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Immune Enhancer of Bee Propolis

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A B S T R A C T

Propolis had been well documented in traditional medicine for treating systemic immune diseases, allergic diseases, viral diseases and organ-specific inflammatory diseases since more than one thousand years. During the last ten years, immunoregulatory and anti-inflammatory properties of propolis have been published. The therapeutic characteristics of propolis have been well known for a very long time. It has been used in folk medicine for different nations as early in Egypt as 3000 BC. In recent years, propolis has become a subject of increasing interest for chemists and biologists. It had various biological and therapeutic activities. In in vitro and in vivo assays provided new information concerning its mechanisms of action. Propolis possesses variable biological activities activity was investigated on antiviral, antibacterial, fungicidal, anti-inflammatory, antitumor, antiparasitic, antioxidant, cytokines and immune response. Immunomodulatory and antitumor properties, considering propolis effects on antibody production and on different cells of the immune system which involving the innate and adaptive immune response. This review was aimed to through more light on the enhancing activity of propolis on immune response, and opens a new perspective on the investigation of propolis biological properties on immune mechanism.

Introduction

Propolis, the resinous product collected by honey bees from plants. Propolis was used specially in antiquity in Egypt. Propolis was very well known to the priests who had monopolized medicine, chemistry and art of mummifying corpses from some thousand years BC (Hegazi, 1998). It is also, demonstrated by the very Greek name as known to the old Greeks. The word propolis is derived from the Greek pro (before) and polis (city). The first head the opinion that bees harvest propolis from resin of willow buds, of poplar, wild chestnut and other plants and other writer assumed that bees harvest it from Styrax (Makashvili, 1978). Propolis. When burnt, it exhibits a smell of aromatic resins of great value. Propolis is used to make the protective shield at the entrance to a hive. Bees use their glue to fill the cracks in the hive, to attach the corners of frames to the grooves in the hive, and also to polish the cells of the honey comb. The bodies of dead lizards, snakes and mice that have entered hives are sealed into the walls with bee glue, thereby

protecting the colonies against the unpleasant odder and bacterial flora of the putrefying corpses (Ghisalberti *et al.,* 1978).

The Holy Qur'an has a long Sorat (chapter) with the name of bees (Al Nahl). The Ayahs number 68-69 In the name of God Most Gracious, Most Merciful (68) "And thy Lord taught the Bee to build cells in hills, On trees and in (men's) habitations; (69) Then to eat of all The produce (of the earth), And find with skill the spacious Paths of its Lord: there issues From within their bodies A drink of varying colors, Wherein is healing for men: Verily in this is Sign For those who give thought".

Abu Ali bin Sina (Avicenna) distinguishes two kind of wax in his will know work The Canon Medical Science the clean and the black wax. The clean wax is that which composes the comb wells where the bees rear the brood and store the honey and the black was is the filth the hive. It is clear enough that the black wax is propolis that after Avicenna's testimony has the characteristic of eliminating the spikes. It also rarefies, cleans and Soaks. He also writes that by its strong smell, the black wax makes you sneeze.

Propolis is used as folk medicine since ancient time. During the last ten years, immunoregulatory and anti-inflammatory properties of propolis have been published. Propolis ointment used in Folk Georgian medicine, to cure some diseases. There was the custom of placing a propolis cake on the belly button of the newborn baby and also, they rubbed children's toys with propolis. Also, in folk medicine, the use of propolis is widely known especially for the treatment of corns. Also, people inhale propolis in case of affections of respiratory tracts and of the lungs. It is also efficient for burns and angina. The therapeutic characteristics of the propolis have been well known for a very long time. This is explained by its very pronounced anti-microbial characteristics. Propolis was used effectively on wounds by doctors during the Anglo- Boer war and during The World War II. It was also used in hospitals. From 1969 Orthodox medicine in USSR accepted the use of propolis 30 % (30 % alcoholic solution of propolis). It is produced by the pharmaceutical product plant in Tallinn (Makashvili, 1978).

Beekeepers well-known propolis, or "bee glue," that find in their hives. It is a resinous product collected by honeybees. It is being dark green or brown in color with a pleasant flavor of poplar buds, honey, wax and vanilla but it can also have a bitter taste. It is used by bees as glue in general-purpose as well as is used in folk medicine for long time in different nations (Hegazi and Abd El Hady, 2008).

