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Review Article

Bee Propolis: Nature's Remedy for Bone Healing – A Narrative Review

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ABSTRACT

Propolis is a resin-like compound bees produce from botanical substances mixed with their saliva and beeswax. It contains antioxidants like flavonoids and phenolic acids that promote bone healing. The promising potential of propolis in supporting bone healing has significant implications in various medical and dental fields, such as orthopedics, periodontology, orthodontics, and oral and maxillofacial surgery. This review aims to evaluate the existing body of research on the impact of propolis on bone healing. A comprehensive literature search spanning the last two decades until 2024 was conducted across reputable databases utilizing the search terms "propolis AND bone AND alveolar bone AND healing. Articles with these keywords, published in English and accessible from reputable databases like PubMed, Cochrane Library, Scopus, and Google Scholar, were included. Articles from unreliable sources, non-English publications, those without full-text access, and review articles or letters to editors were excluded. Initially, 1,974 articles were identified, and after removing duplicates and applying the inclusion and exclusion criteria, 54 articles were selected, and 31 were deemed relevant for the review. The literature indicates that propolis offers significant advantages in halting the progression of bone loss and expediting bone formation and maturation, primarily due to its antioxidant and anti-inflammatory properties. Consequently, incorporating propolis could be an effective and cost-efficient strategy for managing bone defects.

Keywords: Alveolar bone, bone healing, propolis

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INTRODUCTION

Bee products, including honey, royal jelly, beeswax, pollen, and propolis, have long been revered for their therapeutic potential. Propolis, also known as 'bee glue,' is a resinous mixture meticulously crafted by the bees from botanical sources. Its historical applications span ancient Egypt's embalming practices to wound care during the Anglo-Boer War and World War II. Propolis has been widely employed in traditional medicine across various medical fields (Kuropatnicki et al., 2013).

Like honey, the chemical composition of propolis is intricate, with variations that depend on its region's origin. This mixture predominantly contains resins, waxes, essential oils, pollen, and various organic compounds, including flavonoids and phenolic acids (Zabaiou et al., 2017). Additionally, it may contain antibiotics, enzymes, vitamins, and trace elements, all contributing to its remarkable biological properties, such as anti-inflammatory, antioxidant, antimicrobial, antiviral, anticancer, antibiotic, antifungal, and antiseptic effects (Lotfy, 2006; Marcucci, 1995; Orsolic & Jembrek, 2022). One notable aspect of propolis is its rich antioxidant content, particularly polyphenols, which underpin its reputation as a potent antioxidant. Flavonoids and cinnamic acid derivatives, including compounds like caffeic acid phenyl ester and caffeic acid, contribute to their anti-inflammatory attributes (Almeida & Menezes, 2002).

Bone health depends on a delicate balance between osteoblast and osteoclast activities, with the equilibrium between oxidants and antioxidants playing a crucial role. Maintaining this balance is essential for overall bone integrity and strength. Bone healing is the biological process by which bone tissue regenerates and repairs itself after an injury or surgical intervention. It is a dynamic, multi-step process involving coordinating various cell types and signaling networks, progressing through distinct phases: Inflammation, repair, and remodeling (Steppe et al., 2023). For optimal bone healing, balancing oxidative stress and inflammation is crucial. Acute inflammation and controlled oxidative stress are beneficial for initiating and supporting bone repair. However, chronic inflammation and excessive oxidative stress can impair the healing process and lead to complications.

In bone healing, propolis, which is rich in antioxidants, neutralizes reactive oxygen species (ROS) and free radicals, thus reducing oxidative stress (El-Haskoury et al., 2021; Tolay et al., 2024). It also inhibits the production of inflammatory cytokines (e.g., TNF-α, IL-1β) and enzymes involved in inflammation (Zulhendri et al., 2022). Propolis supports overall health by mitigating oxidative stress and inflammation and may enhance healing in various conditions. This review aims to assess the potential bone-healing properties of propolis in the medical and dental field.

MATERIALS AND METHODS

Study Design and Search Strategy

This narrative review synthesized existing research by sourcing articles from PubMed,

Cochrane Library, Scopus, and Google Scholar. A comprehensive search strategy encompassed using specific keywords, including "propolis AND bone AND alveolar bone AND healing," to identify articles for inclusion in this study.

Criteria for Inclusion and Exclusion

The inclusion criteria involved selecting articles that contained the specified keywords, were published in English, and were accessible from reputable databases such as PubMed, Cochrane Library, Scopus, and Google Scholar. Articles released from the year 2000 until August 2024 were taken into consideration. Conversely, articles from unreliable sources (e.g., blogs or personal websites), those published in languages other than English, those lacking accessible full-text versions, and review articles and letters to editors were intentionally excluded.

