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REVIEW ARTICLE

The Virtue of Propolis in Periodontics – A Review

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ABSTRACT

Periodontal disease is the most common chronic infection in adults. In recent times, the use of nature derived products either as a therapeutic agent or as an adjuvant agent is drawing attention. Propolis is one such nature derived product which is being used for treating periodontal diseases. Propolis is a non-toxic and resinous honeybee product obtained from plant resins mixed with saliva of bees. Its chemical composition includes flavonoids, phenylpropanoids, terpenes, stilbenes, lignans, coumarins, and their phenylated derivatives. The flavonoids have been found to be of use to treat aphthous ulcers, candidiasis, gingivitis and periodontitis. This review explains the significance of propolis in the treatment of periodontal diseases.

Keywords: Propolis, Flavanoids, Gingivitis and Periodontitis.

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INTRODUCTION

Periodontitis is a complex disease whose etiology is shared by multiple factors and hence cannot be considered as a simple bacterial infection anymore**.** Management of a periodontal disease is achieved by removing the subgingival microflora. Scaling and Root Planning (SRP) helps in mechanical removal of subgingival microflora[1]. However, disadvantage of these procedures is that it cannot eliminate pathogenic organisms from inaccessible areas. In such situations, an adjuvant therapy involving anti- microbial agents have been introduced to reduce the need for surgical intervention [2]. Currently, there are numerous anti-microbial agents available in market. However, the need to find an anti-microbial agent which does not produce any side effects has led to the introduction of herbal drugs. Propolis is one such nature derived product which is being used for treating periodontal diseases [3].

Propolis is a natural resinous mixture produced by honeybees from substances collected from parts of plants, buds and exudates. The word propolis is derived from Greek, in which pro stands for "at the entrance to" and polis for "community" or "city," which means this natural product is used in hive defense. Another name of propolis is bee glue. Propolis, a bee derived substance stands for its various medicinal properties which includes anti-bacterial, anti-viral, anti-inflammatory, anti-tumoral and

immunomodulatory properties [3]. The purpose of this review is to understand the efficacy of propolis in the treatment of periodontal disease.

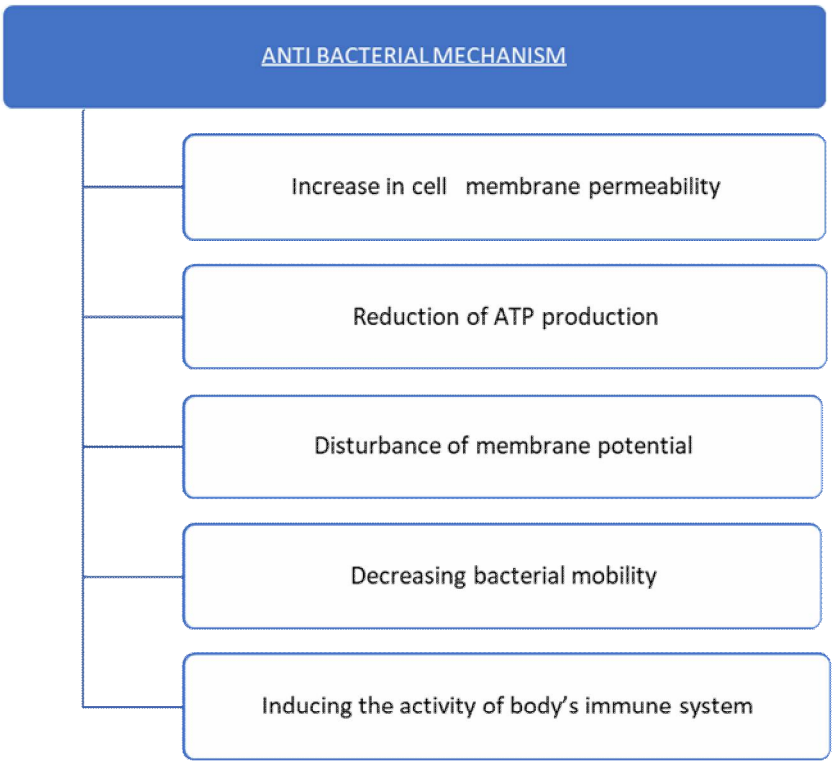
PROPERTIES OF PROPOLIS

a. Anti-bacterial properties

Propolis and several of its constituents have been publicized to have antibacterial properties against bacteria . One of the most common methods for determining antibacterial activity is the disc diffusion method and is determined by measuring the diameter of the growth inhibition zones in the agar layer surrounding the disc, after an incubation period at optimum temperature . Propolis was found to be more efficient against Gram-positive bacteria than Gram-negative bacteria. Propolis is hypothesised to have antibacterial properties by either boosting the organism's immunity or directly attacking the bacteria . The stronger antibacterial effect of propolis against Gram-positive bacteria is thought to be attributable to the outer membrane structure of those bacteria. Artepillin C is one of the various phenolic mixes found in propolis and exhibited efficient antibacterial activity against Methycillin Resistant *Staphylococcus aureus* (MRSA). Flavonoids contain phytochemicals that may target various components and elements of the bacterial cell. Studies have showed that an ethanolic extract of propolis can be used to treat skin infections caused by S. aureus. In addition, kaempferide was found to be particularly efficient against Enterococcus faecalis, Listeria monocytogenes, and Staphylococcus saprophyticus [4].