The knowledge since humans have used propolis for different purposes, its properties with scientific basis is not only of academic interest but also of those who use propolis as well (Sforcin, 2007). The primary function of the innate immune system is the detection of pathogens (Banskota *et al.,* 2001) and the rapid activation of host defense mechanisms (Iwasaki and Medzhitov, 2004 and Yarovinsky and Sher, 2006). The detailed mechanisms of actions of propolis and its components on immune cells, however, are still unknown. Cytokines (Greek cyto-, cell; and -kinos, movement) are a category of signaling molecules that are used extensively in cellular communication (Weaver *et al.,* 2007). They are proteins, peptides, or glycoproteins. The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. (Gilman *et al.,* 2001). Cytokines are small secreted proteins which mediate and regulate immunity, inflammation and hematopoiesis. Cytokine is a general

name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes).

Cytokines are a category of signaling molecules used extensively in cellular communication. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cells (). They released by cells and affect the behavior of other cells, and sometimes the releasing cell itself (Watford *et al.,* 2003). Cytokines acts through receptors, and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations.

The propolis contains a variety of biologically active compounds such as flavonoids, vitamins, antioxidants and hydrogen peroxides (Hegazi and Abd El Hady, 2002 and Abd El-Hady *et al.,* 2007). Due to its biological properties as antiprotozoal (Hegazi *et al.,* 2014b and Hegazi *et al.,* 2018), antiparasitic (Hegazi *et al.,* 2007a,b and Gaddi and Yap, (2007), antimicrobial (Hegazi and Abd El Hady, 2001; Park *et al.,* 2004; and Hegazi *et al.,* 2014a), antifungal (Hegazi *et al.,* 2000), and antiviral agent (Hegazi *et al.,* 2012, and Fan *et al.,* 2013), hepatoprotective (Gonzales *et al.,* 1995), antioxidant (Abd El Hady *et al.,* 2007), immunostimulating (Hegazi and Abd El Hady, 1994, and Takagi *et al.,* 2005), localized plaque psoriasis (Hegazi *et al.,* 2013) and cytostatic (Banskota *et al.,* 2001).

The chemical composition of propolis appeared to be extremely complex and more than 300 compounds have been identified so far (Marcucci, 1995), the most important ones being polyphenols (Hegazi and Abd El Hady, 1997). Propolis is a well-known bee product containing more than 2000 identified compounds (Bojić *et al.,* 2018).

The major components of propolis exerted beneficial effects by polyphenols, caffeic acid phenethyl ester (CAPE), chrysin and other flavonoids (Hegazi *et al.,* 2000; Hegazi and Abd El Hady, 2002; Hegazi *et al.,* 2007a, b). Propolis has modulatory action on murine peritoneal macrophages, increasing their microbicidal activity and stimulant action on antibody production (Sforcin, 2007). The synergistic effects of wide range of compounds present in propolis are the results of antioxidants activity (Hegazi and Abd Al Hady, 2009) and hepatocytes protection (El-Khatib *et al.,* 2002) and anti-inflammatory (Rashid *et al.,* 2016).

Propolis contains natural flavonoid, chrysin (5,7-dihydroxyflavone), it has beneficial effects including anti-tumor and anti-oxidant activities. The mode of action of chrysin is to decrease gene expression of pro-inflammatory cytokines such as, tumor necrosis factor-α, IL (interleukin)-1β, IL-4, and IL-6 in mast cells (Bae *et al.,* 2011). Chrysin also significantly reduced the serum levels of pro-inflammatory cytokines, interleukin-1 beta (IL-1β) and IL-6 (Fitzpatrick *et al.,* 2001 and Ahad *et al.,* 2014). Ansorge *et al.,* (2003) demonstrate that propolis has a direct regulatory effect on basic functional properties of immune cells where cytokines produced by monocytes/ macrophages (IL-1β, IL-12), by Th1 type (IL-2) as well as Th2 type (IL-4) lymphocytes were found to be also suppressed. Also, Mossalayi *et al.,* ((2014) found that propolis decreased both monokines and interferon γ (IFNγ) production and induces potent anti-inflammatory activity due to their complementary immune cell modulation. Propolis inhibitory effects on

lymphoproliferation may be associated to its anti-inflammatory property. In immunological assays, the best results were observed when propolis was administered over a short-term to animals (Sforcin, 2007). Inflammatory cytokines and oxidative stress have a central role in the pathogenesis of acute pancreatitis. Propolis has anti-inflammatory and anti-oxidant effects. The therapeutic role of ethanolic extract of propolis on a cerulein-induced acute pancreatitis model in rats was investigated by üyükberber *et al.,* (2009). They found in the acute pancreatitis group, the tissue revealed massive edema and inflammation with less fatty necrosis when compared to the sham and control groups. In the ethanolic extract of propolis group, in particular, tissue edema was improved markedly (p=0.001). Tissue inflammation and fatty necrosis were decreased with ethanolic extract of propolis treatment.