RESULTS AND DISCUSSION

In our search across four databases (PubMed, Cochrane Library, Scopus, and Google Scholar) using the keywords "propolis AND bone AND alveolar bone AND healing," a total of 1,974 articles were initially identified. Following the removal of duplicates, 759 articles remained. The titles and abstracts of these 759 articles were screened, and those that were not in English, letters to editors, abstracts only, and review articles were eliminated. It reduced the number to a shortlist of 54 potentially relevant articles. After the full-text review, 31 original articles were deemed relevant for our review (Table 1). These articles spanned the years from 2008 to 2024, representing diverse research from various regions, with most studies conducted in the Middle East (48%), followed by Southeast Asia (36%), East Asia (7%), South America (6%), and America (3%), (Figure 1).

The high percentage of propolis studies from the Middle East can be attributed to the region's rich tradition of using natural products and traditional medicine, where propolis has long been valued for its medicinal properties. Among Middle Eastern countries, Türkiye is the most active in conducting this research. Türkiye's Mediterranean climate, which supports a wide variety of flora, promotes abundant bee activity. The Southeast Asian region, with Indonesia leading, shows the second-highest level of research activity. The

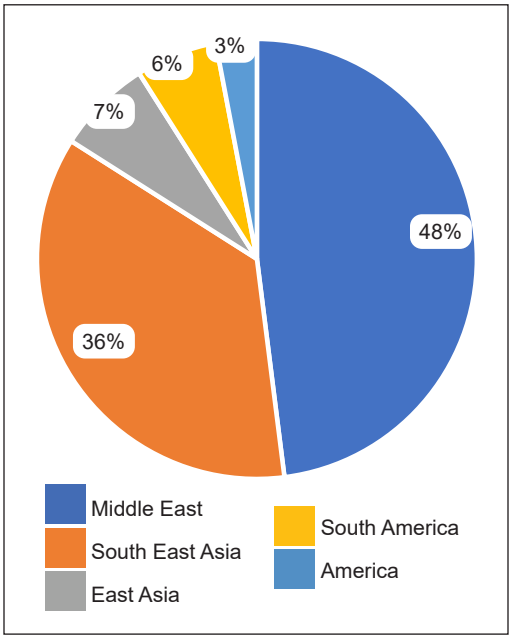

Figure 1. The pie chart illustrates the distribution of 31 studies from various regions

Table 1
An overview of the studies included in this review

	References	Methodology	Results
1	Toker et al. (2008)	• The Wistar rats were randomly assigned to four sets: non-ligated, ligature only, ligature with a propolis dosage of 100 mg/kg body weight per day (Pro100), and ligature with a propolis dosage of 200 mg/kg body weight per day (Pro200). • The ligatures were placed inside the gingival sulcus to induce a periodontitis model. On day 11 of the study, the rats were sacrificed for further analysis. • Alveolar bone loss and histopathological evaluation were measured to assess the effects of the treatments.	• The ligature group exhibited significantly greater alveolar bone loss and osteoclast numbers compared to other groups. • Both doses of propolis effectively reduced periodontitis-associated bone loss, with no variances detected between the two propolis groups.
2	Pileggi et al. (2009)	• Osteoclasts were induced from mouse marrow by culturing it in media containing 1,25-dihydroxyvitamin D3. • Osteoclast-like cells were induced by culturing them in media containing Glutathione S-Transferase Receptor Activator of Nuclear Factor Kappa-B Ligand (GST-RANKL). • These cells were then exposed to ethanol extracts of propolis or vehicle control at predetermined concentrations during the culture period. • The assessment was performed using TRAP and actin ring assays.	• Propolis treatment resulted in a notable and dose-dependent decrease in multinuclear TRAP+ cells, indicating its efficacy in reducing osteoclast formation. • Propolis decreased actin ring formation in osteoclast-like cells, suggesting its direct influence on osteoclast maturation.
3	Guney et al. (2011)	• This study involved 32 male Sprague-Dawley rats aged approximately 6 months, weighing between 280 and 490 g. Prior to their assignment to the groups, all rats experienced experimental femur fracture and fixation. • The treatment groups were administered propolis orally at 200 milligrams per kg body weight per day for 3 or 6 weeks, while the control groups did not receive propolis. • Radiological and biochemical evaluation, bone mineral density assessment and histopathological examination were conducted to evaluate the impact of propolis treatment on bone healing and regeneration.	• The study observed enhancements in bone healing, as well as reduced levels of antioxidant enzymes compared to the control group. • The treatment group also exhibited time-dependent enhancements in both categories.

