Review Article

Use of Propolis in Pediatric Dentistry

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Abstract

Pediatric age groups are the ones that are more susceptible to a drug. Complications/side effects due to the use of man-made drugs have paved way for the natural products for pharmacotherapeutic purposes. Propolis, a natural resinous substance shows dental application based on its antimicrobial, anti-inflammatory and immunomodulating effects. An alternative to gold standard drugs propolis is easy to use, patient friendly, and easily accessible.

Key words: Oro-dental, pediatric, propolis

Introduction

Pediatric age group are the ones that are more susceptible to drug formulations as there is developmental pharmacokinetics difference that is, there is a larger brain/body weight ratio and higher blood-brain barrier permeability in younger children and more body water versus lipid in early life and difference in serum protein composition. Complications/side effects due to the use of man-made drugs have paved way for the natural products for pharmacotherapeutic purposes.

An alternative to gold standard drugs could be seen in propolis which is easy to use, patient friendly, and easily accessible. Propolis, a natural resinous substance, collected by honey bees to fill their hives cracks and crevices, is a complex chemical composition vary according to the source, that is, plant buds and bark exudates. Propolis a known natural antibiotic, its use in medical and dental fields as antibiotic, immunomodulatory and anti-inflammatory effect has led to an extensive research. The antibacterial effect of propolis is bactericidal by inhibiting their mobility.[1] Propolis kills the fungi and also the viruses while the growth of the latter is also inhibited.[1] Immunostimulalting effect by increasing antibody production and by activating B and T lymphocytes, an adjuvant like activity of propolis.[1] Anti-inflammatory effect of propolis is due to inhibition of synthesis of prostaglandins, triggering the thymus gland, supporting the immune system by promoting phagocytic activity, stimulating cellular activity, and enhancing healing effects on epithelial tissues.[2]

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In pediatric dentistry, the role of natural product cannot be overemphasized as nearly all problems related to oro-dental region requires either direct contact of material and medicaments with oral mucosa that is, a mouth rinse, intracanal irrigation, direct contact with capillaries in pulp as in direct pulp capping and pulpotomy, indirect contact to the hard and soft tissue as intracanal medicament and irrigant accidental extrusion. Hence, the child is always at a risk to toxic reactions of man-made formulations either by direct contact or by systemic absorption.

Characteristics

Propolis possesses distinguishing and pleasing aromatic smell and varies in color depending on its source and age.[3] Propolis cannot be used raw due to its complex nature. It's lipophilic property makes possible for it to be dissolved in various solvents before its extraction for various therapeutic purposes and method of extraction express different propolis activity.[4] Temperature variations change the form of propolis. It ranges from hard to brittle a freezing temperature to soft pliable at 20-30°C to sticky and gummy at temperature <45°. It becomes liquid at temperatures 60-70°C.[5]

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Propolis and its extract act as a mild preservative due to their antioxidant and antimicrobial activities prolonging the shelf life of some products in which they are added and also it is observed that propolis does not lose much of its antibiotic activity even when stored for 12 months or longer.[6]

Biological effects of propolis components: Explained in Table 1 in detail.[1]

Potential of Propolis for Oro-dental Use in Pediatric Patients

The main dental application of propolis is based on its antimicrobial, anti-inflammatory, and immunomodulating effects.

Mouth rinse

Due to the usage of oral hygiene aids in pediatric dentistry is nominal they are susceptible to plaque deposition and poor gingival health. Influence of propolis on the plaque inhibition and improvement in gingival health was studied by taking 25 subjects with a mean plaque index of at least 1.5 (PI), and a mean gingival index of at least 1.0 (GI). Subjects were asked to rinse with 10 ml of Brazilian green (MGP 5%) mouthwash for 1 min, instantaneously after brushing in the morning and at night. After 45 and 90 days, a considerable reduction in PI and GI was evident with no significant side effects in soft and hard tissues of the mouth.[7]

Another study also evaluated the effect of propolis on the plaque formation and augmentation of gingival health with PI and GI as parameter. Thirty subjects assigned into three groups of ten subjects each received a propolis-containing mouth rinse, or a negative control (saline) or a positive control (chlorhexidine [CHX] 0.2%). PI and GI were measured at baseline and at a 5-day interval. As propolis improved gingival scores only slightly with respect to CHX, propolis might be used as a mouthwash.[8]

