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Propolis as an Adjunct to Nonsurgical Periodontal Therapy in Periodontitis Management: A Mini-Review

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Abstract

Propolis, a natural resinous compound produced by bees, has gained recognition as an impactful supplement in periodontal therapy owing to its multifaceted properties. It possesses strong antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties, also propolis has shown potential in enhancing fibroblast proliferation and collagen synthesis, essential for periodontal tissue repair. Its immunomodulatory effects contribute to a balanced inflammatory response, promoting a more favorable healing environment and reducing the risk of disease progression. Periodontitis is a chronic inflammatory disease characterized by the destruction of the supporting structures of the teeth, including the periodontal ligament and alveolar bone. This condition arises primarily from an imbalance between pathogenic bacteria and the host's immune response Traditional periodontal treatment, particularly non-surgical periodontal therapy (NSPT), focuses on mechanical plaque removal to reduce bacterial load. However, the limitations of mechanical debridement, particularly in deep periodontal pockets, have necessitated the exploration of adjunctive therapeutic agents. Among these, propolis has demonstrated significant potential in modulating inflammatory pathways, inhibiting periodontopathic bacteria, and promoting tissue regeneration. Studies suggest that propolis can suppress pro-inflammatory mediators, such as prostaglandin E2 (PGE2) and cytokines, thereby mitigating periodontal tissue destruction. Additionally, its antioxidant properties help neutralize oxidative stress, a key contributor to periodontal disease progression. The application of propolis as a local drug delivery system in gel or nanoparticle form enhances its bioavailability and ensures sustained therapeutic effects within the periodontal pocket. This review highlights the multifaceted properties and applications of propolis and emphasizes its role as an adjunctive agent in the management of periodontal diseases.

Keywords: Propolis, Flavonoids, Anti-bacterial, Anti-inflammatory, Antioxidant, Probing, Periodontitis, periodontal therapy.

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1. Introduction

Periodontal disease is a multifactorial immune-inflammatory disease that causes progressive destruction of tooth-supporting structures [1], Periodontal treatment involves a range of therapeutic approaches, including behavioral-change techniques, subgingival debridement to remove soft and hard deposits, local and systemic pharmacotherapy and diverse types of surgery [2]. Herbal medicines have recently been shown to have immense potential for the management of periodontitis owing to their safety and efficacy. They are cost-effective, widely accessible, and have higher safety margins. As per the World Health Organization's report, nearly 80% of the world's population today count on herbal medicines to treat a variety of health issues [3]. Propolis is a natural antibacterial and anti-inflammatory plant-based product. It is produced by bees. Its chemical composition varies significantly due to regional and

seasonal differences. Despite this variability, propolis extracts generally reveal a series of therapeutic properties including anti-inflammatory, antimicrobial, antioxidant, antibacterial, antifungal, antiviral, healing, immunomodulatory, antioxidant and anticancer properties to varying degrees [4].

2. Propolis composition

Propolis is a resinous and balsamic substance formed by bees derived from bud and exudates of the plants, combined with bee enzymes, pollen, and wax [5]. It has been used in human medicine as well as various fields of dentistry, including periodontics. Propolis comprises over 300 potentially active ingredients, including coumarins, phenolic aldehydes, amino acids, steroids, and polyphenols, those could be divided to large core groups made up of essential oils, fatty acids, wax, pollen, and volatile elements. Notably, flavonoids, which make up to 20% of propolis by weight, play a significant role due to their high chemical reactivity and diverse biological activities. These include immunomodulatory, anti-inflammatory, anti-free radical, vaso protective, antithrombotic and gastroprotective effects [6-8]. The composition and biological features of propolis are concerned by the choice of solvents that have been used and extraction methods. Propylene glycol, water and ethanol are used as common solvents for propolis extraction, the choice of solvents depends on the intended application of the final product. Various extraction techniques have also been employed, including ultrasound-assisted, microwave-assisted, maceration and supercritical carbon dioxide extraction. Amongst mentioned methods, propolis extraction with ultrasound-assisted has considered as the peak method, offering the advantages in both extraction time and yield [9].

3. Therapeutic properties of Propolis

The anti-inflammatory, antioxidant, antibacterial attributes of propolis prove its role in restraining and remedying a variability of oral conditions, involving periodontal diseases [10]. Various mechanisms of propolis against periodontal diseases are mentioned as follow:

3.1. Antibacterial properties of Propolis

Propolis has exhibited significant antimicrobial activity against periodontal pathogenic bacteria, including Porphyromonas gingivalis and Prevotella intermedia, as demonstrated in both in laboratory based, animal bases and in humans studies [11]. Its mechanism of action as it interacts with plasma membrane lipids resulting in increases membrane permeability, impaired adenosine triphosphate (ATP) production, disruption membrane potential. Additionally, it disrupt cell envelope, efflux pumps, inhibits bacterial motility and creates an ion imbalance within microenvironment [12]. Propolis components disrupt bacterial cell division by inducing the formation of pseudo-multicellular structures, disorganizing cytoplasm, inhibiting protein synthesis, and ultimately causing cell lysis. About 12 to13 compounds identified in propolis including caffeic acid, ferulic acid, and other constituents target the bacterial membrane or cell wall, leading to functional and structural damage. These compounds also inhibit bacterial DNA dependent RNA polymerases [4-13].

