Introduction

The field of health has always emphasized on the use of natural products for curing diseases. There is a wide variety of natural products (such as silk, herbal tea, chitosan) used today in the biomedical application for treating a large array of systemic diseases. The natural product “propolis” is a non-toxic resinous material with beneficial properties such as antimicrobial, anticancer, antifungal, antiviral and anti-inflammatory; hence it has gained the attention of researchers for its potential for bio-dental applications. This study aims to explore the properties and chemistry of propolis in relation to its biomedical and dental applications. In addition, the status and scope of propolis for current and potential bio-dental applications have been discussed. This review provides an insight for the reader about the possible use of propolis in modern-day dentistry.

Key words: Antimicrobial, dentistry, natural biomaterials, oral health care, propolis, restorations.
ids. The biological activity of propolis is mostly linked with flavonoids and hydroxycinnamic acid. Research has revealed that it is difficult to standardize the chemical constituents and flavonoid contents of propolis as it is dependent on the environmental condition on the site of collection, on its origin and type of plant pollen and species of bees that produced it. Commercial availability of propolis is in the form of lozenges, topically applied cream, mouth rinses and toothpastes. The aim of this study is to explore the properties and chemistry of propolis concerning its biomedical and dental applications. In addition, status and scope of propolis for its contemporary and potential future bio-dental applications have been discussed.

Chemical unpredictability of propolis

The chemical variability of propolis is due to the different origin of plants, i.e. climatic and geographical whereabouts, flora at the site of collection and bee species. For the production of propolis, bees use secretions of different plants as well as substances discharged from wounds in plants, i.e. lipophilic materials on leaves, leaf buds, resins, gums and matrices. Therefore, there is a striking chemical variability in propolis composition mostly from the tropical regions. Kujumgiev et al. compared the antibacterial, antiviral, antifungal and anti-inflammatory properties of propolis from different origins and concluded that all showed significant properties, including important antiviral properties. Similarly, Popova et al. reported the same findings compared to the biological activity of propolis with geographical origin. The chemical constituents of propolis include chrysin, galangin, pinocembrin, pinobasin found in a temperate climate. These are flavonoids without B-ring substituents. The major component of temperate propolis is caffeic acid phenethyl ester (CAPE). Similarly, the chemical composition of propolis originating from tropical regions includes prenylated phenylpropanoids (e.g., artepillin C), whereas propolis found in Pacific and African regions contains geranyl flavanones as the characteristic compounds (Figure 2).}

Properties of propolis in medicinal care

Propolis, having a wide variety of therapeutic advantages, i.e. being cost-effective and biocompatible with the human cell, with no toxicity, limited allergic reaction and ready availability, can be used widely in medicinal care (Figure 3).

Antibacterial property of propolis

There is unequivocal evidence that propolis exhibits...
remarkable antibacterial properties despite modifications in chemical structures and collection from different geographical regions. Proof suggests that this natural resin is effective against gram-positive rods in addition to Mycobacterium tuberculosis, with restricted activity against gram-negative bacilli.21 The ethanolic extract of propolis (EEP) shows high efficacy against the strains of bacteroides and Peptostreptococcus but exhibits less efficiency against the strains of Clostridium, Eubacterium and Archnia.22 Three antimicrobial compounds were discovered from Brazilian propolis, mainly consisting of 3,5 di-prenyl-4-hydroxycinnamic acid, 3-prenyl-4-dihdrocinnamoloxycinnamic acid and 22-dimethyl 6-carboxy-e-thenyl-2H-1-bezopyran, of which the initial compound shows the highest activity against bacteria and is one of the major antimicrobial compounds.22,23 Furthermore, EEP displayed synergism with certain antibiotics and demonstrated the capacity to improve the actions of antifungals. There is a growing medical interest in the antimicrobial potential of propolis alone or in combination with certain antibiotics and antifungals.24

**Antifungal action of propolis**

Antifungals are used for the treatment and prevention of fungal infections. Commonly, these antifungal drugs are prescribed for the fungal infection of skin, hair, nail and oral candidiasis. Furthermore, they are used as a supportive therapy for patients suffering from denture stomatitis and added to denture tissue conditioners.25,26 Propolis extract shows excellent performance regarding in vitro tests against yeasts identified as onychomycosis agents. In low concentrations, propolis extract was not only found to be fungistatic but also fungicidal. C. tropicalis was found to be the most resilient whereas the Trichosporon species were the most vulnerable yeasts. The results reinforce the importance and the potential of propolis extract as a treatment for onychomycosis.27 The results of the study showed that all the yeasts tested were inhibited by low concentrations of propolis extract, including an isolate resistant to nystatin.28 Similarly, Ota et al studied antifungal activity of propolis extract on 80 different strains of Candida yeast and found the yeasts showed a clear antifungal activity with the following order of sensitivity: C. albicans>C. tropicalis>C. krusei>C. guilliermondii.29 Recently, Siquera et al assessed the fungistatic and fungicidal activity of propolis against different species of Candida using fluconazole as control. It was noted that propolis has fungistatic and fungicidal properties better than fluconazole.30