Table 1 *(continue)*

	References	Methodology	Results
4	Altan et al. (2013)	• Twenty-four male Wistar albino rats were grouped into the non-expansion group (control group), the expansion group only (OE), and the expansion with propolis group (PRO), which was given via orogastric tube. After a 5-day expansion phase, both the OE and PRO groups experienced twelve days of mechanical retention before being euthanized. Their upper jaws were isolated and processed for histological investigation. • Histological examination was conducted to evaluate cells and new bone formation.	• The PRO group showed elevated inflammatory cell intensity, increased osteoblast count, and enhanced new bone formation compared to the others. • The propolis group also showed increased bone-resorbing cells and newly formed blood vessels.
5	Aral et al. (2015)	• The rats were grouped into seven sets for the study: negative control (NC), periodontitis (P), diabetes (D), diabetes with periodontitis (DP), periodontitis with propolis treatment (P-Pro), diabetes with propolis treatment (D-Pro), and diabetes with periodontitis and propolis treatment (DP-Pro). Periodontitis and diabetes were induced by ligature placement and streptozocin injection, respectively. • Blood samples were obtained to determine plasma cytokine and matrix metalloproteinases (MMP) levels, and histological analysis was conducted.	• The blood glucose levels of P, P-Pro, and D-Pro did not display significant variances compared to NC. Nevertheless, D, DP, and DP-Pro showed notable differences from NC. • When comparing treatment and non-treatment groups, P-Pro demonstrated significantly lower alveolar bone loss. • DP exhibited more significant bone loss compared to DP-Pro, while no statistically significant difference was observed between the D and D-Pro groups. • The final measurements of the specific plasma component did not show any variations between groups.
6	Al-Molla et al. (2014)	• Forty New Zealand rabbits were grouped into four based on healing intervals of 1, 2, 4, and 6 weeks, with 10 animals in each group. Two bony holes were created in the tibia: one hole received a propolis-coated implant, while the second hole received an uncoated implant (control). • Histological and immunohistochemical tests were conducted on all implants to detect the expression of osteocalcin and collagen type I.	• The histological analysis of titanium implants coated with propolis revealed an early osteogenic process compared to the control implants. • Immunohistochemical findings demonstrated the presence of osteocalcin and collagen type I at the propolis-coated implants, signifying an accelerated osteogenic process.

Table 1 *(continue)*

	References	Methodology	Results
7	Bereket et al. (2014)	• Twenty-one rabbits were grouped into a control group that received water orally daily, a P100 group that received 100 mg/kg/d of propolis orally, and a P200 group that received 200 mg/kg/d of propolis orally. Following an osteotomy, the rabbits underwent distraction osteogenesis of the left mandible. • Stereologic analyses were conducted to measure the connective tissue and new bone. • Dual-energy X-ray measurements were performed 1 and 4 weeks after the procedure to evaluate hard tissue content and density.	• At four weeks, the X-ray results revealed higher hard tissue content and density in the propolis groups, with the P200 group showing the highest values. • No significant differences were observed in connective tissue volume or the quantities of blood vessels among the groups. The volume of new bone was lowest in the P200 group.
8	Sherif et al. (2015)	• Twenty-four rats were grouped into 1. normal control, 2. diabetes + periodontitis, and 3. diabetes + periodontitis + propolis. • An injection of streptozotocin-induced diabetes mellitus and blood glucose levels were measured. Periodontitis was induced by placing a ligature subgingivally on the first molar of the right mandibular molar. Propolis was given by gastric feeding at 400 mg/kg/day for 8 weeks. • A scanning electron microscopic (SEM) examination was conducted to evaluate the integrity of the alveolar bone surface interproximal.	• Group 2 exhibited greater alveolar bone loss compared to the others. • Specimens from groups 1 and 3 displayed a regular bone surface, whereas those from group 2 demonstrated an irregular and porous surface with extensive resorption.
9	Zohery et al. (2017)	• A split-mouth design was implemented using the premolars of three healthy Mongrel dogs. A Grade II furcation defect was surgically created. One side was treated with NanoBone graft, while the other was treated with propolis. Both sides were covered with a collagen membrane. • The dogs were euthanized after 4 weeks, and the defective parts of the jawbone were processed for histological evaluation.	The percentage of bone fill and surface area in defects treated with propolis powder exceeded those in NanoBone-filled defects.
10	Aydin et al. (2018)	• Twenty-four rabbits were grouped into groups of 8. Implants were placed into the tibia in all groups. The control group was implant only, the local group had propolis applied to the slots before implant placement, and the systemic group received oral propolis solution daily after implantation.	• In both propolis groups, SOD activity showed an increase compared to the control group, though it was not statistically significant. • MDA levels were significantly lower in both propolis groups than in control.

