BA have resulted in improvements in glioma, leukemia, melanoma, hepatoma, prostate and breast cancers[67-71].

Anti-ulcer

Singh *et al*., 2008 studied the protective properties of BA enriched B. serrata extract in rats, using models of gastric ulcer induced by pyloric ligation, ethanol – HCl, acetylsalicylic acid, indomethacin and cold restraint stress[72].

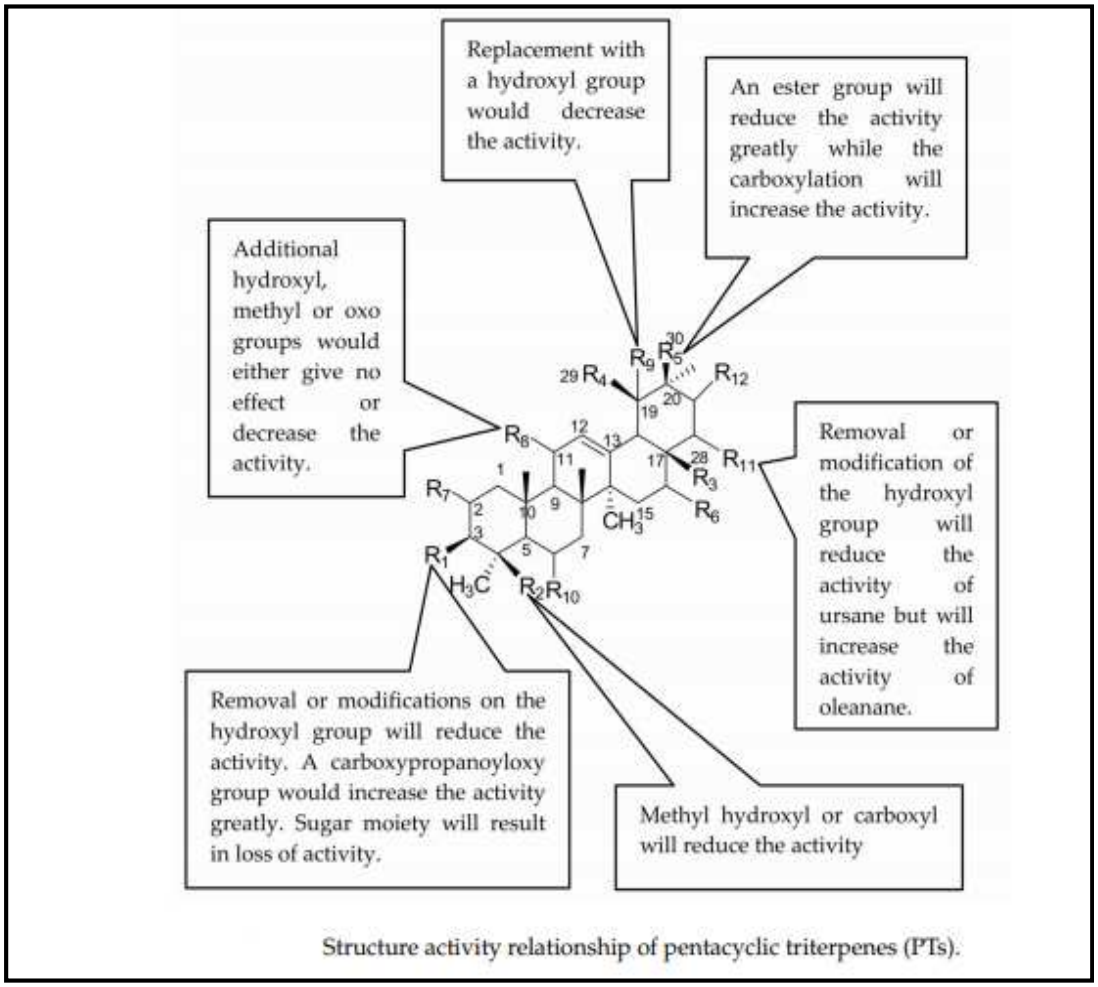
Antimicrobial

Raja *et al*., 2011 have summarized the antimicrobial activity of BA molecules against 112 pathogenic bacteria isolates, including ATCC strains[73].

Antithrombotic

The hemostatic, anti-inflammatory and cardiovascular effects of B. serrata are mentioned in Ayurvedic medicine records[74,75].

So in our study we suggest that Boswellic acid has antibacterial, anti-inflammatory and analgesic effect with no toxic and harmful side effects.



Structure activity relationship of pentacyclic triterpenes (PTs).

RECOMMENDATION

Using of natural plant extract as irrigant like boswellic acid in root canal treatment is safe, easy availability, increased shelf life, cost effectiveness and lack of microbial resistance so it is better than using synthetic antimicrobial agents.

CONCLUSION

The main privileges of natural irrigants are safety, easy availability, increased shelf life, cost effectiveness and lack of microbial resistance so far. The research was conducted (*in vitro*), so far, have shown that herbs can have a promising role as root canal irrigants. However, further clinical trials and investigations are required to be considered as effective alternatives to the synthetic root canal irrigants[76].

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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