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Literature Review

THE BENEFICIAL EFFECTS OF PROPOLIS ON OSTEOBLAST DIFFERENTIATION: A LITERATURE REVIEW

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ABSTRACT

Introduction: Optimal bone regeneration is contingent upon the activities of osteoblasts, which are modulated by signalling molecules. Propolis, an abundantly beneficial natural substance, has the potential to induce the release of signalling molecules.

Review: Four essential elements required for tissue regeneration via tissue engineering: scaffolds, signalling molecules, stem cells, and vascularization. Subsequently, osteoblast differentiation and activity are enhanced by signalling molecules induced by propolis. Propolis contains active ingredients that influence every stage of osteoblast differentiation. Propolis-induced increases in the release of signalling molecules (BMP, FGF, TGF) and the transcription factor RUNX2 stimulate the expression of diverse osteoblastogenic markers at each stage of differentiation: type I alpha 1 collagen during proliferation, alkaline phosphatase during maturation, and osteocalcin during mineralization.

Conclusion: Propolis has the capacity to promote bone regeneration through its involvement in all phases of osteoblast differentiation (inducing the release of signalling molecules, increasing the transcription factor, and increasing the expression of osteoblastogenic markers). Additional research is required to determine how propolis influences the equilibrium between osteoblast and osteoclast activities in order to maintain optimal bone homeostasis and remodelling. The prolonged duration of bone regeneration necessitates the use of a carrier for propolis to remain on bone defects for an extended period of time.

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INTRODUCTION

Periodontitis is a prevalent dental issue that could result in the loss of teeth and disability, affecting the masticatory function and aesthetics, subsequently impacting overall quality of life[1].According to the Global Burden of Diseases Study, there are approximately 1,1 trillion instances of severe periodontitis globally[2]. Based on the Riset Kesehatan Dasar 2018, 67,8% of individuals aged 15 and above in Indonesia are affected by periodontitis [3]. Osteoclastogenesis, leading to irreversible bone damage and loss of tooth support, is the primary indicator of periodontitis[4]. If left untreated, the tooth would become loose due to the damage of the alveolar bone, ultimately leading to tooth loss[5].

The primary objective of periodontal treatments is to facilitate the regeneration of compromised periodontal tissue. Mild periodontitis could be addressed through treatment methods like scaling and root planing. Nevertheless, when significant bone loss occurs, it becomes challenging to achieve periodontal regeneration and the formation of new alveolar bone through conventional periodontal surgery and causal treatments alone. This would subsequently establish elevated anticipations for tissue regeneration therapy utilizing tissue engineering[6]. Tissue engineering consists of four components, one of which involves the utilization of signalling molecules[7]. Signalling molecules exert an impact on the functions of osteoblasts in the alveolar bone. This process commences by prompting progenitor cells to differentiate into pre-osteoblasts and concludes with their terminal differentiation into osteocytes[8,9].

Propolis is a natural substance that has proven to be antimicrobial. In addition, it offers various other benefits such as anti-inflammatory, antioxidant, and tissue regeneration effects. The antibacterial capabilities of propolis have been demonstrated through its ability to reduce periodontal pathogens[10]. Within propolis, there are active components called caffeic acid phenethyl ester (CAPE) and flavonoids, which not only act as antibacterial agents but also contribute to bone regeneration[11]. The active compounds, including flavonoids found in propolis, have the ability to stimulate the release of signalling molecules, deeming them valuable for biomaterials used in bone regeneration[11,12].

A multitude of studies have examined the potential of propolis in promoting bone regeneration. Nevertheless, the investigation examining the impact of propolis on osteoblast differentiation remains limited in scope. The effect of propolis as a signalling molecule stimulator on osteoblast differentiation was the subject of this article. This information will provide the groundwork for further investigation and the development of propolis for bone regeneration.

REVIEW

Periodontitis is an inflammatory condition that specifically targets the tissues that support the teeth. It is triggered by microorganisms known as periodontopathogens. It leads to gradual deterioration of the gingiva, periodontal ligament, and alveolar bone[13]. This condition initiates with gingivitis, which is characterized by a localized inflammation of the epithelial and gingival connective tissue without any evidence of bone damage. Untreated gingivitis could advance to periodontitis, ultimately resulting in tooth loss[14]. Signs and symptoms of periodontitis encompass inflammation of the gingiva, clinical attachment loss, bone loss, increased probing depth, bleeding on probing, and tooth mobility[15].