A study investigated the effect of four different propolis solution and CHX 0.2% on the gingival human fibroblast. Propylene glycol and alcohol were used as solvents for each propolis mouth rinse sample with four different concentrations as 10%, 5%, 2.5%, and 1% with CHX as control group. Agar diffusion test indicated that all propolis samples were found to be less cytotoxic on human gingival fibroblasts than CHX.[2]

Exhibition of less cytotoxicity and ability to inhibit plaque formation makes propolis a worthy candidate as a natural mouthwash.

Anti-cariogenic

Dental caries is the most common dental disease in pediatric age group. Dental caries is initiated mainly by two groups of bacteria *Streptococcus mutans* and lactobacilli. These bacteria cause carbohydrates mainly sucrose which are sticky in nature to form organic acid which in turn demineralizes and denatures the tooth substance leading to dental caries or cavity. Glucans, facilitate the attachment of bacteria to the tooth surface, is synthesized by *S. mutans* with the help of glucosyltransferase (GTF). If dental caries is not managed in time leads to pain, infection and in the later stages extraction of teeth which has a direct bearing on child's esthetics and functional occlusion.

In a study, the effects of propolis on growth and GTF activity of *Streptococcus sobrinus* 6715, *S. mutans* PS14 and *Streptococcus cricetus* OMZ61 *in vitro*, and on dental caries in rats infected with *S. sobrinus* 6715 were explored. Rats which were inoculated with *S. sobrinus* had significantly less ($P = 0.01$) dental caries with about half of their fissures carious. It was found that propolis had antimicrobial activity against *S. sobrinus*, *S. mutans,* and *S. cricetus*, and inhibited both water-insoluble glucan synthesis and GTF activity, hence a marked decrease in dental caries propolis had no detrimental effects on the growth of rats.[9]

The potential effect of propolis on dental caries was investigated with 12 distinct types of Brazilian propolis in which type-3 and type-12 only showed anti-caries activity. Anti-cariogenic potential was observed due to its antimicrobial action against cariogenic bacteria and inhibition of glycosyltransferase enzymes activity. In extension of this study, isolated fractions of type-3 and type-12 Brazilian propolis were taken to see its

Table 1: Biological effects of propolis components

Component, propolis type	Biological activity
Polyphenols and flavonoids mostly poplar, but present in most propolis types	Antibacterial, antiviral, antifungal, antioxidant, antiaging, antiulcer, antitumor, antiallergic, anti-inflammatory, antiosterporotic, antitrombogenic, antiatherosclerosis, cardioprotective, immunomodulating, hepatoprotective, cicatrising
CAPE and other caffeates poplar, Bacharis	Antioxidant, anti-inflammatory, antitumor, antibacterial, antiviral, fungicide, immunomodulatory, cardioprotective, hepatoprotective, antiosteoporosis
CA poplar, Baccharis	Antiviral, antioxidant, antiulcer, antitumor
Polyprenylated benzophenones (Cuba, Venezuela and Brazil)	Antioxidant, anti-inflammatory, antitumor
Artepillin C Baccharis (Taiwan)	Antioxidant, anti-inflammatory, antitumor, apoptosis inducing
Prenylated flavanones (propolins) Taiwan	Antioxidant, anticancer, apoptosis inducing
Terpenes (Greece, Crete, Croatia, Brazil)	Antibacterial, antifungal
Essential oils (Brazil, Poland)	Antibacterial
Furfuran lignans (Canary Islands)	Antibacterial

CAPE: Caffeic acid phenethyl ester, CA: Caffeic acid

effect on streptococci mutans and *S. sobrinus* viability, GTFs activity and caries development in rats. 60 Wistar rats infected with *S. sobrinus* were treated topically twice daily with:

1. Ethanolic extracts of propolis (EEP) type-3,
2. hexane (EEH) H-fr type-3,
3. EEP type-12,
4. EEH H-fr type-12, and
5. control.