Table 1 *(continue)*

	References	Methodology	Results
		• Biochemical tests were conducted before rabbit sacrifice on the 28th day, including assessing Vitamin D, calcium, phosphorus, and antioxidant enzyme values. Additionally, tests were conducted to determine malondialdehyde (MDA) levels, superoxide dismutase (SOD) activity, catalase activity, and glutathione peroxidase (GSH-Px) activity.	• A statistically significant increase was observed in the GSH level of the treated group compared to the control group. • No significant differences were detected in calcium and phosphorus levels. However, vitamin D levels rose significantly in both local and systemic groups.
11	Somsanith et al. (2018)	• Titanium dioxide (TiO_2) nanotubes (TNT) were fabricated on commercially pure Ti (CP-Ti) plates, followed by propolis loading. • In vitro investigations utilized untreated CP-Ti, TNT, and propolis-loaded TNT (PL-TNT-Ti) plates, assessing them through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, alkaline phosphatase (ALP) assay, crystal violet staining, and fluorescence microscopy. • For *in vivo* studies, the rats were grouped into TNT implants and PL-TNT-Ti implants. They were observed for 1 and 4 weeks and evaluated via μ-CT analysis, histological staining, and immunoassay.	• The PL-TNT-Ti group demonstrated enhanced osteoblast cell proliferation and differentiation compared to other groups. μ-CT and Hematoxylin and Eosin (H&E) histological analysis after 1 and 4 weeks of implantation into rat mandibles revealed increased osteogenesis around the PL-TNT-Ti implant. • The staining showed well-formed collagen for bone formation on the PL-TNT-Ti. • The expression of BMP-2 and BMP-7 was increased around the PL-TNT-Ti, enhancing collagen fiber expression and osteogenic differentiation while decreasing inflammatory cytokines.
12	Meimandi-Parizi et al. (2018)	• This study created bone defects in healthy rats and randomly divided them into six groups of 12 rats: (1) autograft, (2) untreated, (3) chitosan, (4) demineralized bone matrix (DBM), (5) chitosan-propolis, and (6) DBM-propolis. • On the 28^{th}, 42^{nd}, and 56^{th} postoperative days, clinical examinations were conducted alongside the evaluation of radiographic images to assess bone repair capabilities. • Histopathological and biochemical evaluations were performed to analyze the outcomes further.	• The DBM-propolis group exhibited superior structural and biomechanical properties compared to others. • In the chitosan and untreated groups, fibrous connective tissue primarily filled the defect site, while the autograft group predominantly showed cartilage with a smaller volume of fibrous bone. • By the 56^{th} day after the injury, the DBM-propolis group displayed newly formed tissues comprised mainly of woven bone and hyaline cartilage.
13	Pereira et al. (2018)	• This study employed thin-layer chromatography and bioautography techniques to analyze propolis and determine the antibacterial assay against Gram-negative bacteria.	• The infected and treated with propolis group exhibited increased new bone tissue within alveoli, featuring bony trabeculae surrounding small cavities filled with loose connective tissue containing blood vessels.

Table 1 *(continue)*

	References	Methodology	Results
		• *In vitro* cytotoxicity assays assessed the immunoregulatory activity of propolis on rat spleen leukocytes. • For the animal model, 32 Wistar rats underwent maxillary first molar extractions, with the right socket immediately contaminated with lipopolysaccharide (LPS). After 14 days, rats were divided into pure propolis extract (EPP) treated and untreated groups. • Histological and TRAP immunohistochemistry analyses were conducted on contaminated and uncontaminated alveolar bone samples to evaluate the effects of therapy on inflammation.	• The uncontaminated group treated with propolis showed bone cells along the periphery of the osteoid tissue trabeculae. It also contained fibrous connective tissue with numerous capillaries filling large cavities.
14	Zohery et al. (2018)	• A split-mouth design was employed in healthy mongrel dogs. Grade II furcation defects were created in mandibular premolars. One side was treated with nanohydroxyapatite graft, while the other was treated with propolis. Both sides were covered with a collagen membrane. • The animals were sacrificed after one and three months for histological evaluation.	• After one month, the histological evaluation indicated new bone formation in both test groups. • After three months, bone trabeculae appeared thinner in the nanohydroxyapatite group compared to the propolis group. • Analysis revealed a notable increase in bone height and surface area in the propolis group compared to the nanohydroxyapatite group.
15	Wimolsantirungsri et al. (2018)	• Osteoclast precursors were isolated from peripheral blood and cultivated with different non-toxic concentrations of propolis extract. • Osteoclast formation was assessed using TRAP staining, actin ring formation, and real-time polymerase chain reaction. Additionally, osteoclast function was evaluated through the resorption pit assay.	• Non-toxic concentrations of propolis extract demonstrated significant suppression of osteoclast formation by reducing the percentages of TRAP-positive multinuclear cells and the ratios of cells with F-actin ring formation in a dose-dependent manner. • Propolis reduced the expression of several osteoclast-specific genes in a dose-dependent manner.
16	Ibrahim et al. (2019)	• Sixteen critical-sized furcation defects were created on the mandibular premolars of dogs, and they were then divided into three groups: Group I received propolis, Group II received nanohydroxyapatite graft, and Group III received a combination of propolis and nanohydroxyapatite graft. • Histological analyses were conducted after one and three months.	• After one month, all three experimental groups exhibited early periodontal tissue regeneration characteristics, including cementum and newly formed bone with inserted periodontal ligament (PDL) fibers. The propolis group demonstrated the highest bone height and bone surface area. • After three months, denser bone occupying a larger surface area of the furcation defect was observed, particularly in the propolis group.

