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Propolis and its therapeutic potential on wound healing

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Abstract – Propolis is a resinous mixture collected by honey bees from tree buds or other plant sources. Propolis compounds have been the focus of many studies due to their anti-microbial, anti-cancer, and anti-inflammatory effects. In addition, propolis is also recognized to have regenerative properties. It has been found to regulate a number of cellular and molecular processes such as wound repair and regeneration, hemostasis, inflammation, cell proliferation, and tissue remodeling. Many in vivo studies on wound models show that propolis has beneficial roles in wound healing. These beneficial roles have also been confirmed by clinical research studies. However, more research is needed on the dose, side effects, and clinical efficacy of propolis on wounds. In conclusion, research with different experimental models is promising as a potential therapeutic strategy in wound healing.

Keywords – Propolis, Wound healing, Proliferation, Inflammation

I. INTRODUCTION

A wound can be defined as the loss of functional function of tissues or cells, or the temporary or complete loss of physiological properties [1], [2]. Wound healing is a therapeutic challenge, and it is known to be a process that limits the human quality of life and social life [3]. The application of synthetic drugs available for relieving inflammation and treating wounds creates limitations such as allergic reactions and drug resistance. These limitations have led scientists to seek alternative ways [4]. In this context, natural products are mostly preferred as anti-inflammatory and healing compounds for the wound. Among these natural products, propolis is an important option [5], [6]. As a result of recent in vivo studies, it has been shown that propolis applied to the skin can also be effective in the treatment of burns [7]–[9].

A. *Propolis and Its Chemical Structure*

Propolis is a natural product collected by bees from many plants, such as leaf buds, resins, pine, and poplar [10], [11]. This waxy substance is used by bees to defend and protect their hives against any danger that may come from outside [12]–[15]. Its color and chemical content vary according to the source, geography, time, and season. [16]-[19]. Its structure varies depending on the temperature [19]. Its distinctive smell is due to the phenolic compounds and terpenes it contains [20]. In general, the content of propolis obtained from beehives consists of approximately 50% resin, 30% waxy structure, 10% essential or aromatic oil, 10% pollen, and other substances [11]. According to the latest studies, more than 300 compounds such as apigenin, acacetin, rutin, chrysin, kaempferol, resveratrol, myricetin, catechin, caffeic acid, cinnamic acid, galangin, and quercetin have been identified [19], [21]. In addition, it contains many vitamins, minerals, and enzymes [21]–[24]. Studies on the recommended dose of propolis for consumption are continuing. It has been shown that the dose accepted as safe in both animal experiments and healthy humans is 70 mg/day [25].

B. *Biological Activities of Propolis Components*

Propolis, which is one of the traditional treatment tools, stands out thanks to some biological activities of its components [1], [26]. Studies have revealed antioxidant, antifungal, anticancer, antidiabetic,

antimicrobial, antitumor, and anti-inflammatory effects, and these effects are mainly based on the flavonoid components in its structure. [27], [28].

Inflammation can be defined as the biological response of tissues to repair tissue damage and eliminate pathogenic agents [29]. The anti-inflammatory activity of propolis occurs through major mechanisms such as inhibition of cyclooxygenase (COX), inhibition of prostaglandin biosynthesis, free radical scavenging activity, and inhibition of nitric oxide synthesis [30], [31]. Studies have suggested that propolis has anti-inflammatory activity in an animal model and has an inhibitory effect on the prostaglandin production mechanism [32]. Propolis has been found to exert anti-inflammatory effects in both acute and chronic inflammation models [33]–[35]. This anti-inflammatory effect is achieved by the presence of cinnamic acids and active flavonoids found in propolis [19], [29]. It contains flavonoids such as propolis, naringenin, quercetin, acacetin, and cinnamic acid derivatives such as caffeic acid (CA) and caffeic acid phenyl ester (CAPE) [14].

The enzyme that converts arachidonic acid to prostaglandin, which is associated with the inflammatory process, is cyclooxygenase-2 (COX-2) [36]. In many studies, it has been found that CAPE inhibits the release of arachidonic acid from the cell membrane and thus inhibits COX-2 activation [37]. In addition, CAPE has been found to inhibit COX-1 and COX-2 activities in macrophages [34]. It has been observed that galangin in propolis also inhibits COX and lipooxygenase (LOX) activities, resulting in decreased COX-2 expression [38]. It has been found that the chrysin compound in propolis exhibits anti-inflammatory activity, and this mechanism is related to the suppression of proinflammatory COX-2 and inducible nitric oxide synthase (iNOS) activity [39], [40].

Depending on the dose, propolis was found to inhibit nitric oxide production through the release of hydrogen peroxide and exhibit an immune response [41]. Many studies have suggested that propolis extracts (such as polyphenols, flavonoids, caffeic acid, CAPE, and kaempferol) prevent damage caused by excessive inflammation by blocking lipid peroxidation in cells [42].

Cytokines appear as auxiliary agents to create the inflammatory response in wound healing. As a result of metabolic disorders, excessive production of proinflammatory cytokines (IL-6, IL-1, and TNF) occurs. In one study, it was observed that propolis improved the inhibition of IL-6, IL-1, and TNF-a in mice and increased anti-inflammatory cytokines. Thus, propolis was found to exert an immunomodulatory effect [43].