**Antiviral activity of propolis**

Propolis extracts demonstrated high levels of antiviral activity against herpes simplex virus-1 (HSV-1). Methods of antiviral action of propolis involved adding propolis extract at different times during the viral infection cycle. Both propolis extracts exhibited high anti-HSV-1 activity when the viruses were pretreated with these drugs prior to infection.31,32 Anti-HIV-1 activity was observed with propolis samples from several geographic regions. The mechanism of propolis antiviral property in CD4+ lymphocytes appeared to involve, in part, inhibition of viral entry, while propolis had an additive antiviral effect on the reverse transcriptase inhibitor zidovudine.33 Isopentyl ferulate in propolis extract has significant inhibitory effects on influenza virus (H3N2) in vitro.32,34

**Anticancer property of propolis**

The caffeic acid-phenethyl ester (CAPE) in propolis is a potential supportive therapy for patients with
oral squamous cell carcinoma (OSCC). CAPE treatment inhibits the proliferation and colony formation and suppresses the cells of OSCC.\textsuperscript{35,36} Furthermore, patients receiving chemotherapy benefit from co-treatment with CAPE. Evidence advocates that CAPE subdues and inhibits cancer lining cells of breast cancer, prostate, lung cancer and oral cancers. CAPE has an inhibitory effect and can be used as a chemical agent to prevent cancer metastasis.\textsuperscript{35} Treatment with CAPE has shown to defend or guard the vital tissues and organs against the toxins produced during chemotherapy.\textsuperscript{35,36}

Propolis has shown overwhelming results and improved quality of life in patients with mucositis, a side effect of radiotherapy and chemotherapy. The natural ingredient was found to be safe and has a characteristic of both prevention and treatment in patients undergoing radiotherapy and chemotherapy.\textsuperscript{38} Table 1 demonstrates evidenced-based properties of propolis.

**Anti-inflammatory property and propolis**

The major component of propolis is CAPE which is a biologically active compound. CAPE has both anti-inflammatory and anti-oxidative properties.\textsuperscript{39} Since CAPE is lipophilic it can easily enter the cell to inhibit the LOX and COX enzymes, which indirectly inhibit arachidonic pathway. The inhibition of arachidonic acid prevents the release of prostaglandins and leukotrienes responsible for inflammation and pain.\textsuperscript{40} CAPE also enhances the production of anti-inflammatory cytokines IL4 and IL10. Furthermore, it decreases infiltration of monocytes and neutrophils.\textsuperscript{40,41}

**The role of propolis in dental care**

Propolis is a natural material mainly obtained from the honeycomb (Figure 4) and has shown promising potential for various bio-dental applications.

| Property                          | References |
|----------------------------------|------------|
| Antibacterial                    | 23-21      |
| Antifungal                       | 29-25,27   |
| Antiviral                         | 34-31      |
| Anti-cancer                      | 35,36      |
| Anti-inflammatory                | 19,37      |

**Propolis and dental caries**

Dental caries is considered as one of the major and chronic dental public health problems. Tailored brushing techniques, diet alteration and use of fluorides play a considerable role in the prevention of carious lesions.\textsuperscript{32,43} Data suggest that the use of "miswak" along with a proper technique as an adjunct to tooth brushing is good for oral as well systemic health.\textsuperscript{6} Similarly, evidence from different studies assessed the effect of propolis on Streptococcus mutans vulnerability, caries development and glycosyl transferase activity on rats and found that the extract of propolis has cariostatic effects.\textsuperscript{44} Similarly, undisputed results from authors showed that propolis extracts limit plaque formation on the tooth surface, which indirectly reduces dental caries.\textsuperscript{45-48} Furthermore, Durate et al\textsuperscript{49} reported that fatty acids in propolis provide a cariostatic effect by decreasing the tolerance of microorganisms to low pH and slowing down acid production.\textsuperscript{50} Recently, Nam et al\textsuperscript{51} reported that Brazilian propolis possesses significant antimicrobial effects against Streptococcus mutans in the oral cavity by inhibiting the enzyme activity and cell division. He further concluded that propolis could be used as an alternative and natural therapy against the infectious condition of the oral cavity with no reported side effects.\textsuperscript{51,52} A study by Cordoso et al\textsuperscript{47} agrees with the findings of Nam et al,\textsuperscript{51} indicating that ethanolic extract of propolis has no inhibitory action on demineralization of caries process.

![Figure 4. The honeycomb as a major source of propolis extraction and its potential applications in the field of dentistry.](image-url)
Propolis and periodontal health

Multiple and diverse effects of propolis on oral health have led to its use in periodontal diseases. Subgingival irrigation with propolis extracts during periodontal treatment yielded better results than root planing and scaling. Furthermore, propolis extracts when used in gingival pockets, are beneficial for periodontal diseases. A study on the histological and morphological picture established that application of propolis systematically prevents further bone loss in periodontal conditions in rats. In addition, Gebara et al reported that in vitro use of propolis extracts not only had antimicrobial activity against periodontopathic bacteria (Capnocytophaga gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Porphyromonas gingivalis) but also against microorganisms that cause supra-infection (Staphylococcus aureus, Escherichia coli, and Candida albicans).

