Short Communication

Access this article online

Quick Response Code:

Website:
www.jfcmonline.com

DOI:
10.4103/jfcm.JFCM_46_18

Immune's-boosting agent: Immunomodulation potentials of propolis

Mohammed Al-Hariri

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

Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Address for correspondence:
Dr. Mohammed Al-Hariri, Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, P.O. Box 2114, Dammam 31451, Saudi Arabia.
E-mail: mtalhariri@iau.edu.sa

How to cite this article: Al-Hariri M. Immune's-boosting agent: Immunomodulation potentials of propolis. J Fam Community Med 2019;26:57-60.

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Al-Hariri MT. Propolis and its direct and indirect hypoglycemic effect. J Family Community Med 2011;18:152-4.
2. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol 1998;36:347-63.
3. Duman M, Özpolat E. Effects of water extract of propolis on fresh shibuta (*Barbus grypus*) fillets during chilled storage. Food Chem 2015;189:80-5.
4. Huang S, Zhang CP, Wang K, Li GQ, Hu FL. Recent advances in the chemical composition of propolis. Molecules 2014;19:19610-32.
5. Moreno MI, Isla MI, Sampietro AR, Vattuone MA. Comparison of the free radical-scavenging activity of propolis from several regions of Argentina. J Ethnopharmacol 2000;71:109-14.
6. Orsolić N, Basić I. Immunomodulation by water-soluble derivative of propolis: A factor of antitumor reactivity. J Ethnopharmacol 2003;84:265-73.
7. Koo H, Rosalen PL, Cury JA, Park YK, Ikegaki M, Sattler A, *et al.* Effect of apis mellifera propolis from two Brazilian regions on caries development in desalivated rats. Caries Res 1999;33:393-400.
8. Kimoto T, Arai S, Kohguchi M, Aga M, Nomura Y, Micallef MJ, *et al.* Apoptosis and suppression of tumor growth by artepillin C extracted from Brazilian propolis. Cancer Detect Prev 1998;22:506-15.
9. Maksimova-Todorova V, Manolova N, Gegova G, Serkedzhieva Iu, Uzunov S. Antiviral action of fractions isolated from propolis. Acta Microbiol Bulg 1985;17:79-85.
10. Dimov V, Ivanovska N, Bankova V, Popov S. Immunomodulatory action of propolis: IV. Prophylactic activity against gram-negative infections and adjuvant effect of the water-soluble derivative. Vaccine 1992;10:817-23.
11. Li B, Wei K, Yang S, Yang Y, Zhang Y, Zhu F, *et al.* Immunomodulatory effects of taishan pinus massoniana pollen polysaccharide and propolis on immunosuppressed chickens. Microb Pathog 2015;78:7-13.
12. Ashry el SH, Ahmad TA. The use of propolis as vaccine's adjuvant. Vaccine 2012;31:31-9.
13. Yuan J, Liu J, Hu Y, Fan Y, Wang D, Guo L, *et al.* The immunological activity of propolis flavonoids liposome on the immune response against ND vaccine. Int J Biol Macromol 2012;51:400-5.
14. Tao Y, Wang D, Hu Y, Huang Y, Yu Y, Wang D, *et al.* The immunological enhancement activity of propolis flavonoids liposome *in vitro* and *in vivo*. Evid Based Complement Alternat Med 2014;2014:483513.
15. Fischer G, Conceição FR, Leite FP, Dummer LA, Vargas GD, Hübner Sde O, *et al.* Immunomodulation produced by a green propolis extract on humoral and cellular responses of mice immunized with suHV-1. Vaccine 2007;25:1250-6.
16. Fan Y, Ma L, Zhang W, Xu Y, Suolangzhaxi, Zhi X, *et al.* Microemulsion can improve the immune-enhancing activity of propolis flavonoid on immunosuppression and immune response. Int J Biol Macromol 2014;63:126-32.
17. Moriyasu J, Arai S, Motoda R, Kurimoto M. *In vitro* activation of mouse macrophage by propolis extract powder. Biotherapy 1994;8:364-5.
18. Georgieva P, Ivanovska N, Bankova V, Popov S. Anticomplement activity of lysine complexes of propolis phenolic constituents and their synthetic analogs. Z Naturforsch C 1997;52:60-4.
19. Ivanovska ND, Dimov VB, Bankova VS, Popov SS. Immunomodulatory action of propolis. VI. Influence of a water soluble derivative on complement activity *in vivo*. J Ethnopharmacol 1995;47:145-7.
20. Shinmei Y, Yano H, Kagawa Y, Izawa K, Akagi M, Inoue T, *et al.* Effect of Brazilian propolis on sneezing and nasal rubbing in experimental allergic rhinitis of mice. Immunopharmacol Immunotoxicol 2009;31:688-93.
21. Wang LC, Chu KH, Liang YC, Lin YL, Chiang BL. Caffeic acid phenethyl ester inhibits nuclear factor-kappaB and protein kinase B signalling pathways and induces caspase-3 expression in primary human CD4+T cells. Clin Exp Immunol 2010;160:223-32.
22. Park SG, Lee DY, Seo SK, Lee SW, Kim SK, Jung WK, *et al.* Evaluation of anti-allergic properties of caffeic acid phenethyl ester in a murine model of systemic anaphylaxis. Toxicol Appl