3.1.1. Three pathways ending in disruption of the bacterial membrane by propolis

First one, binding to the bacteria cell wall, resulting in lysis of cell and ultimately causing bacteria's demise. Second, it interacts between polar headgroup of propolis and the hydrophobic regions of membrane. Third, the capability to suppress protein production. Moreover, flavonoids can attach to cell walls of bacterial causing cells lysis or restricting bacterial growing by blocking topoisomerase IV-dependent deactivation activity [12]. Caffeic acid phenethyl ester (CAPE) rises membrane permeability and restrains RNA polymerase in bacteria. In Porphyromonas gingivalis, a phenolic part, artepillin C induces membrane vesiculation contributing to its bacteriostatic activity. Moreover, compounds like 2-dimethyl-8-prenylchromene and 3-Prenyl-cinnamic acid allyl ester, present in propolis, they suppress glycosyltransferase enzymes by stimulating insoluble glycan induction, further reinforcing its antimicrobial activity [14].

Artepillin C, mostly present in ethanolic propolis extracts, induces membrane blebbing, exerts its bacteriostatic effects. This is attributed to its ability to inhibit prostaglandin and nitric oxide synthesis by modulating NF-kappa pathway [11]. Flavonoids also hold a pivotal role in propolis biological effects with blocking production of nucleic acid, decreasing bacterial resistance to many antibacterial agents, this occur by linking to bacterial cell wall, producing cell lysis or suppressing bacterial growth [15-16]. Propolis has demonstrated collaborative results with antibacterial mediators by blocking protein synthesis through suppression of RNA polymerase. Antibacterial mechanisms of propolis include modification of cytoplasmic membrane, enhancing cell membrane permeability, inhibition of protein synthesis, and lowering energy metabolism through its synergistic effects, all of which have been proposed as various pathways for its antibacterial mechanisms of propolis [4].

3.2. Anti-inflammatory properties of Propolis

Propolis has become traditionally utilized as a homeopathic remedy, renowned for its anti-inflammatory properties. These properties of propolis involve cyclooxygenase (COX) inhibition, thereby blocking prostaglandins biosynthesis, and neutralization of free radical. Furthermore, it inhibits production of nitric oxide, lowers inflammatory cytokines levels, and immunosuppressive effects are observed [12]. Additionally, numerous studies have demonstrated that the presence of various active flavonoids in propolis contributes to its anti-inflammatory properties. These flavonoids impede cyclooxygenase (COX) and lipoxygenase (LOX) activity, reducing prostaglandin E levels (PGE2) [17-18]. Moreover, caffeic acid phenyl ester (CAPE) prevents nuclear factor kappa B ignition also suppresses enzymatic activity of myeloperoxidase and tyrosine kinase. Furthermore, caffeic acid reduces the production of arachidonic acid and blocks the enzymatic activity of COX-1 and COX-2 [19-20].

Meanwhile, pinocembrin has been documented to significantly lower inflammatory promoting cytokines levels like IL-6, TNF-α, and IL-1, chemokines among which are vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, it also reduces aquaporin-4 and inducible nitric oxide synthase in mice. In addition, pinocembrin inhibits TNF-α expression and nuclear translocation of NF-κB [12]. Artepillin C exhibits anti-inflammatory properties, demonstrating

a reduction in prostaglandin E2 synthesis, formation of nitric oxide and NF-B activity [4], also propolis plays a role in modulating inflammation within the innate immunity. It trims down cytokines expression among these are granulocyte-macrophage colony- stimulating factors (GM-CSF), IL-1α, IL1-3, IL-1β, IL-4, IL-6, and monocyte chemoattractant protein-1 (MCP1). Propolis supplementation significantly elevated serum IgA and IgG immunoglobulin levels while reducing serum concentrations of cytokines such as IFN-γ, PGE2, IL-1β, and TNF-α, and IL-6. Furthermore, propolis maintained toll like receptors such as TLR-4, TLR-2, CD80, and CD40 expression from healthy individuals monocytes [21].

