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Review

Potential role of propolis in wound healing: Biological properties and therapeutic activities

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ABSTRACT

Propolis is a resinous mixture that honey bees collect from the tree buds, sap flows, or other botanical sources. The chemical composition of propolis varies and depends on the geographical area, time of collection, seasonality, illumination, altitude, and food availability during propolis exploitation. The goal of this review is to discuss important concepts including mechanisms of action and therapeutic activities of propolis. The PubMed, ScienceDirect, and Cochrane Library databases were searched for the literature published from January the 1st 2000 to October the 1st 2017. Sixteen animals and three clinical studies were included. A quantitative and qualitative review was performed on the clinical trials and the animal studies were comprehensively overviewed. In this study, the clinical trials have been combined and the results were provided as meta-analysis. Propolis is a non-toxic natural product; however some cases of allergy and contact dermatitis to this compound have been described mainly among beekeepers. An important factor in impaired wound healing is biofilm formation; propolis as an anti-microbial agent can reduce biofilm generation and result in accelerated healing processes. Most of the *in vivo* studies on various wound models suggested the beneficial roles of propolis on experimental wound healing and this has also been approved in the clinical trial studies. However, there is a lack of information concerning, dose, side effects and clinical effectiveness of propolis on wounds. As the effectiveness of propolis between different products is variable, more characterizations should be done and future investigations comparing different propolis based products and characterization of their specific roles on different models of wounds are highly appreciated.

1. Introduction

Healing of a skin wound displays an extraordinary mechanism of cascading cellular functions which is unique in nature. Wound healing is a complex series of reactions that involves a number of overlapping processes, including induction of an acute-inflammatory process, regeneration, migration and proliferation of both parenchyma and connective tissue cells, synthesis of extra cellular matrix (ECM) proteins, and remodeling of connective tissue leading to formation of a scar tissue that is in coincidence with the development of wound contraction and epithelialization [1,2]. Wound defects are managed by several options. Wound coverage is the best option for managing small wound defects with no complication. However, managing some of the complicated wounds such as diabetic, chronic, infected, burned and large sized wound defects is technically demanding [3,4]. Healing of such wounds is a complicated situation and in addition to preventing and eliminating wound infection, the goal is to increase wound contraction and epithelialization while controlling the amount of scar tissue formation and consequently inhibiting the scar tissue contracture [4–6].

Propolis, or bee glue, is a natural resinous substance collected by honey bees from the tree buds or other botanical sources such as poplar, willow, birch, elm, alder, beech, conifer, and horse-chestnut trees [7–9]. Propolis is used by honeybees as a building material in the hive and protects the hive against bacterial and fungal infections [9]. Propolis has been used in traditional medicines for thousands of years [10]. *In vitro* studies have shown some types of propolis have antibacterial [7] and antifungal [11] activities based upon their constituents including flavonoids such as galangin [12] and hydroxycinnamic acids like caffeic acid [13]. One important factor in impaired burn wound healing is infection that may lead to death. Biofilm formation is an important factor in impaired wound healing and is responsible in delayed wound healing. Therefore, control of infection is a crucial step in healing processes [14]. The antimicrobial activity in addition to its role in inhibiting the biofilm formation have been suggested to be the most

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important biological properties of propolis, making it able to successfully fight against different bacteria such as *Staphylococcus aureus*, streptococci, *Moraxella catarrhalis* and some strains of tuberculosis mycobacteria which are resistant against most of the available antibiotics [15].

The biological properties of propolis are not limited to its anti-microbial activity. Preliminary *in vivo* studies suggest that propolis may be effective in treating the inflammatory component of skin burns in rats [16,17]. In addition, a clinical trial study has also shown that the Brazilian propolis skin cream is superior to silver sulfadiazine in treatment of partial thickness burn wounds [18]. Propolis has been shown to exhibit both immunosuppressive and immunostimulant effects [1,19]. Additionally, antioxidant activity of propolis has been shown previously so that it reduced the chances of cataracts in rat pups [20]. Finally, propolis has been shown to accelerate tissue repair by stimulating glycosaminoglycan synthesis and release that is necessary for granulation tissue formation in the wound bed, tissue growth, and wound closure [21]. Other biological properties such as hepatoprotectivity [22], antitumoral [2], and cytostatic activities [22] have been attributed to propolis. Although the *in vitro* and *in vivo* studies have proved the positive effects of propolis in wound healing, there is a lack of information concerning, dose, side effects and clinical effectiveness of this natural product on wound healing. The present review has mechanistically focused on the biological properties and therapeutic activities of propolis and reviewed the most recent *in vivo* and clinical trial studies to find out whether propolis is a valuable option in wound healing, modeling and remodeling.

2. History of propolis in medicine

Many records show that propolis have been used by ancient Egyptians, Persians, and Romans [23]. In 460–377 BC, Hippocrates favored the use of propolis to cure the external and internal wounds and ulcers [8,24]. However, propolis has often been used in elderly patients and lower interest can be found for the middle aged patients [8]. Renewed interest for application of propolis as a remedy for wounds coincided with the Renaissance theory of ad Fontes and propolis was used as a major ingredient of healing ointments, in the seventeenth century [8]. Development of research on propolis was strictly connected with the development of chemistry and the chemical composition of propolis was determined in the 19th and 20th centuries [8]. However, it has only been in the last fifty years that the scientists proved that propolis is an active and important medical substance in wound healing, tissue regeneration, and treatment of burns, neuro-dermatitis, leg ulcers, psoriasis, morphoea, herpes genitalis, pruritus ani and is also potentially active against dermatophytes [25].