In general, the H-fr from both types of propolis exhibited the highest antibacterial activity and GTFs inhibition. In addition, the EEP and H-fr type-3 and-12 were equi-effective in decreasing dental caries in rats.[10]

Another study also investigated a flavonoids-free Brazilian propolis (type-6) ethanolic extract of a novel type of propolis (EEP) and its purified hexane fraction (EEH) on mutans streptococci *S. sobrinus* biofilms and the development of dental caries in rats. In *in vivo* study, the rats were infected with *S. sobrinus* 6715 and fed with cariogenic diet 2000 and treated topically twice a day with each of the extracts (or control) for 5 weeks. EEP and EEH significantly reduced acid production, a significant reduction in the incidence of smooth surface caries *in vivo* and also inhibited the activity of F-ATPase (60-65%). It could be proposed that the cariostatic properties of propolis type-6 are related to its effect on acid production and acid tolerance of cariogenic streptococci.[11]

Ex vivo isolation of *S. mutans* and *Lactobacillus* from stimulated saliva was performed by in office CRT bacteria dip slide test. The exposure and extract of propolis affect *S. mutans* and *Lactobacillus* sp. viability, exhibiting antibacterial efficacy on both while lactobacilli was more susceptible to EEP.[12]

Direct pulp capping

Children are prone to traumatic injuries leading to fracture of their anterior permanent teeth. A challenge arises to maintain a functional and healthy pulp-dentine complex. Direct pulp capping involves placement of biocompatible agent to pulp tissue to seal pulp against bacterial penetration, initiate dentine bridge, and maintenance of healthy pulp tissue.

In order to determine the effect of propolis on dental pulp, a study was done in which 36 intact human premolars were mechanically exposed. Teeth were divided into six groups of 6 teeth each, and direct pulp capping was performed using propolis, mineral trioxide aggregate (MTA) and Dycal (Ca(OH)2). Final restoration was done with posterior composite resin using light-cured glass ionomer cement as a liner. The teeth after extraction on the 15th or the 45th day were administered for histological evaluation. On the 15th as well as on the 45th day teeth treated with propolis and MTA observed less pulp inflammation than Dycal. Propolis and MTA treated teeth demonstrated not only more dentine bridge formation but also closer proximity to pulp capping material which was evident on 45th day than teeth treated with Dycal. The response of pulps to propolis as a pulp capping agent was comparable to MTA and Dycal.[13]

The tolerance of fibroblasts of the periodontal ligament (PDL) and dental pulp to propolis and compared with that of calcium hydroxide *in vitro* was investigated. Cells from human dental pulp and PDL were obtained from healthy third molars and subjected to various concentrations of propolis (0-20 mg/ml) and calcium hydroxide (0-250 mg/ml). The cell viability after propolis treatment was evaluated by crystal violet staining of the cells followed by spectrophotometric analysis. 4 mg/ml or lower concentrations of propolis resulted in >75% viability of PDL cells or pulp fibroblasts cells. On the contrary, calcium hydroxide 0.4 mg/ml was cytotoxic and <25% of the cells were found to be viable.[14]

Ca(OH)2 is considered as gold standard in pulp capping. The above-mentioned studies have concluded that propolis is not only less cytotoxic but also exhibits comparable dentine bridge formation and anti-inflammatory and antimicrobial properties. Thus, may be an alternative to commonly used Ca(OH)2 as a direct pulp capping agent.

Pulpotomy

In primary teeth, if caries is near pulp then pulpotomy is initiated. The success of pulpotomy lies in formation of hard tissue barrier beneath the medicament and maintenance of pulp vitality. After application of pastes containing propolis extract associated with calcium hydroxide, calcium hydroxide, and propolis extract as pulpotomy agents were applied in 4 mandibular primary incisors of pig teeth. A histological study was done after their extraction after 7, 14, and 42 days. It was found propolis extract showed least inflammation and greater fibrous tissue formation and maintained pulp vitality also after 42 days complete calcific bridge was formed. Hence, propolis has a potential to be used as pulpotomy agents.[15]

Endodontic therapy

The objective of endodontic therapy is not just simple cleaning and filling of root canals but also one of the essential factors for successful root canal therapy is the elimination of bacterial contaminants without causing irritation to periapical tissues.