Girgin *et al.,* (2009) studied, the immunomodulatory effects of six Turkish propolis samples were evaluated by using the in vitro model of peripheral blood mononuclear cells (PBMC). The benefit of propolis, in most of the diseases the cellular immune reaction is activated, neopterin levels in body fluids are increased and enhanced tryptophan degradation is observed. Concentrations of neopterin, tryptophan, kynurenine and pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) were determined. In PBMC treated with mitogen phytohaemagglutinin, neopterin production and tryptophan degradation by enzyme indoleamine 2,3-dioxygenase (IDO) as well as release of cytokines was significantly enhanced and upon treatment with propolis extracts all these effects were dose-dependently suppressed. Caffeic acid phenethyl ester (CAPE) is a biologically active component of propolis, a resinous material obtained from bee hives. Song *et al.,* (2008) evaluated the anti-inflammatory effect of CAPE on cultured human middle ear epithelial cells (HMEECs). They suggested that the anti-inflammatory effect of caffeic acid phenethyl ester (CAPE) is due to its inhibition of tumor necrosis factor (TNF)-alpha expression and interleukin (IL)-8 production. The anti-inflammatory effect of CAPE is possibly through the inhibition of nuclear factor (NF)-kappaB via the suppression of inhibitor-kappaB-alpha (IkappaB-alpha) degradation.

Caffeic acid phenethyl ester (CAPE) is an active component of honeybee propolis extracts. It has several positive effects, including anti-inflammatory, anti-oxidation, anti-cancer, anti-bacterial, anti-viral, anti-fungal, and immunomodulatory effects. In particular, the suppressive effect of NF-kappaB may disrupt a component of allergic induction. Jung *et al.,* (2008) determined whether treatment with CAPE results in significant inhibition of asthmatic reactions in a mouse model. An increase in the number of eosinophils in bronchoalveolar lavage (BAL) fluid; a marked influx of inflammatory cells into the lung around blood vessels and airways, and airway luminal narrowing; the development of airway hyperresponsiveness (AHR); the presence of tumor necrosis factor-alpha (TNF-alpha) and Th2 cytokines, including IL-4 and IL- 5, in the BAL fluid; and the presence of allergen-specific IgE in the serum.

Choi and, Choi (2008) reported that CAPE exerts its anti-inflammatory action (inhibition of tumor necrosis factor-induced expression of intercellular adhesion molecule-1 and CC chemokine ligand-2) via NF-kappaB inhibition by two distinct molecular mechanisms in a cell-specific manner: CAPE inhibited downstream pathways of inhibitor kappaB (IkappaB) degradation in monocytic cells, while activation of upstream IkappaB

kinase was suppressed by CAPE pre-treatment in astroglial cells; and (ii) CAPE paradoxically activates the c-Jun N-terminal kinase (JNK) pathway, which might be responsible for its pro-apoptotic action and divergent regulation of proinflammatory mediators such as CXC chemokine ligand-8. Park *et al.,* (2004) evaluated the effects of CAPE on the active systemic anaphylaxis induced by ovalbumin (OVA) challenge in mice. Histopathological analysis, nuclear factor (NF)-kappaB activation, and the plasma levels of histamine and total IgE after allergen challenge were evaluated. After challenges, all of the sham-treated mice developed anaphylactic symptoms, increased plasma levels of histamine and OVA-specific IgE, marked vascular leakage, NF-kappaB activation, platelet-activating factor (PAF) production, and histological changes. Sy *et al.,* (2006) found that the higher dose of propolis extracts decreases the level of IL- 5 in BALF. The splenocytes from mice administered with propolis extracts (low- and high-dose groups) exhibit a strong inhibition of IL-10 secretion and up-regulation of IFN-gamma secretion in splenocytes stimulated with concanavalin A (ConA). In addition, cytokine (IFN-gamma, IL-6, and IL-10) secretion in OVA-stimulated splenocytes from the propolis groups was significantly lower than that in the control group. These results suggest that propolis extracts may be a potential novel therapeutic agent for asthma.