Table 1 *(continue)*

	References	Methodology	Results
17	Lim et al. (2019)	• The experimental groups included a control group (1% DMSO) and various combinations of mangosteen extract and propolis extract, denoted as mangosteen extract complex (MEC) ratios, ranging from 1:0 to 0:34. • The assessments included cell viability tests, evaluation of inflammatory cytokine expression via Enzyme-Linked Immunosorbent Assay (ELISA), alkaline phosphatase activity tests, alizarin red staining for mineralization, and osteoblast gene expression.	• Treatment with MEC 1:34 significantly decreased IL-6, IL-8, and PGE2 expression levels in hTERT-hNOF cells exposed to the same LPS concentration. • MEC 1:34 and MEC 0:34 exhibited a higher *in vitro* bone formative effect on MG63 cells, as indicated by higher M20 levels compared to other experimental groups. Furthermore, the mangosteen extract complex induced the expression of osteoblast differentiation genes.
18	Wiwekowati et al. (2020)	• The rats were grouped into G1 (control -no orthodontic tooth movement (OTM) and no propolis), G2 (no OTM with propolis), G3 (OTM without propolis), and G4 (OTM with propolis). • Five percent propolis gel was applied along with a 30gf helical spring force for OTM on rat maxilla incisors, and the treatment lasted 17 days. • On day 18, blood samples were tested for MDA using ELISA. Following hematoxylin-eosin staining	• , the number of osteoblasts was calculated. • The application of propolis resulted in significant differences in the number of osteoblasts compared to groups without propolis (G2>G1, G4>G3). • Propolis application significantly reduced MDA serum levels compared to both groups without propolis (G2<G1; G4<G3) • OTM significantly increased MDA levels compared to the control group.
19	Kresnoadi et al. (2020)	• The *Cavia cobaya* were grouped into eight, each comprising seven samples. Lower left incisors were removed and induced with polyethylene glycol (PEG), propolis extract, bovine bone graft (BBG), and a mixture of propolis extract + BBG. The animals were euthanized on days 3 and 7 postextraction. • Immuno- and histological assays were conducted to detect Heat Shock Protein-70 (HSP-70) expression, osteocalcin expression, and the number of osteoblasts and osteoclasts.	• On days 3 and 7, both groups treated with the propolis extract and BBG mixture exhibited the highest levels of HSP70 and osteocalcin expression, a higher number of osteoblast cells, and a lower number of osteoclasts.
20	Handayani, Margaretha et al. (2021)	• Twenty-eight *Cavia cobaya* were divided into four groups: two control (healthy and with orthodontic tooth movement) and two treatment groups (3% and 5% propolis extract). • RUNX-2 and ALP expressions were evaluated using immunohistochemical staining after 17 days.	• Increment of the RUNX-2 and ALP expression was observed on the tension side. • 5% propolis extract effectively enhanced bone remodeling by increasing RUNX-2 and ALP expression during orthodontic tooth movement.

Table 1 *(continue)*

	References	Methodology	Results
21	Kresnoadi et al. (2021)	• This study used a post-test-only control group design. Fifty-six *Cavia cobaya* were randomly assigned to four groups: Control (polyethylene glycol), EEP (ethanol extract of propolis), BBG (bovine bone graft), and EEP-BBG. • The left mandibular incisors were extracted, treated with the assigned materials, and sutured. BMP7 and NFATc1 expressions were observed on days 7 and 14 using immunohistochemical staining.	• On days 7 and 14, the propolis-BBG combination group had the highest BMP7 expression and the lowest NFATc1 expression. • Significant differences were observed compared to the control group. BMP7 and NFATc1 expressions were strongly correlated (r = -0.598).
22	Handayani, Brahmanta et al. (2021)	• Twenty-eight male *Cavia cobaya* were divided into four groups: no orthodontic tooth movement (OTM) or propolis (K-), OTM with rubber separators (K+), OTM with 3% propolis gel (P1), and OTM with 5% propolis gel (P2). • TGF-β expression in alveolar bone osteoblasts on the tension side during OTM was evaluated using immunohistochemical staining.	• TGF-β expression increased significantly with propolis gel application, with the 5% concentration being the most effective.
23	Kusumawati et al. (2021)	• Six male rabbits were periodontitis-induced using *Porphyromonas gingivalis* LPS. • They were divided into three groups: Group A (Open flap debridement (OFD) only), Group B (OFD + carbonated hydroxyapatite (CHA)), and Group C (OFD + 10% propolis-CHA). CHA blocks were soaked in a 10% propolis solution for 24 hr prior to usage. • On days 7 and 14, the rabbits were euthanized, and immunohistochemistry was carried out for collagen type I in tissue samples.	• Collagen type I expression was significantly higher in Group C compared to Group A and Group B on both days (p=0.000). • The 10% propolis-CHA treatment increased collagen type I expression in the alveolar bone of rabbits on days 7 and 14
24	Ari et al. (2023)	• Eighty-four *Cavia cobaya* were divided into 4 groups, each containing 7 subjects. • The subjects' mandibular incisors were extracted, and the sockets were filled with either PEG (K1), propolis extract (K2), BBG (K3), or a combination of propolis extract and BBG (K4). • After days 3, 7, and 30, the animals were sacrificed, and the specimens were processed to assess SMAD3 expression and measure the area of woven bone.	• All groups showed SMAD3 expression and woven bone formation. • On days 3, 7, and 30, the K4 group had the highest SMAD3 expression and woven bone area. Significant differences were observed in SMAD3 expression and woven bone area across groups. • The combination of propolis extract and BBG enhances bone formation by increasing SMAD3 expression and woven bone area.