Reactive oxygen species (ROS) are important for maintaining cellular homeostasis. They are reactive signaling molecules that cause structural and functional deterioration in the cell [44]. They are also neutralized through cellular antioxidant systems [45]. ROS are involved in the detoxification process through enzymes such as glutathione, superoxide dismutase, and catalase [46]. Prolonged exposure of macromolecules such as DNA, lipids, and proteins in cells to ROS causes undesirable effects [47]. Phenolic acids, lignans, stilbenes, flavonoids, and benzoic acids are known to have antioxidant properties [44]. Studies have shown that the antioxidant activity of propolis is effective through intracellular mechanisms [48]. The compound has been shown to prevent hydrogen peroxide-induced DNA damage in cultured fibroblast cells [49]. In both animal and human studies, propolis has been found to increase antioxidant capacity and significantly reduce lipid peroxidation, which is associated with cardiovascular diseases [50]. The potent antioxidant properties of propolis have been attributed to its many components, such as quercetin, pinocembrin, CAPE, kaempferol, flavones, and flavonols [51], [52]. It is known that CAPE, one of the active compounds of propolis obtained from especially temperate climates, has a strong antioxidant property. It has been determined that this compound inhibits the activities of various enzyme systems such as LOX, COX-1, COX-2, xanthine oxidase, and glutathione S-transferase [19].

Other studies investigating the antioxidant capacity of propolis have reported a protective effect against heavy metal toxicity and liver damage [53, 54]. In addition, propolis and its active devices have been found to be potent inhibitors of nuclear transcription factor-kB (NF-kB) activation [55]. In the light of these studies, it has been shown that the oxidative stress groups in the group are potent antioxidants of propolis in many diseases [44].

It is known that there have been important developments in the diagnosis and treatment of cancer in recent years. However, due to its high mortality and therapeutic failures, it became popular

overnight as a naturally occurring drug with anticancer activity [56, 57]. Among these native cells, the anti-tumor effect of propolis was found [58], and the nuclei of apoptosis signaling pathways [59]–[61] had an inhibitory effect on the migration of cancer cells [62], [63]. In addition, in vitro studies have proven the anti-tumor effect of the substance in question on various cell lines such as leukemia, colon, pancreatic cancer, lung carcinoma, hepatocellular carcinoma, and breast carcinoma [64], [65]. Other propolises, such as galangin, nemoroson, and chrysin, are known to slow tumor formation rates [44].

C. *Effects of Propolis on Health*

According to studies, it is known that propolis has anti-diabetic activity. In a study of Sprague-Dawley rats, a significant reduction in blood sugar was observed in the propolis-treated group compared to the control group [66]. In addition, recent studies have shown that diabetes has a negative effect on heart disease and that the CAPE compound in propolis reduces the oxidative stress caused by diabetes [67]. Another study in diabetic rats found that oral propolis supplementation contributed to weight loss and the regulation of high blood sugar levels [68]. In one study, propolis was shown to be an alternative treatment, especially for diabetic foot ulcers, as it accelerates wound healing [69].

Parasite infection in the gastrointestinal tract usually occurs on contact. Symptoms of parasitic infection in this system include diarrhea, abdominal pain, bloating, and nausea. It has been shown that propolis, which is used in the treatment of viral infections, can also be used in the treatment of stomach ulcers thanks to its antacid and anti-inflammatory effects [70].

It has been determined that propolis polyphenols prevent the formation of pathogenic bacteria in the intestinal flora. Propolis is thought to have probiotic properties, but further research needs to be supported [71]. Studies have shown that propolis has a positive effect on a wide variety of pathological and physiological processes and significantly alters the gut microbiota [72].

Oxidative stress causes acute or chronic damage to brain tissue. Propolis and its content increase the activities of antioxidant enzymes, and as a result, lipid peroxidation protectors are known. In addition, oxidative stress has been observed in free brain tissue resulting from radiation via radical inhibition [73]. One of the components of propolis, pinosembrin, protects cells resulting from ischemia-reperfusion in mouse brain tissue and roots against apoptosis [74]. In addition to these studies, it is suggested that propolis is a preferable option in neurological diseases such as Parkinson's disease, cerebral artery occlusion, and epilepsy. However, these findings need to be supported by further studies [75].

Propolis is becoming popular in skin care products such as creams and emollients. This interest in care products is based on the anti-inflammatory and anti-microbial properties of propolis, in addition to its collagen-promoting effect. Silver sulfadiazine is generally used as a drug in wound treatment. In a study, it was reported that propolis supports repair more than silver sulfadiazine and significantly reduces free radical activity [21]. The ethanolic extract of propolis used in a clinical study on people with acne problems was found to have significant efficacy in the treatment of acne vulgaris [76].

D. *Propolis and Wound Healing*

It has been shown that the activities of propolis on tissue regeneration and repair may be related to its immunomodulatory, anti-microbial, and anti-inflammatory properties [77]. The normally occurring healing process continues with the initiation of the hemostasis process and the consequent activation of a complex inflammatory cell cascade [78]. Inflammatory cells such as neutrophils, monocytes, macrophages, fibroblasts, and lymphocytes, respectively, migrate towards the wound site after a certain period of time after injury [79]. It is known that mast cells play an important role in wound healing throughout the whole process. Neutrophils, with the help of mast cells, perform the first defense against infection by phagocytizing the remaining wastes and microorganisms. Macrophages then provide the second defense by eliminating the bacteria. Studies have shown that propolis reduces the number of mast cells and thus has a high potential for wound healing [80]. It has been shown that propolis, which is rarely on the agenda with its allergic effect and has no toxic effect as far as is known, is a good candidate to increase the proliferation and growth potential of cells in burn treatments [81].

II. CONCLUSION

As a result, it has been shown that propolis can be a new strategy to accelerate wound healing in various wounds, such as incisions, excisions, diabetic wounds, and burns. This is because there are many mechanisms to accelerate wound healing. However, its mechanisms are specific to the type of propolis and are known to depend on many factors. In addition, it is thought that propolis will provide new perspectives in the treatment of various diseases and wound healing and can be accepted as a new alternative treatment method due to its relatively easy accessibility and high efficiency. However, more research is needed to produce more effective evidence on this subject.

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