Alveolar bone homeostasis is maintained through the synchronized actions of two cell types: osteoblasts and osteoclasts[5]. Osteoblasts, which originate from mesenchymal stromal cells, are cuboid cells that develop on the surface of the bones[16]. This cell releases extracellular matrix proteins, such as type I collagen, osteocalcin, and alkaline phosphatase[17]. During the inflammation of periodontal tissue, the presence of inflammatory cells that secrete antimicrobial agents, reactive oxygen species, and enzymes hinders the function of osteoblasts, thereby impeding bone regeneration[5]. Hence, an additional substance is required to elicit the suppressed osteoblast activity.

The objectives of periodontal treatments are to halt the advancement of the disease, preserve a healthy and stable condition of the periodontium, and facilitate the regeneration of damaged tissue[18]. Regeneration refers to the biological process of replacing tissue that has been damaged or lost. This process encompasses cell growth, differentiation, and tissue morphogenesis[19,20]. Tissue engineering is a technique employed to regenerate impaired tissue, leading to healing and restoration of mechanical function[21,22].

The tissue engineering paradigm comprises four essential elements: scaffold, biological agents or signalling molecules, stem cells, and vascularization. Scaffolds serve as a structural framework that aids in the infiltration of cells and the formation of new blood vessels[7]. Biological agents or signalling molecules, such as growth factors, cytokines, and proteins, have an impact on cell functions, specifically in terms of promoting proliferation and differentiation, which in turn stimulates the formation of bone. Stem cells expedite tissue regeneration by undergoing differentiation into the specific cell types necessary for regeneration[22]. Signalling molecules exert an impact on the function of osteoblasts in alveolar bone. This process commences with the commitment of progenitor cells to pre-osteoblasts, followed by cell proliferation, bone matrix formation, mineralization, and ultimately, terminal differentiation into osteocytes[8,9].

Propolis is a sticky plant-derived substance that bees frequently employ to fortify and safeguard their hives against bacterial and fungal infections[23]. Propolis is composed of 10% aromatic and essential oils, 30% wax, 50% plant resin, and 10% pollen and other organic constituents. Propolis possesses a wide range of pharmacological properties, such as anti-cancer, antioxidant, fungicidal, antibacterial, antiviral, anti-inflammatory, and various others. Propolis has been formulated into oral hygiene products such as mouthwash and toothpaste, which have the ability to decrease the formation of biofilm and provide protection against caries, gingivitis, and periodontitis[24,25].

Propolis exhibits antibacterial and anti-inflammatory properties when employed in clinical settings. The antimicrobial properties of propolis are ascribed to the presence of the cinnamic acid compound. Propolis exhibits antibacterial properties by enhancing bacterial cell membrane permeability, reducing ATP synthesis and bacterial motility, and activating the body's immune response against bacteria[26]. Propolis, in the form of toothpaste and mouthwash, is utilized as a herbal remedy to regulate the proliferation of pathogenic microorganisms responsible for periodontitis. Propolis exhibits bactericidal properties against periodontal pathogens, specifically *P. gingivalis* and *T. forsythia*. Furthermore, propolis also exhibits antibacterial properties against *T. denticola*, *P. intermedia*, and *F. Nucleatum*[10,25].

The biological efficacy of propolis arises from its intricate composition, encompassing flavonoids and CAPE[27]. The antioxidant properties of propolis could enhance the function and survival of osteoblasts while inhibiting the formation of osteoclasts. Propolis contains flavonoids that hinder cell damage induced by hydrogen peroxide through the elimination of free radicals and safeguarding the cell membrane against lipid peroxidation[28]. The anti-inflammatory properties of propolis enhance the process of wound healing by reducing the levels of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6[29,30]. Additionally, multiple studies have demonstrated the beneficial effects of applying propolis on the augmentation of osteoblast count[27,29,31,32], bone mineralization[33,34,35], and overall bone formation[27].