Table 1 *(continue)*

	References	Methodology	Results
25	Ayyad et al. (2023)	• Eighteen male New Zealand white rabbits were used in this study. Bilateral critical-size bone defects (CSD) were created in the right and left tibias of 12 rabbits. • The right tibia defects (positive control) were treated with hydroxyapatite, while the left tibia defects (study group) received a combination of hydroxyapatite (HA) and propolis. In 6 additional rabbits (negative control), CSDs were made in both tibias but left untreated. • The rabbits were sacrificed at 3 and 6 weeks post-surgery for evaluation using histomorphometric analysis and light microscopy.	• At 3 weeks, the positive control group showed new bone formation, while the study group had thicker trabeculae, more organized osteocytes, and smaller marrow spaces. • At 6 weeks, both groups had increased bone formation, but the study group had a higher bone surface area, though not statistically significant. The negative control group showed the least bone regeneration. • Overall, HA + propolis produced better histological results than other groups.
26	Kresnoadi et al. (2023)	• Fifty-six males of *Cavia cobaya* were divided into eight groups of seven. After removing the lower left incisor, four materials — PEG, propolis extract + PEG, BBG + PEG, and propolis extract + BBG + PEG—were applied to the sockets. • The animals were sacrificed at 3 and 7 days, and RANKL and osteoprotegerin (OPG) expression was examined using a light microscope at 1,000× magnification.	• On days 3 and 7, the combination group showed significantly lower RANKL and higher OPG expression. • The combination of propolis extract and BBG effectively increases OPG and decreases RANKL in post-extraction sockets.
27	Colak et al. (2023)	• Twenty-nine male Wistar-Albino rats were divided into four groups: control, 35 Gy Irradiation (group 1), 35 Gy Irradiation + 100 mg/kg Propolis (group 2), and 35 Gy Irradiation + 200 mg/kg Propolis (group 3). Propolis was administered via oral gavage starting the day after radiotherapy, except for the control group. • The first and second molars were extracted three weeks post-radiotherapy, and samples were collected seven weeks later. • Histomorphometric analysis assessed osteoblast and osteoclast counts, and immunohistochemical analysis measured BMP-2 and TGFβ-3 levels.	• Group comparisons showed no significant differences in osteoblast and osteoclast counts. • However, group 1 had the lowest and highest mean osteoblast counts. • The osteoblast/osteoclast ratio differed significantly between groups, with significant differences between the control and groups 1 and 2, but not Group 3. • The control group's BMP-2 and TGFβ-3 levels were significantly different from the other groups except group 3.
28	Suryono et al. (2024)	• Twenty-four samples from six male rabbits were induced with periodontitis by ligation and injected with *Porphyromonas gingivalis* LPS.	• A 10% propolis-CHA group showed a significant improvement compared to other groups.

Table 1 *(continue)*

	References	Methodology	Results
		• After two weeks of periodontitis induction, the rabbits were treated and divided into three groups: group 1 (OFD only), group 2 (OFD with CHA), and group 3 (OFD with 10% propolis-CHA). • Decapitation was performed on days 7 and 14 for sample collection.	
29	Fauzi et al. (2024)	• A post-test-only control group design with 30 patients is divided into two groups: one receiving *Trigona* sp. propolis after mandibular third molar extraction and the other without propolis.	• The propolis group significantly reduced pain intensity and edema from day 0 to days 1, 3, and 7. • Trismus and periodontal healing improved significantly from day 0 to days 3 and 7. • Trabecular values and radiographic density also showed significant improvement by week 8.
30	Askari et al. (2024)	• Electrospinning scaffolds were immersed in a propolis extract solution. • Adipose-derived mesenchymal stem cells (AD-MSCs) were cultured on the scaffold and induced to differentiate into osteogenic cells. • Cell viability was assessed using the MTT assay, while osteogenic differentiation was evaluated by measuring calcium levels, alkaline phosphatase (ALP) activity, and the expression of bone-specific genes.	• Cell viability was unchanged by either propolis-coated or uncoated scaffolds. • However, the propolis-coated Poly (lactic-co-glycolic acid (PLGA) scaffold showed higher calcium content, ALP activity, and expression of RUNX-2, collagen type I, osteocalcin, and osteonectin on days 7, 14, and 21 of cell differentiation compared to the uncoated PLGA scaffold.
31	Florez et al. (2024)	• The 3D scaffolds were printed and impregnated with propolis extract. FTIR spectroscopy confirmed the presence of propolis. • The scaffolds' mechanical strength was evaluated. Biological testing included assessing antimicrobial activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* using minimum inhibitory concentration (MIC), zone of inhibition (ZOI), and biofilm assays. • The bmMSCs cultures were utilized to assess cell proliferation through the Alamar Blue assay, and osteogenic potential was evaluated using von Kossa, Alizarin Red, and ALP staining at various time points up to 28 days.	• Propolis impregnation maintained the scaffolds' mechanical properties, matching those of human trabecular bone. • The addition of propolis provided antibacterial activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*. • The presence of propolis in the scaffolds increases the cell proliferation of the bmMSCs for up to 21 days. • Osteogenic potential can be seen in propolis and untreated groups.