3. Origin and chemical composition of propolis

Until 2000, much work has been performed on the chemical composition of propolis and more than 300 chemical compounds have been identified [26]. The composition of propolis varies from hive to hive, from district to district, and depends on the time of collection, seasonality, illumination, altitude, collector type, and food availability and activity developed during propolis exploitation [27,28] (Table 1). The color of propolis is often dark brown, but it can be found in green, red, black, and white hues, depending on the sources of resin found in the particular hive area. Honey bees are opportunists so that they gather what they need from available sources; thus the chemical composition of propolis varies considerably from region to region, along with the vegetation. For instance, in northern temperate climates, bees collect resins from trees (*e.g.* poplars and conifers).″Typical" northern temperate propolis has approximately 50% resin and balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% impurities.

Generally, the flavonoids, phenylpropenoid, cinnamic acids and their esters, and glycerides are the important compounds in propolis [50,51]. Caffeic acid phenefthyl ester (CAPE) is also a component of some varieties of propolis from New Zealand [40]. Propolis also contains some volatile oils, terpens and sesquiterpens, bee wax, naphthalene, stilbene derivatives and other components such as vitamins, proteins, amino acids, β steroid, alcohols and sugar [19]. The aromatic compounds are responsible for the anti-bacterial, anti-fungal, antiviral, anti-inflammatory and anti-cancer properties of propolis [27]. Propolis also contains persistent lipophilic acaricide, a natural pesticide that deters mite infestations [28].

The most widespread propolis types are green, poplar, birch, red, Mediterranean, Clusia, Pacific, Tunisian, Iranian, and Egyptian propolis that are different in geographic origin and plant source. Brazilian green propolis is the most commonly studied propolis and *Baccharis dracunculifolia* DC (Asteraceae), a plant native to Brazil, is its most important botanical source. The Brazilian green propolis is rich in prenylated, phenylpropanoids (*e.g.*, artepillin C) and diterpenes. Caffeoylquinic and prenylated cinnamic acids, such as artepillin C and baccharin have been reported as the main constituents of the Brazilian green propolis that are responsible for antioxidant effects and inhibitory activity against some enzymes [52–54]. It has been demonstrated that artepilin C can inhibit the mobilization of neutrophils in abdominal cavity [55,56].

Although the red propolis, similar to green propolis, originates from the *Apies mellifera*, they show different compositions as the bees additionally collect another plant (*Dalbergia ecastophyllum*) to make red propolis. Phenylpropanoids are dominating chemical component in red propolis. Terpenes, flavonoids, aromatic acids and fatty acids are also frequently found in red propolis. Furthermore, the main inorganic elements such as copper, manganese, iron, calcium, aluminum, vanadium, and silicon are identified in red propolis [57]. Daugsch et al. showed that Brazilian red propolis contain daidzein, formononetin, biochanin A (isoflavonoids), liquiritigenin, dalbergin and isoliquiritigenin [58]. Presence of these isoflavonoids has also been confirmed in *D. ecastophyllum* plant [59]. It has been observed that the content of flavonoids is higher in the red propolis than the green propolis. These values have been variable in different studies and such discrepancies may be due to natural factors, such as the seasonality and flora of each region [60,61]. de Almeida et al. proposed that there is a consistent relationship between the healing rate and presence of the flavonoids in propolis and the beneficial results obtained with red propolis may be due to presence of higher concentration of these compounds in this substance. Although the positive role of propolis on wound healing has been reported, its chemical composition has not yet been fully determined [61].

It has been demonstrated that the chemical profile of poplar propolis is similar to the propolis collected from many countries including China, Korea, Croatia, Tiwan, New Zealand, and Africa [62–64]. Poplar propolis is rich in flanvonoids, phenylpropanoids, terpenoids, stilbenes, lignans, coumarins, and their prenylated derivatives. Most compounds present in poplar propolis such as aromatic acids, esters, and flvonoids originate from poplar exudates, bee metabolism, and contamination with honey [65]. The quercetin and kaempferol derivatives are also found frequently in poplar propolis while it contains the lowest level of phenolic acids. In contrast, phenolic acids are dominating chemical compositions in Iranian propolis [66]. Besides poplar, *Ferula* species are another plant source of Iranian propolis, which is responsible for composition of tschimgin, tschimganin, ferutinin, and tefernin [26]. The database have demonstrated that flavonoids and phenolics or their synergistic effects are responsible for beneficial biological activities of poplar propolis [67]. In neotropical regions, in addition to a large variety of trees, bees may also gather resin from flowers in the genera Clusia and Dalechampia, which are the only known plant genera that produce floral resins to attract pollinators [68]. Clusia resin contains polyprenylated benzophenones [41,69].

Although there are poplar in Egypt, the chemical composition of the Egyptian propolis is also affected by the subtropical and tropical