3.3. Antioxidant properties of propolis

Propolis demonstrates significant antioxidant properties, including lipid peroxide inhibition and the reduction of LPS-induced oxidative stress by decreasing nitric oxide (NO) and reactive oxygen species (ROS) concentrations while increasing superoxide dismutase (SOD) activity. Its strong antioxidant properties are attributed to the inhibition COX-2 gene transcriptional activity in epithelial cells, suppression of nitric oxide synthetase gene expression and reduction of nitric oxide construction in macrophage cell lines which increases SOD by acting as free radical scavengers [22]. Propolis exhibited strong antioxidant property by not only decreasing lipid peroxidation and DNA damage, but also by acting as a free radical scavenger and reducing INF-γ production by increasing SOD levels. Treatment with a propolis-loaded collagen membrane has been shown to significantly elevate SOD levels and improve clinical parameters, further confirming its effectiveness in halting the progression of periodontal disease [22].

3.4. Immunosuppressive activity

Caffeic acid phenethyl ester (CAPE) displays immunosuppressive activity in human T cells by blocking activation of both early and late stages of T cell, which in turn reduces the secretion of cytokines like IL-2. Additionally, flavonoids share in regulating the nonspecific immune response by stimulating macrophages activity, promoting hydrogen peroxide release and suppress nitric oxide production in a dose-related manner. These mechanisms highlight the immunomodulatory potential of propolis and its components [18].

4. Propolis formulas

Various commercially available propolis-containing products include chewable tablets, lozenges, drops, oral capsules, sprays, ointments, creams, oral syrups, toothpastes, mouthwashes and mucoadhesive gels. Additionally, research has explored the use of propolis based ointments and gels as a complementary treatment in periodontal therapy highlighting their potential to reduce plaque formation and suppress inflammation [9].

5. Evidence from Preclinical and Clinical Studies

Propolis has shown significant therapeutic potential in the management of periodontitis, as supported by multiple studies. For instance, Aral et al., 2015 proved that propolis decreased loss of alveolar bone in periodontitis-experimental rats models, improved glucose and lipid metabolism, and suppressed levels of serum endotoxin caused by P. gingivalis [23]. A randomized controlled trial accomplished by El-Sharkawy et al., 2016, oral administration of propolis improved glycemic control (reduced HbA1c and fasting glucose), while also improving periodontal parameters such as probing pocket depth (PPD) and clinical attachment level (CAL) in patients with type 2 diabetes and chronic periodontitis. Additionally, topical application of propolis was effective in plummeting P. gingivalis levels in gingival crevicular fluid (GCF) [24]. Nakao et al., 2020, observed that the local application of propolis ointment led to significant improvements in probing pocket depth (PPD) and clinical attachment level (CAL) in patients with chronic periodontitis, alongside a notable reduction in Porphyromonas gingivalis levels [25]. In another study, Giammarinaro et al., 2018, proved that propolis gel was more beneficial than chlorhexidine (CHX) in normalizing antioxidant levels in saliva, thereby enhancing oxidative homeostasis in patients with gingivitis.

These findings highlight therapeutic ability of propolis in managing periodontal diseases through its antimicrobial, anti-inflammatory, and antioxidant properties [26]. Zarch et al., 2021, researched impact of subgingival delivered propolis separate in the treatment of periodontitis and reported a significant reduction in the gingival index compared to control group [27]. Likewise, Jung et al., 2024, found that propolis significantly modulated levels of multiple cytokines, including prostaglandin E2 (PGE2) and matrix metalloproteinase-8 (MMP-8) in gingival crevicular fluid (GCF) of periodontitis patients [28]. A systematic review by Assunção et al., 2021 settled that propolis, when used as an adjunctive therapy to nonsurgical periodontal treatment significantly improved clinical parameters such as gingival index probing pocket depth, clinical attachment level, and bleeding on probing, while also reducing periodontal pathogens and oxidative stress. These results point out importance of propolis as a valuable supplementary treatment in periodontal therapy [29]. The application of propolis in various forms as a supplementary agent for periodontal therapy has garnered considerable scientific attention. Numerous experimental and clinical research have explored its efficacy in lowering pathogenic microbial levels and managing inflammation in periodontal tissues [9].

6. Conclusions

Propolis, a complex resinous compound delivered from bees, has shown great promise as an adjunct in managing periodontal diseases owing to its antioxidant, anti-inflammatory, antibacterial and immunomodulatory effects, its rich composition, including flavonoids and phenolic acids, helps reduce periodontal pathogens like Porphyromonas gingivalis and improves clinical indicators such as plaque and gingival index, bleeding on probing, probing depth and clinical attachment loss. Propolis also modulates oxidative stress and promotes tissue healing, its anti-inflammatory effects, through inhibition of COX, PGE2 and NF-κB, and synergy with antibacterial agents enhances its therapeutic potential. Despite variations in composition due to geographic and seasonal factors, propolis consistently demonstrates therapeutic benefits. Its versatility in formulations (gels, ointments, mouthwashes) makes it a valuable addition to periodontal care. Future research should focus on standardizing extraction methods, optimizing delivery systems, and conducting long-term trials to fully establish its role in periodontal treatment.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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