Quercetin a flavanoid present in propolis binds to the E. coli DNA gyrase component and inhibits bacterial activity. Furthermore, propolis is thought to promote fractional bacterial lysis and have an effect on bacterial proteins. Antiinfection drugs and propolis have a synergistic effect, according to numerous studies. Chloramphenicol was efficient against Salmonella typhi when combined with Bulgarian propolis and Brazilian honey, and the combination of 4 Brazilian red propolis and fluconazole was beneficial against Candida sp. Other flavonoids in propolis, such as pinocembrin and apigenin, were studied in Chilean propolis and found to have antibacterial action against *Streptococcus mutans*. Pinocembrin has also been demonstrated to have antibacterial action against *Klebsiella pneumoniae, Listeria monocytogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus sobrinus, Enterococcus faecalis*, and *Streptococcus mutans*. Apigenin, on the other hand, was found to be effective against *P. aeruginosa, K. pneumoniae, Salmonella enterica serotype Typhimurium, Proteus mirabilis*, and *Enterobacter aerogenes*, all Gram-negative bacteria. Cinnamic acid works by breaking the bacterial cell membrane, preventing the action of ATPases, bacterial binary fission and the formation of biofilms [5].

Figure 1: Anti bacterial mechanism of propolis



b. **Anti-inflammatory properties**

Inflammation is the complex biological response of vascular tissues to adverse stimuli such pathogens, damaged cells, irritants, and free radicals. The fundamental effect of the host defense system is anti-inflammatory action. Almeida et al in 2014, studied the anti-inflammatory properties of propolis in guinea pig mast cells and proposed that propolis inhibits myeloperoxidase activity, NADPH-oxidase ornithine decarboxylase, tirosine-protein kinase, and hyaluronidase. The presence of active flavonoids and cinnamic acid derivatives can explain this anti-inflammatory effect . Acacetin, quercetin, and naringenin are among the former, whereas caffeic acid phenyl ester (CAPE) and caffeic acid are among the latter (CA) [6]. CAPE and galangin, two common elements of poplar propolis, have anti-inflammatory properties and dramatically reduced carrageenan oedema, pleurisy, and adjuvant arthritic inflammations in rats [7]. In vitro and during zymosan-induced acute peritoneal inflammation in vivo, an ethanol extract of propolis inhibited prostaglandin and leukotriene production by mouse peritoneal macrophages. During inflammation in vivo, dietary propolis dramatically reduced the lipoxygenase pathway of arachidonic acid metabolism. Caffeic acid, quercetin, and naringenin were all found to be fewer effective modulators of arachidonic acid metabolism than CAPE [8].

c. Anti-oxidant properties

Antioxidant qualities distinguish propolis. Propolis' immunomodulatory activities are mostly due to the antioxidants it contains. Propolis contains a high concentration of flavonoids, which are potent antioxidants. The depletion of free radicals by the addition of scavenger compounds is one of the most widely used techniques for evaluating antioxidant potential. Measurements of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical consumption are related to the intrinsic ability of a substance or a complex mixture to donate hydrogen atoms or electrons to this reactive species in a homogeneous system. It was reported that propolis increases the cellular immune response through the increase of mRNA for interferon-γ and activates the production of cytokines [9]. The antioxidant activity of water extracts of propolis was assessed utilizing a - carotene bleaching and 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging test method. Because of the total phenols and flavonoids included in propolis, it was discovered that it possessed considerable antioxidant action. The sample from Desouk had the maximum activity, followed by those from Kafr El- Sheikh and then those from Motobes. In comparison to BHT and TBHQ, freeze-dried extract of propolis can be utilized as a natural antioxidant in sunflower oil. At 200 and 300 ppm, propolis from Desouk and Kafr El- Sheikh had equal reducing peroxide values, and both at 300 ppm were better than BHT but lower than TBHQ in reducing peroxides and hydro peroxidase formation in sunflower oil at 63°C for 4 days[10]. Antioxidants have been demonstrated to scavenge free radicals, preventing lipids and other molecules such as vitamin C from being oxidized or destroyed [11]. In disorders including cardiovascular disease, arthritis, cancer, diabetes, Parkinson's disease, and Alzheimer's disease, active free radicals, together with other factors, are most likely to blame for cellular ageing and degradation. Poor liver function can also be caused by oxidative injury. In vitro studies on rats show that propolis extracts protect liver cells from damage [12].