Root canal irrigant

An *in vivo* randomized controlled trial was conducted in a group of 60 children aged 6-12 years presenting with an acute apical abscess of the maxillary primary molars for assessment of the antimicrobial and inflammatory/irritant potential of propolis against mixed endodontic aerobic and anaerobic bacteria. Fifteen children each were divided randomly into four groups. Irrigation during pulpectomy was accomplished using normal saline as the control irrigant and 2% CHX, 4% calcium hydroxide or 4% dimethyl sulfoxide (DMSO) extract of propolis as study irrigants. To study mixed aerobic and anaerobic bacterial cultures microbiological samples were taken from the disto-buccal root canal before initiating the pulpectomy as well as after 3 days later. In all the four groups, a significant decrease in mean aerobic colony forming units count was seen.[16]

It has been established that *Candida albicans* are the most

common fungi and E fecalis the most common bacteria that is existing in infected endodontic cases. Henceforth, a study was undertaken to evaluate the antimicrobial effect by measuring the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of EEP propolis, BioPure MTAD, 5% sodium hypochlorite (NaOCl), and 2% CHX on *Enterococcus faecalis* and *C. albicans in vitro*. Using the macrobroth dilution method, MIC and MBC values of irrigants on the growth of *E. faecalis* and *C. albicans* were evaluated. Propolis showed antimicrobial activity against *E. faecalis* and *C. albicans*. It appears that propolis is an effective intracanal irrigant in eradicating *E. faecalis* and *C. albicans*.[17] Hence, propolis may be a breakthrough to the problems of endodontic flare-ups and failures.

Another study assessed the inflammatory/irritant potential of propolis in comparison with CHX and calcium hydroxide, with a normal saline solution as a control using an animal (Wistar rats) model. After intravenously injecting 2% Evans blue into the lateral caudal vein. 0.1 ml each of the test solutions was intradermally injected into the experimental sites. Each piece of skin containing the injected solution was excised after sacrificing the animal, optical density (OD) was measured. At 620 nm irrespective of time, the mean OD with calcium hydroxide was found to be maximum (0.197 ± 0.095) while that with DMSO propolis was found to be minimum (0.070 ± 0.016). On short-term valuation, maximum inflammation was observed with calcium hydroxide followed by CHX and DMSO extract of propolis which was minimal to nonsignificant.[18]

Intracanal medicaments

Intracanal medicaments are used in endodontic therapy as they are believed to reduce inflammation and act as analgesic along with disinfecting the root canal system and preventing resorption of root and periradicular bone. As the indiscriminate use of antibiotics has led to increase in resistant strains and their adverse effects have prompted the researchers to look for an herbal alternative.

Calcium hydroxide as an intracanal medicament in primary teeth is still a matter of debate but is used widely. Therefore, an *in vitro* study was done in which two experimental pastes containing propolis extract associated with calcium hydroxide and calcium hydroxide and propylene glycol was used against polymicrobial cultures obtained from 16 necrotic and fistulae root canals in primary molars of 4-8 years old. Antimicrobial activity was determined in duplicate by the agar well diffusion technique. Two experimental pastes containing propolis extract associated with calcium hydroxide exhibited larger growth inhibition zones. Hence, it could be proposed that a combination of these two could be a better option as an intracanal medicament in primary teeth.[19]

A histological evaluation of the periapical tissue response to propolis paste, corticosteroid-antibiotic preparation nonmedicament (negative control) or nonpulpectomy at all (positive control) when used as an intracanal medication in the 72 dog's incisors after pulpectomy was done. The medications were left inside the root canal for 7, 14 or 28 days. There were statistically significant differences between the tissue reactions. The low tissue reactions demonstrating fewer inflammatory reactions from propolis paste advocate that this material could be considered as a choice for root canal medication after pulpectomy.[20]