Pharmacol 2008;226:22-9.
23. Yasar M, Savranlar Y, Karaman H, Sagit M, Silici S, Ozcan I, *et al.* Effects of propolis in an experimental rat model of allergic rhinitis. Am J Otolaryngol 2016;37:287-93.
24. Sy LB, Wu YL, Chiang BL, Wang YH, Wu WM. Propolis extracts exhibit an immunoregulatory activity in an OVA-sensitized airway inflammatory animal model. Int Immunopharmacol 2006;6:1053-60.
25. Jung WK, Lee DY, Choi YH, Yea SS, Choi I, Park SG, *et al.* Caffeic acid phenethyl ester attenuates allergic airway inflammation and hyperresponsiveness in murine model of ovalbumin-induced asthma. Life Sci 2008;82:797-805.
26. Dantas AP, Salomão K, Barbosa HS, De Castro SL. The effect of bulgarian propolis against *Trypanosoma cruzi* and during its interaction with host cells. Mem Inst Oswaldo Cruz 2006;101:207-11.
27. MacFarlane AS, Schwacha MG, Eisenstein TK. *In vivo* blockage of nitric oxide with aminoguanidine inhibits immunosuppression induced by an attenuated strain of *Salmonella typhimurium*, potentiates salmonella infection, and inhibits macrophage and polymorphonuclear leukocyte influx into the spleen. Infect Immun 1999;67:891-8.
28. Chan J, Xing Y, Magliozzo RS, Bloom BR. Killing of virulent *Mycobacterium tuberculosis* by reactive nitrogen intermediates produced by activated murine macrophages. J Exp Med 1992;175:1111-22.
29. Pagliarone AC, Orsatti CL, Búfalo MC, Missima F, Bachiega TF, Júnior JP, *et al.* Propolis effects on pro-inflammatory cytokine production and toll-like receptor 2 and 4 expression in stressed mice. Int Immunopharmacol 2009;9:1352-6.
30. Scheller S, Gazda G, Pietsz G, Gabrys J, Szumlas J, Eckert L, *et al.* The ability of ethanol extract of propolis to stimulate plaque formation in immunized mouse spleen cells. Pharmacol Res Commun 1988;20:323-8.
31. Sforcin JM, Orsi RO, Bankova V. Effect of propolis, some isolated compounds and its source plant on antibody production. J Ethnopharmacol 2005;98:301-5.
32. Orsi RO, Sforcin JM, Funari SR, Bankova V. Effects of Brazilian and Bulgarian propolis on bactericidal activity of macrophages against *Salmonella typhimurium*. Int Immunopharmacol 2005;5:359-68.
33. Park JH, Lee JK, Kim HS, Chung ST, Eom JH, Kim KA, *et al.* Immunomodulatory effect of caffeic acid phenethyl ester in Balb/c mice. Int Immunopharmacol 2004;4:429-36.
34. Rezzani R, Giugno L, Buffoli B, Bonomini F, Bianchi R. The protective effect of caffeic acid phenethyl ester against cyclosporine A-induced cardiotoxicity in rats. Toxicology 2005;212:155-64.
35. Gao W, Wu J, Wei J, Pu L, Guo C, Yang J, *et al.* Brazilian green propolis improves immune function in aged mice. J Clin Biochem Nutr 2014;55:7-10.
36. Chen YJ, Huang AC, Chang HH, Liao HF, Jiang CM, Lai LY, *et al.* Caffeic acid phenethyl ester, an antioxidant from propolis, protects peripheral blood mononuclear cells of competitive cyclists against hyperthermal stress. J Food Sci 2009;74:H162-7.
37. Takeda K, Nagamatsu K, Okumura K. A water-soluble derivative of propolis augments the cytotoxic activity of natural killer cells. J Ethnopharmacol 2018;218:51-8.