d. Hepatoprotective Properties

In the livers of mice, propolis was tested for its ability to protect against mercury-induced oxidative stress and antioxidant enzymatic changes. Mercuric chloride (HgCl2; 5 mg/kg; i.p.) caused oxidative stress by raising lipid peroxidation and oxidized glutathione levels while simultaneously decreasing glutathione levels. Glutathione and the antioxidant enzymes glutathione and glutathione reductase Mercury. The activity of a liver marker enzyme was altered by intoxication in the serum Propolis therapy (200 mg/kg; p.o.) in combination lipid peroxidation was prevented, and glutathione levels were oxidized. Increased glutathione levels, on the other hand, Antioxidants' activity superoxide dismutase, catalase, and glutathione peroxidase are examples of enzymes[13]. The enzymes S-transferase and glucose 6-phosphate dehydrogenase were discovered [14]. After propolis administration, it was likewise repaired concomitantly toward control. The serum transaminases alkaline phosphatase, lactate dehydrogenase, and -glutamyl transferase are all released. After the procedure, transpeptidase was largely restored to normal levels therapy with propolis Propolis , according to the findings, boosts the immune system. Antioxidant protection against mercury-related toxicity Research demonstrates that it has therapeutic potential hepatoprotective agent [13].

e. Anti- protozoal properties

An invitro growth inhibitory impact on a culture of parasites following incubation in the presence of different doses of propolis is used to assess antiprotozoal activity. Several papers have reported on the effect of European propolis on protozoa that cause diseases in humans and animals such as trichomoniasis, toxoplasmosis, giardiasis, Chagas disease, leishmaniasis, and malaria. Anti-protozoan activity has been observed in *Giardia lamblia, Trichomonas vaginalis, Toxoplasma gondii*,

Leishmania donovanii, and *Trypanosoma cruzi*, among others[15]. EEP has also been shown to have anti-protozoan action against *G. duodenalis*[16].

f. Anti-tumoral activity

Orsolic et al. examined the anticancer activity of propolis. The ability of propolis to limit DNA synthesis in tumour cells, induce death in tumour cells, and stimulate macrophages to create proteins that regulate the function of B, T, and NK cells, respectively, is thought to be the cause of its chemopreventive effect in animal models and cell cultures [17]. Furthermore, these findings imply that propolis flavonoids protect mice from the toxicity of chemotherapeutic drugs or radiation, suggesting that they may have a similar protective effect in people. Combining chemotherapy with an adjuvant antioxidant therapy may improve the efficiency of chemotherapy by reducing side effects on leukocytes, liver, and kidneys, allowing for dose increases[18]. Although several polyphenols have anti-metastatic properties, the most effective anticancer drugs have been found as caffeic acid phenethyl esters (CAPE) from poplar propolis and Artepillin C from Baccharis propolis[19]. Propolis' anticarcinogenic activity in human lymphocytes was examined in vitro. Blood samples were taken from 10 healthy nonsmoking male volunteers and incubated with increasing quantities of propolis (0.01, 0.05, 0.1, 0.2, 0.5, 0.7, and 1.0 mL). The micronucleus rates ranged from 1.4770.38 to 4.0270.64. The mitotic index rate ranged from 19.4572.22 to 0.2870.33. There were statistically significant differences between the control and exposed cells (pp 0 : 05). In vitro, varying doses of propolis had no influence on the carcinogenicity of peripheral human cells. Increased micronucleus (MN) rates, on the other hand, suggested that propolis could be carcinogenic at high quantities[20].

USES OF PROPOLIS

a. Oral Hygiene

The mouth environment is rich in bacterial flora, which can contribute to diseases like caries and periodontal diseases in some cases [21]. *Streptococcus mutans* and, to a lesser extent, Lactobacillus sp. play a key role in the development of dental caries. It's debatable whether other bacteria like Streptococcus, Enterococcus, or Actinomyces have a cariogenic effect [22]. *Streptococcus mutans*' virulence is due to its ability to adhere, acid-forming capabilities, and tolerance to low pH environments [23]. Propolis has a multidirectional effect on bacterial flora, according to Ikeno et al., who found that it lowers tooth cavities in rats by limiting the number of microorganisms, slowing the production of insoluble glucans, and slowing the activity of glucosyltransferase [24]. Propolis has cariostatic properties, according to Duarte et al., since it contains a high number of fatty acids, which slow down the formation of acids by *Streptococcus mutans* and reduce microorganism tolerance to acid pH[25]. Propolis can also be used to disinfect toothbrush fibres in the form of a solution[26]. Propolis has a preventive impact on periodontal tissues by reducing the production of calcium phosphate precipitates, and as a result, it can be utilised as a component in mouthwashes or toothpastes to reduce the accumulation of dental plaque [27]. Unpleasant breath, or halitosis, is also closely linked to oral cavity cleanliness. One of the causes of foul breath is the results of the breakdown of bacteria in the mouth [28]. The red complex bacteria, as well as *Prevotella intermedia*, *Porphyromonas endodontalis*, and *Eubacterium*, are all linked to the development of bad breath [29]. Sterer and Rubinstein and Barak and Katz [30] used the Halimeter to evaluate the concentration of volatile sulphur components in exhaled air and found that propolis lowers halitosis.

