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Immune's-boosting agent: Immunomodulation potentials of propolis

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Abstract:

With a concomitant increase in immune-related diseases such as allergic diseases, Type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease and other immune-related responses such as immunodeficiency, various infectious, diseases, vaccines, and malignancies, it has become very important to have a well-balanced and properly functioning immune system for the maintenance of human health. Recent scientific research has strongly suggested propolis as one of the most promising immunomodulation agents. This review describes recent findings with respect to propolis and its ingredients that show potential in this respect and evaluate their potential mechanisms. The author believes that propolis or/and its ingredients alone and in combination could be promising in manipulating the immune response and inducing immunomodulation. Further exploratory studies are needed to support large clinical trials toward further development of propolis.

Keywords:

Allergic diseases, immunodeficiency, immunomodulation, malignancies, propolis

Introduction

Propolis (bee's glue) has become the focus of interest of researchers in the last few decades because of its several biological and pharmacological properties.[1]

To produce propolis, honeybees collect glue materials actively exuding from wounds and different parts of plants.[2] The chemical composition of propolis is quite complicated. More than 600 constituents, such as polyphenols (flavonoids, phenolic acids, and their esters), terpenoids, steroids, and amino acids,[3,4] have been identified in different propolis samples in the world. However, studies attribute the biological and pharmacological properties of propolis to its high content of flavonoids.[5]

The aims of this review is to describe the recent findings with respect to propolis and its ingredients that show potential and evaluate their mechanisms. Owing to its multidisciplinary nature, the literature on propolis is scattered in a variety of the citations and indexes. Databases including Google Scholar, PubMed, Web of Science, and MEDLINE as well as online catalogs of some libraries were searched to identify related citations. Full bibliographical details were searched and verified for each citation selected. EndNote program was used to create a bibliographic database of the selected literature.

Immunomodulatory Effect

The immunomodulatory effects of propolis have been considered complementary and/or alternative treatment for many immune disorders.[6] In an *in vitro* study, propolis showed immunomodulatory effects on macrophages,[7] while propolis increased the ratio of $CD4^+/CD8^+$ T-cells *in vivo* in mice.[8] This could explain why

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propolis is used in acute and chronic inflammations in the lower and upper airway diseases, cutaneous ulcers, pharingotracheitis, periodontis, and sinusitis.[9]

In immunosuppressant models, administration of propolis prevented the cyclophosphamide effects and enhanced the survival rate of the mice.[10] The synergistic effects of propolis with Taishan Pinus massoniana pollen polysaccharide, "Taishan Pinus massoniana" pollen polysaccharide improved the function of immune system and decreased the viral loads in chickens coinfected with immunosuppressive viruses. This provided an insight into more effective natural preparations for the prevention and treatment of immunosuppressive diseases.[11] Propolis has been shown to increase its protective index when used as a vaccine adjuvant, offering a higher phagocytic activity, eliciting a persistent and higher antibody titers and mucosal immunity, enhancing cellular response, while promoting peripheral lymphocyte proliferation, increasing leukocytic reaction, reducing the optimum dose concentration, extending vaccine protection, inducing early protection, and enhancing nonspecific immunity.[12,13]

Propolis potentiates the host defense system and biological immune response modifiers. A study has shown that *in vitro* and *in vivo* supplementation of propolis flavonoids liposome with ovalbumin enhances cellular immune and humoral responses in mice. In addition, it can significantly enhance the phagocytic function of macrophages, the release of interferon-gamma (IFN-γ), interleukin-6 (IL-6), and IL-1β and could induce higher concentrations of many kinds of immune cells and various immunomodulatory cytokines that are vitally important for the maintenance of homeostasis.[14] Fischer *et al*. studied the adjuvant capacity of green propolis.