Pulpal and periapical inflammation and induction of osteoclastogenesis are known to be associated with lipopolysaccharide (LPS) bacterial constituents. In a study, mouse odontoblast-like cells (MDPC-23), macrophages (RAW 264.7), and osteoclasts were exposed to 0-20 μg/ml LPS, in the presence of propolis or vehicle control in order to induce an inflammatory response. The results demonstrated that propolis suppresses the LPS-induced inflammatory response of key cells within the root canal system.[21]

Apart from the fact that propolis exhibits good antibacterial and anti-inflammatory activity its removal from the root canal is also important for it to be used as a medicament a study was undertaken to investigate through scanning electron microscopy the cleaning of root canal walls after the use of experimental propolis or calcium hydroxide root canal dressings using 20 single-rooted teeth. Removal was initiated with a K-file and 5 ml of 1% NaOCl irrigation with 2 ml of 17% ethylenediaminetetraacetic acid for 3 min as a final flush. The cleaning of the root canal walls was determined by the number of open dentinal tubules. The experimental propolis pastes presented acceptable physical characteristics and can be used as intracanal medicaments as no statistically significant difference between the calcium hydroxide and propolis groups was evident.[22]

Propolis as storage media for avulsed teeth

The preservation of cellular viability of the avulsed teeth is critical for restoring the PDL health and cessation of root resorption after tooth reimplantation.

Seventy freshly extracted human teeth were divided into five experimental groups and two control groups. The positive and negative controls corresponded to 0-min and an 8-h dry time, respectively. Subsequent to storing teeth dry for 30 min, teeth were immersed in one of the five media (Hank's balanced salt solution [HBSS], milk, saline, propolis 50%, and propolis 100% for 45 min). The teeth were then treated with dispase grade II and collagenase for 30 min. Propolis groups kept significantly more PDL cells viable compared to either milk, saline, or HBSS propolis may be a better substitute to HBSS, milk, or saline in terms of conserving PDL cell viability after avulsion and storage.[23]

In another study, 60 maxillary central incisors of rats were extracted and divided into five groups. In groups I and II, teeth were kept in propolis for 60 min and 6 h, respectively; in group III, teeth were kept in milk for 6 h; in group IV, teeth were kept dry for 60 min; and in group V, they were immediately reimplanted. All teeth after filling the root canals with calcium hydroxide paste were reimplanted in their sockets. The results obtained showed the comparable occurrence of

inflammatory resorption, dental ankylosis, and the formation of the connective tissue parallel to the root surface. Thus, it could be concluded that propolis could be used as a storage media for preserving avulsed teeth with 6-h period more appropriate than the 60-min period.[24]

New bone formation

In order to increase esthetics in children which have small maxilla, expansion of the maxilla or premaxilla is the only option. The role of propolis in new bone formation in the expanded premaxilla was done by giving propolis systemically to rats. After 5 days of expansion and 12 days of retention, rat's premaxilla was dissected. It was seen that there was greater new bone formation and intensity of inflammatory cells and also increase in number of osteoclast (indicating acceleration of bone turnover), osteoblasts and newer capillaries in rats which were given propolis with respect to cases in which only expansion was done without propolis. Thus, propolis may decrease the tendency of relapse in expansion cases.[25]

Wound healing

Due to high caries activity in children and insufficient knowledge in parents about the significance of primary teeth, tooth extraction becomes the treatment of choice for parents. Extraction wound could be painful to children, therefore, wound healing acceleration may alleviate pain. The effects of 30% propolis alcoholic extract propolis on the population of mast cells in oral surgical wounds of hamsters were studied in comparison with 0.1% dexamethasone in orabase cream as mast cells participate in all phases of wound healing. The anti-inflammatory action of propolis mediated by mast cells was more effective than dexamethasone in the inflammatory phase of healing.[26]

Allergic reactions to propolis

Allergic reactions may be seen as contact cheilitis, contact stomatitis, perioral eczema, labial edema, oral pain, peeling of lips, and dyspnea.[27,28]

Conclusion

Through various studies, an encouraging alternative, propolis, has emerged which can be used in different formulations in future. Further research with the collaboration of dentist with plant biologist and pharmacologist will see a complete development of propolis as a substitute to commonly used products in the dental field.

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Conflict of interest

There are no conflicts of interest.

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