Propolis mouthwashes and toothpastes

Mouthwashes are used as commercial antiseptics and used as a home remedy for better oral hygiene. These mouthrinses can be both cosmetic and therapeutic. Therapeutic mouthwashes reduce bacterial counts, have antiplaque effects, work as an astringent and help in reducing gingivitis and carious lesions. A study assessed the effect of propolis mouthwashes by comparing plaque and gingival index scores at baseline and at a five-day interval. Chlorohexidine mouthwashes were more effective when compared to propolis extract-based mouthwashes. Furthermore, the effect of propolis mouthwashes on gingival fibroblasts showed less cytotoxicity than chlorohexidine mouthwashes. Ozan et al and Arsalan et al concluded that propolis mouthwashes were not as effective as chlorohexidine mouthwashes in caries prevention. A recent in vitro study by Akca et al showed that ethanolic extract of propolis was more effective against gram-positive bacteria than against gram-negative bacteria in their planktonic state and can be used as an alternative to chlorohexidine in order to avoid its side effects. Studies are required to find the effects of propolis on biofilms. Research has proven that mouthrinses containing propolis in an alcohol aqueous solution heals intra-buccal surgical wounds; therefore, it plays a role in epithelial repair after tooth extraction and exerts anti-inflammatory effect on orofacial pain. Propolis in toothpaste was seen to greatly improve oral health and showed inhibitory effect on dental plaque formation, which is considered as the main etiology of most oral diseases. Propolis-based toothpastes should be used as adjuncts to other substances in subjects who are at a higher risk for periodontal-related problem.

Effect of propolis on dentin hypersensitivity

Dentin hypersensitivity is defined as a sudden sharp short pain arising from tactile, osmotic, thermal or other stimuli from exposed dentin. There are various theories for dental hypersensitivity. Amongst these theories, the hydrodynamic theory is considered as the most acceptable and relevant. It is proposed that propolis reduces dentinal hypersensitivity by decreasing hydraulic conductance of dentin. A recent study by Hussain et al showed that propolis, when used in the treatment of dentinal hypersensitivity at chair side after bleaching, yielded convincing results. Similarly, another study by Hongal et al showed contrasting results when Indian propolis was compared with RecaldentTM. RecaldentTM showed significant results in reducing dentinal hypersensitivity no difference was observed between the two groups. Propolis used as a natural desensitizer is still a vague concept and needs further verification through research.

Propolis used as a cavity disinfectant in vivo

Good caries prognosis is directly related to removal of infected dentin. Due to improved understanding of the caries process, there is a dramatic advancement in the management of carious lesions. Cavity disinfection is an adjunctive method to minimize or reduce bacterial counts in the residual dentin after cavity preparation. Propolis along with other cavity disinfectants, i.e. APF (acidulated phosphate fluoride) gels, diode lasers and 2% chlorhexidine, was used against S. mutans and L. bacilli and it was observed that there was a significant decrease in bacterial counts in all the groups. Nevertheless, APF gels showed the least reduction, whereas both Brazilian propolis and diode lasers were equally effective when compared to the control group of 2% chlorhexidine. A randomized controlled trial by Prabhakar et al and evidence from others demonstrated that after minimal invasive hand excavation both aloe vera and propolis can be used as a potential cavity disinfectant.

Effect of propolis against endodontic pathogens

Endodontic infection is the infection of the dental root canal system and the chief etiologic agent of apical periodontitis. The evidence clearly recom-
mends that microorganisms are crucial for the advancement and continuation of diverse forms of apical periodontitis. The rationale behind the endodontic treatment is to eliminate the infection and to prevent microorganisms from infecting or re-infecting the periradicular tissues. Ethanol-based propolis was tested as an endodontic disinfectant compared to the conventional disinfectant (chlorohexidine and calcium hydroxide) against gram-positive facultative anaerobe Enterococcus raeacalis (E. faecalis) in vitro. The results showed that antimicrobial effect of propolis was found to be between chlorohexidine and calcium hydroxide. Chlorohexidine was the most effective endodontic antiseptic against E. faecalis. Propolis samples exhibited antimicrobial effects but their efficiency was not beyond chlorohexidine. For propolis to be used as an endodontic irrigant, more human trials are needed to find out cytotoxicity and tissue response of the material. Similarly, Ferreira et al reported the effect of propolis against different endodontic pathogens, concluding that Brazilian propolis was effective against all strains. E. faecalis was considered as the least susceptible strain.

**Propolis and pulp inflammation**

An in vitro and in vivo study revealed that propolis has a strong anti-inflammatory effect and can be used as a pulp capping agent. Flavonoids and caffeic acid are the main ingredients in propolis, responsible for anti-inflammatory response by inhibiting the lipooxygenase and arachidonic pathway. In addition, the flavonoids and caffeic acid provide acceleration of the immune system by enhancing the phagocytic activities. There are numerous studies over the years that have demonstrated the anti-inflammatory effects of propolis. Bachiega et al showed that cinnamic acid and coumaric acid in propolis impede IL-6 and IL-10 but encourage IL-B production by macrophages. Evidence suggests this anti-inflammatory effect of propolis depends upon the potential dose and route of administration.