Furthermore, CAPE suppressed *H. pylori*-induced cell proliferation and production of the cytokine's TNF-alpha and IL- 8. In addition, CAPE blocked *H. pylori*-induced COX-2 expression. The inhibition of such transcription by CAPE could result in suppression of many genes during *H. pylori*-induced inflammation, and also provide new insights into the anti-cancer and anti-inflammatory properties of CAPE (Abdel-Latif *et al.,* 2005). Márquez *et al.,* (2004) evaluated the immunosuppressive activity of CAPE in human T-cells, discovering that this phenolic compound is a potent inhibitor of early and late events in T-cell receptor-mediated T-cell activation. They found that CAPE specifically inhibited both interleukin (IL)-2 gene transcription and IL-2 synthesis in stimulated T-cells. To further characterize the inhibitory mechanisms of CAPE at the transcriptional level. Takagi *et al.,* (2005) focused on immune stimulation by Propolis, and examined changes in the effect of irradiation after Propolis administration. They found that cytokines released from macrophages in mouse peripheral blood after Propolis administration activated helper T-cells to proliferate. In addition, activated macrophages in association with the secondary T-lymphocyte activation increased IFN-gamma production and stimulated proliferation of cytotoxic T-cells and suppressor T-cells, indicating the activation of cell-mediated immune responses. Blonska *et al.,* (2004) indicated that EEP exerts its inhibitory effect on the IL-1beta and iNOS gene expression in J774A.1 macrophage at the transcriptional level.

Tested flavone derivatives contribute to the anti-inflammatory activity of propolis. The cytokine, IL-2, IL-4 and IFN-gamma were significantly increased at the dose of 20 mg/kg CAPE group. These results suggest that CAPE could have immunomodulatory effects in vivo (Park *et al.,* 2004). Ansorge *et al.,* (2003) studied the effects of different propolis extracts, of the flavonoids hesperidin and quercetin as well as of caffeic acid phenethyl ester (CAPE) on basic human immune cell functions by measuring the effects on DNA synthesis and production of different types of cytokines, namely IL-1beta, IL-12, IL-2, IL-4, IL-10 and TGF-beta1, of mitogen-activated peripheral blood mononuclear cells (PBMC) as well as of purified T lymphocytes. The data clearly

showed that propolis was capable of dose-dependently suppressing phythemagglutinin (PHA)-induced DNA synthesis of PBMC and T cells. Moreover, cytokines produced by monocytes/macrophages (IL-1beta, IL-12), by Th1 type (IL-2) as well as Th2 type (IL-4) lymphocytes were found to be also suppressed, whereas the production of TGF-beta1 by T regulatory cells was ascertained to be increased.

The immune system has a variety of regulatory/suppressive processes, which are decisive for the development of a healthy or an allergic immune response to allergens. NK1 and NK2 subsets have been demonstrated to display counter regulatory and provocative roles in immune responses, similar to Th1 and Th2 cells. T regulatory cells suppressing both Th1 and Th2 responses have been the focus of intensive research during the last decade. Deniz *et al.,* (2008) investigated the regulatory NK cells in humans, by characterization of NK cell subsets according to their IL-10 secretion property. Freshly purified IL-10-secreting NK cells expressed up to 40-fold increase in IL-10. The effect of IL-10+ NK cells on Ag-specific T cell proliferation has been examined in bee venom major allergen, phospholipase A2- and purified protein derivative of *Mycobecterium bovis*-induced T cell proliferation. IL-10+ NK cells significantly suppressed both allergen/Ag-induced T cell proliferation and secretion of IL-13 and IFN-gamma, particularly due to secreted IL-10 as demonstrated by blocking of the IL-10 receptor. These results demonstrate that a distinct small fraction of NK cells display regulatory functions in humans. Immunomodulatory and antitumor properties, considering propolis effects on antibody production and on different cells of the immune system which involving the innate and adaptive immune response. The propolis modulatory action on murine peritoneal macrophages leading to increase their microbicidal activity, this was confirmed by in vitro and in vivo assays. Also, its stimulant antibody production and increase action on the lytic activity of natural killer cells against tumor cells. The inhibitory effects of propolis on lymphoproliferation may be associated to its anti-inflammatory property (Sforcin, 2007).

Yang *et al.,* (2014) found that in vitro propolis flavonoids liposome can significantly enhance the phagocytic function of macrophages and the release of IL-1β, IL-6, and IFN-γ and activate the cellular and humoral immune response, including higher-level of IgG, IL-4, and IFN-γ in serum and the proliferation rates of splenic lymphocytes. Hegazi *et al.,* (2017) studded the influence of Egyptian propolis on immunological responses with special reference to cytokine levels of infected rats with *Toxoplasma gundi* and treated with 0.1 ml propolis day after day till the end of the experiment (28 days). Immune response of rats was evaluated weekly. They found that the propolis was the highest in the toxoplasma antibodies titer when comparing with control group from the 2nd week to the end of experiment. Serum level of cytokines was consistently higher in the treated and propolis infected rats compared with controls. Serum levels of IFN-γ, IL-1B and IL-6 were decreased in propolis and returned to infection at day 7 post-infection.

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