b. Treatment for Periodontal Pathologies

The effectiveness of propolis in combating periodontitis etiological elements has led some authors to incorporate these preparations in periodontologic treatment protocols. When applied to gingival pockets, Bruschi et al. demonstrated that a mucoadhesive hydrophilic gel containing propolis can be effective in the treatment of periodontitis [31].

c. Anti Bacterial Properties

Caries and periodontal disorders are both caused by bacterial flora in the mouth. Bacterial plaque accumulating on and under the gums causes inflammation of the tissues next to teeth, resulting in clinical attachment loss and alveolar process loss [32]. Microbes found in the subgingival plaque were grouped into five complexes by Socransky et al. The "red complex," which includes *Tannerella forsythensis, Porphyromonas gingivalis,* and *Treponema denticola*, has a strong link to increased periodontal pocket depth and probing bleeding [33]. *Prevotella intermedia* and *Fusobacterium nucleatum* were also identified as possible etiologic factors of periodontitis in few investigations [34]. Propolis mouth rinses and propolis-based toothpastes appear to be promising not only as preventive but also as therapeutic agents, as they inhibit the growth of gingivitis and periodontitis bacteria [35].

d. Anti Inflammatory Properties

Artepillin C, one of the phenolic compounds found in high concentrations in Brazilian green propolis, has a wide range of biological properties, including the ability to act as an anti-oxidant for free radicals and nitric

oxide radicals, as well as the ability to interfere with the inflammatory response by inhibiting the activities of iNOS and COX-2 [36]. The aqueous extract is said to have good antioxidant activity and a high number of phenolic components. In yeast Saccharomyces cerevisiae, the antioxidative activity of propolis and its primary phenolic constituents, caffeic acid, p-coumaric acid, ferulic acid, and caffeic acid phenethyl ester, was examined. Intracellular oxidation was reduced in yeast cells, but there were no significant changes between the various phenolic compounds. The antioxidative action of Ethanol Extract Propolis (EEP) was also studied at the mitochondrial proteome level, with alterations in the amounts of antioxidative proteins and proteins involved in ATP generation observed. Guimaraes et al. examined the preventive properties of *B. dracunculifolia* glycolic extract against oxidative stress in isolated rat liver mitochondria (RLM). As a result,

B. dracunculifolia exhibits high antioxidant activity, shielding liver mitochondria from oxidative damage, and this action likely contributes to green propolis' antioxidant and hepatoprotective properties[37].

E. Anti Viral Properties

Herpes simplex, the virus that causes oral mucosa illness, is one of the most common human infections[38]. In cases of infection induced by this virus, propolis-based extracts were tried as a therapy. Schnitzler et al. discovered that bee glue has a strong antiviral effectiveness when they used propolis solutions. Single components of propolis do not have the same antiviral impact as their combined in the form of bee glue, according to research. The conclusion that propolis extracts can be employed locally in viral infections is based on this [39]. Recurrent aphthoid stomatitis is also treated with propolis. Although it is a prevalent disease with symptoms that manifest in the mouth, the actual cause has yet to be identified, making treatment more complicated [40]. Bee glue has been found to be useful in the treatment of recurrent stomatitis, as it reduces the frequency of recurrence and enhances the quality of life of patients [41].

ADVERSE EFFECTS OF PROPOLIS

Propolis use is considered safe and has therapeutic benefits on the basis of results obtained in *In vitro, In vivo,* animal model studies and Human clinical trials,. However, propolis, like other bee-related products, can induce allergic reactions. Cases of contact dermatitis and other allergic reactions related to the use of propolis have been reported [42].

CONCLUSIONS

Propolis have therapeutic uses in dentistry, oral health, and medicine. Wide ranging therapeutic uses due to its antibacterial, antiviral, antifungal, anti-inflammatory, and anticancer properties have been demonstrated in various in vitro, in vivo, and ex vivo studies, as well as in human clinical trials. But standardization of the constituents of propolis should be done for enhancing the overall therapeutic benefits.

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