tropical climate there is also ideal for bee colonization, potentially involving different varieties of bees than those in the Middle East, which fosters further research. In contrast, fewer studies are conducted in North America and East Asia, likely due to challenges in obtaining propolis and a research focus that may be more centered on honey and other bee products.

In vivo Studies

Among the 31 selected articles, 25 were animal studies. These investigations utilized a range of animal models, including rodents (Wistar, Sprague-Dawley, and *Cavia cobaya*), rabbits, and Mongrel dogs. The predominance of animal studies indicates a significant gap in human clinical research on propolis, suggesting the need for more human trials to confirm its efficacy and safety. The use of diverse animal models helps validate findings across species but also introduces variability, making consistent conclusions challenging. Additionally, the unspecified details in some studies point to inconsistencies in research quality and reporting standards, potentially affecting the reliability of the results.

The application of propolis in these studies was categorized into local, systemic, or a combination of both. Local applications targeted surgically-created bone defects, implants, and extracted tooth sockets, while systemic administration dosages ranged from 100 to 400 mg/kg daily, with treatment durations spanning from 3 to 56 days. Commonly assessed regions included molars, premolars, incisor areas, and long bones, such as the tibia. The primary method of evaluating outcomes in these animal studies was histological analysis, complemented by various other techniques such as immunohistochemical tests, biochemical tests, scanning electron microscopy, stereological analysis, and radiological studies.

Out of 25 animal studies, four studies evaluated the impact of propolis on the loss of alveolar bone in an in vivo periodontitis rat model (Aral et al., 2015; Kusumawati et al., 2021; Sherif et al.,2015; Suryono et al., 2024). Periodontitis is a predominant oral inflammatory disease that affects the teeth' periodontium, denoted by the formation of periodontal pockets, clinical attachment loss, and the resorption of alveolar bone. Systemic administration of propolis reduced periodontitis-related bone loss, suggesting potential benefits in periodontal treatment. (Aral et al., 2015; Sherif et al., 2015). It is supported by studies that showed an increase in the expression of TGF-β1 and collagen type I, both significant components in bone formation (Kusumawati et al., 2021; Suryono et al., 2024). However, these studies did not thoroughly investigate long-term and potential side effects.

Propolis demonstrated potential in treating alveolar bone contaminated with bacterial endotoxin, resulting in increased formation of new bone tissue (Pereira et al., 2018). Although the study indicated that propolis was applied locally, the application method was not clearly explained. This lack of detail raises concerns about the consistency and reproducibility of the

results. More recent studies show that propolis promotes bone formation by increasing the expression of key bone-related proteins, including RUNX2 and ALP (Askari, 2024; Handayani, Margaretha et al., 2021), TGF-β1 (Handayani, Brahmanta et al., 2021; Suryono, 2024), collagen type I (Kusumawati et al., 2021), and SMAD3 (Ari, 2023). It also increases osteoprotegerin (OPG) while reducing receptor activator of nuclear factor kappa-B Ligand (RANKL) (Kresnoadi, 2023) and boosts osteonectin and osteocalcin levels (Askari, 2024).

In a rat femur fracture model, systemically administered propolis was found to increase bone mineral density and enhance radiological and histological evaluation assessments, indicating its potential to accelerate fracture healing (Guney et al., 2011). Propolis was evaluated in a rabbit mandible model for its effects on bone regeneration following distraction osteogenesis. The findings indicated that propolis speeds up bone formation and could potentially reduce the consolidation phase during distraction osteogenesis (Bereket et al., 2014). Wiwekowati et al. (2020) demonstrated that propolis enhances osteogenesis during orthodontic tooth movement in rats by reducing malondialdehyde (MDA) levels and increasing the number of osteoblast cells. MDA is related to bone through its role as a marker of oxidative stress and tissue damage. High MDA levels can have implications for bone health, particularly in conditions where oxidative stress is a contributing factor. In addition, it was also shown that systemic propolis supports bone formation in a rat model of premaxillary suture expansion, which could be useful for orthodontic treatments (Altan et al., 2013). However, these results need to be interpreted with caution, as the varying quality and composition of propolis can affect the reproducibility and reliability of the findings.