**Propolis and tooth restorative material**

Glass-ionomer cement (GIC) is a fluoride releasing material used for restorative purposes. GIC is considered as the only material of choice for atraumatic restorative treatment (ART). Favorable characteristics of this material may include biocompatibility, chemical bonding, constant fluoride release, inhibition of bacterial acid metabolism and bactericidal potential. Propolis, when added to GIC, has a distinct antibacterial and anti-biofilm efficacy and can be used as a promising material in future restoration. In vitro extracts of propolis were added to GIC for evaluation of microhardness and microleakage. The results showed that GIC treated with propolis resulted in an increase in microhardness with no changes or effects on microleakage. In addition, when 1% ethanolic extracts of propolis were added to GIC it enhanced the fluoride releasing capacity of GIC without a change in shear bond strength. Alternatively, a recent study by Subramaniam et al suggests that physiochemical properties of GIC tend to wear off when propolis is added. In the limelight of the above evidence, it is suggested that GIC with propolis is still a debatable issue and more features of GIC with propolis need to be tested before conclusions regarding their effectiveness can be drawn.

**Harmful effects of propolis and future challenges**

The most common and reported side effect of propolis is allergy to the resinous wax-cum material. Thirty-seven German beekeepers out of 1051 were allergic to propolis and showed symptoms of skin rashes after working in bee farms professionally. Similarly, Brailo et al reported a subjective case of a 20-year-old women who experienced irregular erosions of the lips and oral mucosa. She used propolis-based ointments for treatment of aphthous ulcers. Moreover, Zirwas and Otto claimed that with time allergic cases of propolis have increased from 0.4% to 1.4%. Furthermore, due to certain impurities in propolis, there is limited literature to recommend it in pregnant women. Propolis preparation may contain high levels of alcohol and may result in nausea when taken as an adjunct to metronidazole. Contents in propolis may interact with antiviral, anticancer, antibiotic and anti-inflammatory drugs and may manifest allergic reactions which may range from eczema, cheilitis, oral pain, labial edema and peeling of lips. Additionally, more research should be carried out to define the parameters of the use of propolis both in the dental and medicinal fields.

**Conclusions**

Propolis is rated among few natural remedies, which has still maintained its popularity over time due to its wide range of applications in both dentistry and medicine. Its extensive and wide-ranging variety of properties such as anti-inflammatory, anti-bacterial, antiviral and anti-fungal has maintained the focus and attention of many researchers. Most of the work on propolis is in vitro or animal studies. There is a
need for human clinical trials to get the best benefit out of this natural ingredient. There is a great need for outlining the algorithms of its use in the dental and medical fields based on its biological properties.

Competing interests

The authors declare that they have no competing interests with regards to authorship or publication of this paper.