Osteoblast progenitor cells undergo three distinct stages of differentiation: proliferation, secretion and maturation of extracellular matrix, and mineralization of the matrix[36]. Following matrix mineralization, osteoblasts have the potential to either undergo apoptosis, transform into bone-lining cells, or become incorporated into the bone matrix as osteocytes[37]. The differentiation of osteoblast progenitor cells is regulated by signalling molecules, such as bone morphogenetic proteins (BMP), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β). The signalling molecules stimulate the production of transcription factors within the cell nucleus, including the runt-related transcription factor 2 (RUNX2), which in turn enhances the expression of osteoblastogenic markers such as alkaline phosphatase (ALP), type I alpha 1 collagen (COL1A1), sialoprotein, osteopontin, osteocalcin, and osteonectin[9,38].

Propolis contains flavonoids and CAPE that could enhance the expression of BMP-2, BMP-7 (27), FGF-2[39], and TGF-β[40], all of which are essential during the phase of cell proliferation. The elevation levels of these signalling molecules would affect the transcription factor RUNX2, which is also stimulated after the application of propolis[33,35,41]. RUNX2 would subsequently promote the proliferation of osteoblasts and stimulate the expression of COL1A1, thereby facilitating the maturation and mineralization of the bone matrix[9,42].

During the maturation phase, there is a decrease in cell growth, and osteoblast progenitor cells differentiate into mature osteoblasts. The cells would release COL1A1 and ALP to facilitate the maturation of the matrix. The elevation of ALP activity signifies the completion of bone matrix maturation[9,42]. Following extracellular matrix maturation, it undergoes mineralization by expressing different osteoblastogenic markers, including osteopontin, osteocalcin, sialoprotein, as well as the continuous expression of COL1A1 and ALP [9,36].

Propolis enhances the expression of COL1A1 and ALP [27,33–35,41]. COL1A1 plays a significant role in the extracellular matrix, while ALP facilitates the development of the bone matrix, thereby speeding up bone formation [9,27]. In addition, propolis has the ability to increase the expression of osteoblastogenic markers, specifically osteocalcin, which is expressed during the maturation of the bone matrix [33,43]. This marker controls the process of the calcium metabolism and stimulates the formation of minerals in the extracellular matrix [9].

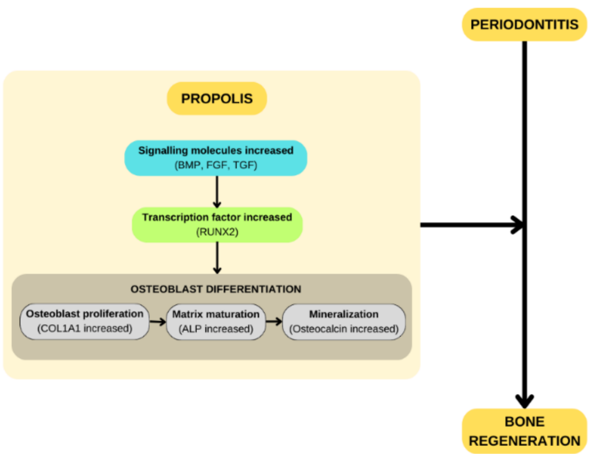

Figure 1. The proposed mechanism by which propolis induces bone regeneration in the context of periodontitis

CONCLUSION

Propolis exerts a diverse array of advantageous impacts on osteoblast functions, encompassing cell proliferation, extracellular matrix formation, cell maturation, and mineralization of the bone matrix. This illustrates that propolis is involved in every stage of osteoblast differentiation, and ultimately contributes to the overall process of bone regeneration. Nevertheless, bone homeostasis is governed by the equilibrium between the osteoblasts' bone formation activities and the osteoclasts' bone resorption activities. Therefore, further investigation is necessary to obtain additional information regarding the impact of propolis on the equilibrium of osteoblast and osteoclast activities. Moreover, for propolis to function as a stimulator of molecule release for signalling purposes, it needs to be released gradually and continuously, while offering advantages at every stage of osteoblast differentiation until the regeneration of alveolar bone is accomplished.

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