In the context of dental implants, propolis-coated titanium implants in the tibiae of rabbits demonstrated earlier bone formation, mineralization, and maturation, suggesting potential benefits for implant osseointegration (Al-Molla et al., 2014). Similarly, a rat model study showed that propolis-loaded TiO_2 nanotubes on dental implants improved osseointegration by enhancing collagen fiber formation and reducing inflammatory cytokines (Somsanith et al., 2018). Further research in rabbits highlighted the antioxidant effects of propolis, showing improved bone healing around dental implants (Aydin et al., 2018).

When combined with bovine bone graft, propolis could preserve extraction sockets and promote bone regeneration (Kresnoadi et al., 2020). In a study involving the extraction sockets of *Cavia cobaya*, propolis combined with bovine bone graft exhibited higher expressions of heat shock protein (HSP) 70, osteocalcin, and osteoblasts, indicating improved bone regeneration (Pereira et al., 2018). The combination of propolis and NanoBone Graft in the management of dog furcation defects showed that propolis, either alone or in combination with NanoBone graft, improved bone regeneration in periodontal furcation defects (Ibrahim et al., 2019;

Zohery et al., 2017, 2018). Promising findings were also observed in a rat model of bone defects, where the combination of propolis/chitosan/decalcified bone matrix scaffolds led to significant improvements in bone formation (Meimandi-Parizi et al., 2018).

While the result from animal studies suggests that propolis has significant potential in enhancing bone regeneration and implant osseointegration, several limitations must be considered, as the research has been conducted on animal models, which may not fully replicate the complexities of human physiology and bone healing processes. This difference can impact the generalizability of the findings to human clinical scenarios. Furthermore, propolis's long-term effects and safety in humans are not fully understood. Therefore, further research, including well-designed clinical trials, is essential to confirm these effects in humans and establish safe and effective guidelines for using propolis in dental and orthopedic applications. Based on our keyword-specific search, only one study used human samples to assess the effects of propolis on extraction sockets (Fauzi et al., 2024). The results indicated that the pain and edema significantly improved within 7 days, and trabecular values and radiographic density significantly improved by 8 weeks.

In vitro Studies

Only five of the selected articles presented are *in vitro* studies. These studies employed different cell types, including human gingival fibroblasts (hTERT-hNOF) cell line, human peripheral blood mononuclear cells, osteoclast-like cells derived from the murine cell line, adipose-derived mesenchymal stem cells and bone marrow mesenchymal stem cells. In these studies, propolis was either administered as a supplement within the cell culture media or coated on a titanium implant or scaffold. The in vitro results indicated that propolis supplementation may stimulate bone formation (Askari et al., 2024; Florez et al., 2024; Lim et al., 2019) and inhibit osteoclastogenesis (Pillegi et al., 2018; Wimolsantirungsri et al., 2018). Moreover, propolis was found to reduce the expression of inflammatory cytokines, which then promote in vitro bone formation in human gingival fibroblasts (Lim et al., 2019). Another study using human peripheral blood mononuclear cells showed propolis reduced osteoclast formation, suggesting anti-osteoclastogenic effects (Pillegi et al., 2018).

The outcomes of the in vitro studies strongly corroborated the *in vivo* findings, demonstrating a reduction in inflammation, an increase in bone formation, and a significant anti-osteoclastogenic effect. However, it is important to note that in vitro studies, while valuable, have limitations in replicating the complex biological environment of a living organism. The cell types and culture conditions may not fully represent the *in vivo* situation. Additionally, the dosage used in vitro cannot be translated directly to the dosage used *in vivo* without considering the pharmacokinetics aspects of propolis, which can affect the applicability of the results.

CONCLUSION

This review encompasses animal studies and in vitro research, highlighting the potential advantages of propolis in promoting bone health and facilitating the healing process. Remarkably, both systemic and local administrations of propolis have been linked to decreased alveolar bone loss, heightened bone mineral content and density, enhanced osseointegration of dental implants, and expedited bone healing across diverse experimental models. Moreover, propolis exhibits anti-inflammatory and antioxidant attributes, amplifying its therapeutic efficacy in addressing inflammatory bone disorders like periodontitis. Incorporating propolis in bone healing strategies offers a cost-efficient approach utilizing its natural, anti-inflammatory, antimicrobial, and bone-regenerative properties. It will reduce the need for expensive synthetic drugs and extended treatments and enhance patient outcomes and healthcare efficiency.

These findings support the potential of propolis as a natural therapeutic agent with promising applications in dentistry and medicine. Its multifaceted impact on bone health, including the modulation of various stages of the bone healing process, warrants significant consideration for future research and clinical implementation. However, further investigations, particularly well-designed randomized clinical trials, are essential to confirm the efficacy and safety of propolis in human applications. In conclusion, this review highlights that propolis may become a valuable contributor to improving bone healing and managing bone-related conditions in the future. Nonetheless, the current review may be limited by the selection of keywords used to search for relevant studies, which could have affected the comprehensiveness of the research covered.

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