References

1. Zafar M, Khurshid Z, Almas K. Oral tissue engineering progress and challenges. Tissue Engineering and Regenerative Medicine 2015;12:387-97. doi: 10.1007/s13770-015-0030-6.
2. Zafar MS, Al-Samadani KH. Potential use of natural silk for bio-dental applications. Journal of Taibah University Medical Sciences 2014;9:171-7. doi: 10.1016/j.tumed.2014.01.003.
3. Husain S, Al-Samadani KH, Najeeb S, Zafar MS, Khurshid Z, Zohaib S, Qasim SB. Chitosan biomaterials for current and potential dental applications. Materials 2017;10:602. doi: 10.3390/ma10060602.
4. Qasim SB, Najeeb S, Delaime-Smith R, Rawlinson A, Rehan IU. Potential of electrospun chitosan fibers as a surface layer in functionally graded GTR membrane for periodontal regeneration. Dental Materials 2017;33:71-83. doi: 10.1016/j.dental.2016.10.003.
5. Khurshid Z, Zafar MS, Zohaib S, Najeeb S, Naseem M. Green tea (camellia sinensis): Chemistry and oral health. The Open Dentistry Journal 2016;10:166-73. doi: 10.2174/1874210610016100166.
6. Niazi F, Naseem M, Khurshid Z, Zafar MS, Almas K. Role of salvadorapersica chewing stick (miswak): A natural toothbrush for holistic oral health. European Journal of Dentistry 2016;10:301-8. doi: 10.4103/1305-7456.178297.
7. Wilson-Rich N. Genetic, individual, and group facilitation of disease resistance in honey bees (Apis mellifera) and two species of paper wasps (Polistesdominulus and P. Fuscatus). Tufts University. 2011.
8. Deswal H, Singh Y, Grover HS, Bhaward J. Healing effect of propolis in medicine and dentistry: A review. Innovaare Journal of Ayurvedic Sciences 2016;1-4.
9. Rathod S, Brahmanak R, Kolte A. Propolis-A natural remedy. Indian J Dent Res 2012;50:99-103.
10. Xiaobo H, Lifet Z, Baizhen L. Recent progress in the studies on pharmacological activity of propolis. China Pharmaceuticals 2006;1:018.
11. Kamburoglu K, Ozen T. Analgesic effect of anatolian propolis in mice. Agra2011;23:47-50.
12. Toreti VC, Sato HH, Pastore GM, Park YK. Recent progress of propolis for its biological and chemical compositions and its botanical origin. Evidence-Based Complementary and Alternative Medicine 2013;2013:1-13. doi: 10.1155/2013/697390.
13. Salatino A, Fernandes-Silva C, Righi AA, Salatino MLF. Propolis research and the chemistry of plant products. Nat Prod Rep 2011;28:925-36. doi: 10.1039/CNP0072H.
14. Huang S, Zhang C, Wang K, Li GQ, Hu F. Recent advances in the chemical composition of propolis. Molecules 2014;19:19610-32. doi: 10.3390/molecules191219610.
15. Bankova V. Recent trends and important developments in propolis research. Evidence-based complementary and alternative medicine 2005;2:29-32.
16. Kujumgiev A, Tsvetkova I, Serkedjieva Y, Bankova V, Christov R, Popov S. Antibacterial, antifungal and antiviral activity of propolis of different geographic origin. J Ethnopharmacol 1999;64:235-40. doi: 10.1016/S0378-8741(98)00131-7.
17. Popova M, Bankova V, Naydensky C, Tsvetkova I, Kujumgiev A. Comparative study of the biological activity of propolis from different geographic origin: A statistical approach. Macedonian Pharmaceutical Bulletin 2004;50:9-14.
18. Sforcin JM, Fernandes A, Lopes C, Bankova V, Funari S. Seasonal effect on brazilian propolis antibacterial activity. J Ethnopharmacol 2000;73:243-9.
19. Martinotti S, Ranzato E. Propolis: A new frontier for wound healing? Burns & Trauma 2015;3:1.
20. Cheng PC, Wong G. Honey bee propolis: Prospects in medicine. Bee World 1996;77:8-15.
21. Kalogeropoulos N, Konteles SJ, Troullidou E, Mourtzinos I, Karathanos VT. Chemical composition, antioxidant activity and antimicrobial properties of propolis extracts from greece and cyprus. Food Chem 2009;116:452-61.
22. Lotfy M. Biological activity of bee propolis in health and disease. Asian Pac J Cancer Prev 2006;7:22-31.
23. Inui S, Hatano A, Yoshino M, Hosoya T, Shimamura Y, Masuda S, Ahi MR, Tazawa S, Araki Y, Kumazawa S. Identification of the phenolic compounds contributing to antibacterial activity in ethanol extracts of brazilian red propolis. Nat Prod Res 2014;28:1293-6. doi: 10.1080/14786419.2014.898146.
24. Stepanović S, Antić N, Đakšić I, Đakić V, Milena. In vitro antimicrobial activity of propolis and synergism between propolis and antimicrobial drugs. Microbiol Res 2003;158:353-7.
25. Akpan A, Morgan R. Oral candidiasis. Postgrad Med J 2002;78:455-9.
26. Iqbal Z, Zafar MS. Role of antifungal medications added to tissue conditioners: A systematic review. Journal of Prosthodontic Research 2016;60:231-9. doi: 10.1016/j.jpor.2016.03.006.
27. Oliveira ACP, Shinobu CS, Longhini R, Franco SL, Svidzinski TIE. Antifungal activity of propolis extract against yeasts isolated from onychomycosis lesions. Memórias do Instituto Oswaldo Cruz 2006;101:493-7. doi: 10.1590/S0074-02762006000500002.
28. Dalben-Dota K, Faria MG, Bruschi ML, Pelloso SM, Lopes-Consolaro M, Svidzinski TIE. Antifungal activity of propolis extract against yeasts isolated from vaginal exudates. The Journal of Alternative and Complementary Medicine 2010;16:285-90.
29. Ota C, Unterkircher C, Fantinato V, Shimizu MT. Antifungal activity of propolis on different species of candida. Mycoses 2001;44:375-8. doi: 10.1046/j.1439-0507.2001.00671.x.
30. Siqueira ABS, Rodriguez, Larissa Rodrigues Nolasco De Araújo, Santos RB, Marinho RRB, Abreu S, Peixoto RF, Gurgel, Bruno César de Vasconcelos. Antifungal activity of propolis against candidaspecies isolated from cases of chronic periodontitis. Brazilian oral research 2015;29:1-6. doi: 10.1590/1807-3107BOR-2015. vol29.0083.
development of new drugs? J Ethnopharmacol2011;133:253-60. doi: 10.1016/j.ejep.2010.10.032.