On cellular and humoral responses of mice immunized against inactivated Suid herpesvirus type 1, the results showed that propolis increased the cellular immune response, evidenced by the increase in the expression of mRNA to IFN-γ. Besides, it increased the percentage of mice protected against the challenge of a lethal dose of Suid herpesvirus type 1.[15] These findings may indicate the possibilities of using propolis and/or its ingredients as potential vaccine adjuvant. Nowadays, to improve the immune-modulating effect, propolis is made into microemulsion, a preparation which improves the therapeutic activity and targets specificity and which also offers a novel vehicle for drug delivery by controlling and allowing sustained release for local, enteral, and parenteral administration routes of propolis.[16]

Propolis stimulates the production of IL and tumor necrosis factor, by peritoneal macrophages of mice.[17] The bioactive compounds of propolis (phenolic and flavonoids) were considered major anticomplementary compounds.[18] *In vitro* assays showed that water-soluble preparations of propolis inhibited the alternative and classical pathways of the complement system.[19]

It has been found that propolis could relieve allergic disorders through inhibition of histamine release. It produced significant inhibition of both sneezing and antigen-induced nasal rubbing.[20] Furthermore, previous research found that caffeic acid phenethyl ester induced caspase-3 expression and inhibited nuclear factor-kB (NF-kB) and protein kinase-B signaling pathways in primary human $CD4^+$ T cells.[21] Other studies have confirmed that the antiallergy effect of propolis or/and its active constituents was due to the inhibition of platelet-activating factor release and NF-κB activation which result in the suppression of immunoglobulin E levels.[22] Consistent with these observations, a study has reported that the administration of oral propolis 200 mg/kg in an ovalbumin-induced rat model of allergic rhinitis was lower; eosinophil count, vascular proliferation, ciliary loss, inflammation, and allergic rhinitis symptom score compared to ketotifen, furoate, and mometasone groups.[23] These results support the antiallergic activity of propolis.

The results of study by Sy *et al*. on the effect of propolis on ovalbumin-induced asthma, animal model suggest that propolis or/and its extracts might be useful as a potential novel therapeutic agent or an adjuvant for the treatment of asthma.[24] This finding was confirmed by another study.[25] Dantas *et al*. reported that propolis could act directly on the T-cells inhibiting their differentiation and consequently the development of acquired immune response.[26]

Propolis activates macrophage through nitric oxide generation, from L-arginine.[27] Nitric oxide is an important microbicidal mechanism of macrophages for inhibiting mitochondrial respiration, DNA synthesis, and active transport in the bacterial and fungal membrane.[28] It was proved that propolis treatment counteracted the inhibition on toll-like receptor-4 expression and restored at least partially toll-like receptor-2 mRNA expression, and in animals, it contributed to the recognition of microorganisms during stressful conditions.[29]

With regard to the humoral immune response, the ethanolic extract of propolis has been found to increase the antibody production. Scheller *et al.* administered the ethanolic extract for short term in immunized mice (with sheep's red blood cell) and demonstrated higher antibody levels. They have associated this stimulatory activity with macrophage activation that leads to cytokine production and thereby the regulation on the functions of B- and T-cells.[30]

Orsolić and Basić also suggested that the increased IL-1 production by macrophages from propolis-treated mice might be associated with enhanced T- and B-cell proliferation.[6] Similarly, propolis administration in rats has been found to increase antibody production after 15 days of immunization.[31]

It has been shown that propolis has a robust effect on different cells of innate immune response through its ability to modulate antibody synthesis.[32] Furthermore, caffeic acid phenethyl ester administration to female mice for 14 days has been shown to increase antibody production, and it is attributed to the increased T-lymphocyte proliferation and secretion of IL-4 and IL-2 by splenocytes.[33] Moreover, the administration of caffeic acid phenethyl ester can protect against cyclosporine A-induced cardiotoxicity in rats.[34] Thus, propolis showed a positive effect on adaptive and innate immunity in aged mice.[35]

In athletes, it was found that propolis played a useful role against hyperthermal stress. It can reduce or reverse necrosis, hyperthermia-induced survival inhibition, glutathione depletion, superoxide production, and intracellular superoxide burst in a dose-dependent manner, which suggests that caffeic acid phenethyl ester can enhance hyperthermal tolerance in immune mononuclear cells of competitive cyclists.[36]

Recently published are promising results that indicate the possibility of using propolis derivative for the treatment or the prevention of the development of cancer through natural killer cytotoxic activity.[37]

Conclusion

Propolis is a complementary and alternative agent that promises to achieve a more effective immune system when the immune response is not sufficient to control a specific infection or pathological condition and a pathologically decreased/compromised condition. Further exploratory studies are needed to support large clinical trials toward further development of propolis.

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Conflicts of interest
There are no conflicts of interest.

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