33. Gekker G, Hu S, Spivak M, Lokensgard JR, Peterson PK. Anti-HIV-1 activity of propolis in CD4+ lymphocyte and microglial cell cultures. J Ethnopharmacol2005;102:158-63. doi: 10.1016/j.ejep.2005.05.045.
34. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. Fitoterapia2002;73:SI-6.
35. Kumar LS. Propolis in dentistry and oral cancer management. North American journal of medical sciences 2014;6:250-9. doi: 10.4103/1947-2714.134369.
36. Kuo Y, Jim W, Su L, Chung C, Lin C, Hsu C, Tseng J, Huang S, Lai C, Chen B. Caffeic acid phenethyl ester is a potential therapeutic agent for oral cancer. International Journal of molecular sciences 2015;16:10748-66. doi: 10.3390/ijms160510748.
37. Olczyk P, Wisowski G, Komosinska-Vassev K, Stojko J, Klimek K, Olczyk M, Kozma EM. Propolis modifies collagen types I and III accumulation in the matrix of burnt tissue. Evidence-Based Complementary and Alternative Medicine 2013;2013:1-10. doi: 10.1155/2013/423809.
38. de Mendonça, Izabel Cristina Gomes. Propolis as an adjunct to prevention and treatment of radiotherapy-and chemotherapy-induced oral mucositis. Nursing and Palliative Care 2016;1:97-100. doi: 10.15761/NPC.1000125.
39. Borrelli F, Maffia P, Pinto L, Iarano A, Russo A, Capasso F, Ialenti A. Phytochemical compounds involved in the anti-inflammatory effect of propolis extract. Fitoterapia2002;73:S53-63. doi: 10.1016/S0367-326X(02)00019-0.
40. Natarajan K, Singh S, Burke TR, Gruberger D, Aggarwal BB. Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proc Natl Acad Sci U S A 1996;93:9090-5.
41. de Moura SA, Ferreira MA, Andrade SP, Reis ML, NoveloMde L, Cara DC. Brazilian green propolis inhibits inflammatory angiogenesis in a murine sponge model. Evid Based Complement Alternat Med 2011;2011:182703. doi: 10.1093/ecam/nep197.
42. Niaz MO, Naseem M, Siddiqui SN, Khurshid Z. An outline of the oral health challenges in “Pakistani” population and a discussion of approaches to these challenges. JPDA 2013;21:219-26.
43. Gooch BF, Griffin SO, Gray SK, Kohn WG, Rozier RG, Sklarew M, Rosalen PL. Effect of neovestitol–vestitol containing mouthrinse on oral microorganisms and human gingival fibroblasts. Eur J Dent 2007;1:195-201.
44. Arslan S, Silici S, Percin D, Ko AN, Er Ö. Antimicrobial activity of propolis on different oral bacteria. JIOH 2016;65:77-81. doi: 10.1016/j.jarchoralbio.2016.02.001.
45. Tanasiewicz M, Skucha-Nowak M, Dawiec M, Król W, Skaba D, Twardawa H. Influence of hygienic preparations with a 3% content of ethanol extract of brazilian propolis on the state of the oral cavity. Advances in Clinical and Experimental Medicine 2012;21:89-92.
46. Duarte S, Rosalen PL, Hayacibara MF, Cury JA, Bowen WH, Marquis RE, Rehder VLG, Sartoratto A, Ikegaki M, Koo H. The influence of a novel propolis on mutans streptococci biofilms and carries development in rats. Arch Oral Biol2006;51:15-22. doi: 10.1016/j.archoralbio.2005.06.002.
47. Libério S.A., Pereira A. A., Araújo MJ.A.M., Dutra RP, Nascimento FRF, Monteiro-Neto V, Ribeiro MNS, Gonçalves A.G., Guerra RMN. The potential use of propolis as a cariostatic agent and its actions on mutans group streptococci. J Ethnopharmacol2009;125:1-9. doi: 10.1016/j.ejep.2009.04.047.
48. Nam S, Choi Y, Jang S, Shim Y, Han G. Antimicrobial activity of propolis on different oral bacteria. Indian Journal of Science and Technology 2016;9:1-4. doi: 10.17485/ijst/2016/v9i16/89174.
49. Choi Y, Nam S, Jiang HB, Jang S, and Shim Y. Antimicrobial activity of propolis on different oral bacteria. International Conference on Convergence Technology 2015; 5: 1040-1041.
50. Coutinho A. Honeybee propolis extract in periodontal treatment: A clinical and microbiological study of propolis in periodontal treatment. Indian Journal of Dental Research 2012;23:294.
51. Parolia A, Thomas MS, Kundabala M, Mohan M. Propolis and its potential uses in oral health. International Journal of Medicine and Medical Science 2010;2:210-5.
52. Wijőckiewicz W, Miernik M, Wijőckiewicz M, Morawiec T. Does propolis help to maintain oral health? Evidence-Based Complementary and Alternative Medicine 2013;2013:1-8. doi: 10.1155/2013/351062.
53. Toker H, Ozan F, Ozer H, Ozdemir H, Eren K, Yeler H. A morphometric and histopathologic evaluation of the effects of propolis on alveolar bone loss in experimental periodontitis in rats. J Periodontol2008;79:1089-94. doi: 10.1902/jop.2008.070462.
54. Nebauer ECE, Lima LA, Mayer M. Propolis antimicrobial activity against periodontopathic bacteria. Brazilian J Microbio2002;33:365-9. doi: 10.1590/S1517-83822002000400018.
55. Akca AE, Akca G, Topcu FT, Macit E, Pikdoken L, Özgen Ş. The comparative evaluation of the antimicrobial effect of propolis with chlorhexidine against oral pathogenes: An in vitro study. BioMed research international 2016;2016:1-8. doi: 10.1155/2016/3627463.
56. Mhaske M, Samad BN, Jawade R, Bhansali A. Chemical agents in control of dental plaque in dentistry: An overview of current knowledge and future challenges. AdvApplSci Res 2012;3:268-72.
57. Prasad KR, John S, Deepika V, Dwijendra KS, Reddy BR, Chincholi S. Anti-plaque efficacy of herbal and 0.2% chlorhexidine mouthwash: A comparative study. Journal of international oral health: JOIH 2015;7:98.
58. Dodwad V, Kukreja BJ. Propolis mouthwash: A new beginning. Journal of Indian Society of Periodontology 2011;15:121.
59. Ozan F, Sümer Z, Polat Z, Er K, Ozan U, Deger O. Effect of mouthrinse containing propolis on oral microorganisms and human gingival fibroblasts. Eur J Dent 2007;1:195-201.
activity of poplar propolis on mutans streptococci and caries development in rats. *Turkish Journal of Biology* 2012;36:65-73. doi: 10.3906/bij-1101-180.

64. Rajoo M, Parolia A, Pau A, Amalraj FD. The role of propolis in inflammation and orofacial pain: A review. *Annual Research & Review in Biology* 2014;4:651.

65. Morawiec T, Dziedzic A, Niedzielska I, Mertas A, Tana-siewicz M, Skaba D, Kasperski J, Machorowska-Pieni/o-=ek A, Kucharczewski M, Szaniawiska K. The biological activity of propolis-containing toothpaste on oral health environment in patients who underwent implant-supported prosthodontic rehabilitation. *Evidence-based complementary and alternative medicine* 2013;2013:1-12. doi: 10.1155/2013/704947.

66. Bllagana A, Vohra P, Nagpal A. Diagnosis and treatment of dentinal hypersensitivity. *J Innov Dent* 2011;1:1-4.

67. Lin P, Cheng Y, Chu C, Chien K, Lin C, Tu Y. In-office treatment for dentin hypersensitivity: A systematic review and network meta-analysis. *J ClinPeriodontol* 2013;40:53-64. doi: 10.1111/jcpe.12011.

68. Hussain RA, Dannan A, Al-Ahmad M. Propolis treatment for dental sensitivity after tooth bleeding. *Imperial Journal of Interdisciplinary Research* 2017;2:1436-9.

69. Hongal S, Torwane NA, Goel P, Chandrashekar B. The effect of 30% ethanolic extract of indian propolis on replica of human dentin compared against commercially available desensitizing agent: A methodological SEM study in vitro. *Pharmacognosy research* 2014;6:113-9. doi: 10.4103/0974-8490.129026.

70. Purra AR, Mushfaq M, Acharya SR, Saraswati V. A comparative evaluation of propolis and 5.0% potassium nitrate as a dentine desensitizer: A clinical study. *Journal of Indian Society of Periodontology* 2014;18:466-71. doi: 10.4103/0972-124X.138695.

71. de AN, Coutinho E, Cardoso MV, Lambrichts P, Van Meerbeek B. Current concepts and techniques for caries excavation and adhesion to residual dentin. *J Adhes Dent* 2011;13:7-22. doi: 10.3290/j.jad.a18443.

72. Mohan PU, Uloopi KS, Vinay C, Rao RC. In vivo comparison of cavity disinfection efficacy with APF gel, propolis, diode laser, and 2% chlorhexidine in primary teeth. *Contemporary clinical dentistry* 2016;7:45-50. doi: 10.4103/0976-237X.177110.

73. Prabhakar AR, Karuna YM, Yavagal C, Deepak BM. Cavity disinfection in minimally invasive dentistry-comparative evaluation of aloe vera and propolis: A randomized clinical trial. *Contemporary clinical dentistry* 2015;6:S24-31. doi: 10.4103/0976-237X.152933.

74. Mangayarkarasi SP, Manigandan T, Elumalai M, Cholan PK, Kaur RP. Benefits of aloe vera in dentistry. *Journal of pharmacy & bioal lied sciences* 2015;7:S255-9. doi: 10.4103/0975-7406.155943.

75. Sardana D, InduShekar KR, Manchanda S, Saraf BG, Sheoran N. Role of propolis in dentistry: Review of the literature. *Focus on Alternative and Complementary Therapies* 2013;18:118-25. doi: 10.1111/fct.12034.

76. Narayanan LL, Vaishnavi C. Endodontic microbiology. *Journal of Conservative Dentistry* 2010;13:233.

77. Siqueira JF, Lopes HP. Treatment of endodontic infections. Quintessence London. 2011.

78. Kayaoglu G, Ömürli H, Akça G, Müğem, Gürel Ö, Sorkun K, Salih B. Antibacterial activity of propolis versus conventional endodontic disinfectants against enterococcus faecalis in infected dental tubules. *J Endod* 2011;37:376-81. doi: 10.1016/j.joen.2010.11.024.

79. Mattigatti S, Ratnakar P, Moturi S, Varma S, Rairam S. Antimicrobial effect of conventional root canal medicaments vs propolis against enterococcus faecalis, staphylococcus aureus and candida albicans. *J Contemp Dent Prac* 2012;13:305-9.

80. de AF, Torres SA, da SR, Ferreira CM, Garcia RB, Marcucci MC, Gomes BPFA. Antimicrobial effect of propolis and other substances against selected endodontic pathogens. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology* 2007;104:709-16. doi: 10.1016/j.tripleo.2007.05.019.

81. Sabir A. The healing actions of propolis on direct pulp capping treatment: A review. *Journal of Dentomaxillofacial Science* 2016;1:186. doi: 10.15562/jdms.v1i1.145.

82. Ramos A, Miranda J. Propolis: A review of its anti-inflammatory and healing actions. *Journal of Venomous Animals and Toxins Including Tropical Diseases* 2007;13:697-710. doi: 10.1590/S1678-919920070004000002.

83. Ardo Sabir D ed. Analysis of Tumor Necrosis Factor-Alpha (TNF-a) Expression In Inflamed Rat Dental Pulp Tissue Following Propolis Application (An Immunohistochemistry Study). The 3rd ASEAN Plus And Tokushima Joint International Conference, Program And Proceeding Book. 2014.

84. Ardo Sabir D. Using propolis as A therapeutic agent in dentistry. *Cakradonya Dental Journal* 2012;4:480-6.

85. Bachiega TF, Orsatti CL, Pagliarone AC, Sforcin JM. The effects of propolis and its isolated compounds on cytokine production by murine macrophages. *Phytotherapy Research* 2012;26:1308-13.

86. Zafar MS, Ahmed N. Therapeutic roles of fluoride released from restorative dental materials. *Fluoride* 2015;48:184-94. doi: http://www.fluorideresearch.org/483/files/FJ2015_v48_n3_p184-194_pg.pdf.

87. Zafar MS. Effects of surface pre-reacted glass particles on fluoride release of dental restorative materials. *World Applied Sciences Journal* 2013;28:457-62. doi: 10.5829/idosi.wasj.2013.28.04.1869.

88. Najaee S, Khurshid Z, Zafar MS, Khan AS, Zohaih S, Marti JMN, Sauro S, Matinlinna JP, Rehman IU. Modifications in glass ionomer cements: Nano-sized fillers and bioactive nanoceramics. *International Journal of Molecular Sciences* 2016;17:1134. doi: 10.3390/ijms17071134.

89. Altunsoy M, Tanriver M, Türkam U, Uslu ME, Silici S. In vitro evaluation of microleakage and microhardness of ethanolic extracts of propolis in different proportions added to glass ionomer cement. *J ClinPeditrat Dent* 2016;40:136-40. doi: 10.17796/1053-4628-40.2.136.

90. Topcuoglu N, Ozan F, Ozyurt M, Kulecik G. In vitro antibacterial effects of glass-ionomer cement containing ethanolic extract of propolis on streptococcus mutans. *Eur J Dent* 2012;6:428-33.

91. Prabhakar AR, Balehosur DV, Basappa N. Comparative evaluation of shear bond strength and fluoride release of conventional glass ionomer with 1% ethanolic extract of propolis incorporated glass ionomer cement-invitro study. 2016;10:ZC88-91. doi: 10.7860/JCDR/2016/17056.7818.

92. Subramanian P, Girish Babu K, Neeraja G, Pillai S. Addition of propolis to glass ionomer cements: Nano-sized fillers and bioactive nano-ceramics. *International Journal of Molecular Sciences* 2016;17:1134. doi: 10.3390/ijms17071134.

93. Altunsoy M, Tanriver M, Türkam U, Uslu ME, Silici S. In vitro evaluation of microleakage and microhardness of ethanolic extracts of propolis in different proportions added to glass ionomer cement. *J ClinPeditrat Dent* 2016;40:136-40. doi: 10.17796/1053-4628-40.2.136.

94. Topcuoglu N, Ozan F, Ozyurt M, Kulecik G. In vitro antibacterial effects of glass-ionomer cement containing ethanolic extract of propolis on streptococcus mutans. *Eur J Dent* 2012;6:428-33.

95. Prabhakar AR, Balehosur DV, Basappa N. Comparative evaluation of shear bond strength and fluoride release of conventional glass ionomer with 1% ethanolic extract of propolis incorporated glass ionomer cement-invitro study. 2016;10:ZC88-91. doi: 10.7860/JCDR/2016/17056.7818.
95. Zirwas MJ, Otto S. Toothpaste allergy diagnosis and management. *The Journal of clinical and aesthetic dermatology* 2010;3:42.

96. Naseem M, Khurshid Z, Khan HA, Niazi F, Zohaib S, Zafar MS. Oral health challenges in pregnant women: Recommendations for dental care professionals. *The Saudi Journal for Dental Research* 2016;7:138-46. doi: 10.1016/j.sjdr.2015.11.002.

97. Basavaiah ND, Suryakanth DB. Propolis and allergic reactions. *J Pharm BioalliedSci* 2012;4:345,7406.103279. doi: 10.4103/0975-7406.103279 [doi].

98. Czarnobilska E, Ohtulowicz K, Dyga W, Spiewak R. The most important contact sensitizers in polish children and adolescents with atopy and chronic recurrent eczema as detected with the extended european baseline series. *Pediatric Allergy and Immunology* 2011;22:252-6. doi: 10.1111/j.1399-3038.2010.01075.x.