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Effects of Propolis on Immune System

Hayriye ALP*

NecmettinErbakan Üniversites Getat Merkezi Konya / TURKEY

** Corresponding author (Sorumlu yazar): hayriyebalp@yahoo.com*

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ABSTRACT: *Propolis is a natural product derived from plant resins collected by honey bees. It is used by bees as glue, a general-purpose sealer, and as draught-extruder for bee hives. Propolis has been used in folk medicine for centuries. It is known that propolis possesses anti-microbial, antioxidative, anti-ulcerand anti-tumor activities. Therefore, propolis has attracted much attention in recent years as a useful or potential substance used in medicine and cosmetics products. Furthermore, it is now extensively used in food sand beverages with the claim that it can maintain or improve human health. The chemical composition of propolis is quite complicated. More than 300 compounds such as polyphenols, phenolic aldehydes, sequiterpenequinines, coumarins, amino acids, steroid sand inorganic compounds have been identified in propolis samples. The contents depend on the collecting location, time and plant source. Consequently, biological activities of propolis gathered from different phytogeographical area sand time periods vary greatly. The chemical composition and beneficial properties of propolis vary greatly depending on the phytogeographical areas, seasonal collection time, and botanical source. Polyphenols found in fruits and vegetables are beginning to receive increased attention due to the vital role in protecting neural cells from oxidative stress and neuroinflammation associated with normal aging and chronicage-related diseases.*

Keywords: *Propolis, immune system, biological activities,* ***Apis mellifera*** L.

Propolisin İmmun Sistem Üzerine Etkileri

ÖZ: *Propolis, bal arıları tarafından toplanan bitki reçinelerinden elde edilen doğal bir üründür. Arılar tutkal, genel amaçlı sızdırmazlık maddesi ve arı kovanları için taslak ekstrüzyon makinesi olarak kullanılır. Propolis yüzyıllardır halk tıbbında kullanılmıştır. Propolis'in anti-mikrobik, antioksidatif, anti-ülser ve anti-tümör aktivitelerine sahip olduğu bilinmektedir. Bu nedenle, propolis son yıllarda tıp ve kozmetik ürünlerinde kullanılan yararlı veya potansiyel bir madde olarak dikkat çekmiştir. Dahası, artık insan sağlığını koruyabileceği veya geliştirdiği iddiasıyla gıda kumları içeceklerinde yaygın bir şekilde kullanılmaktadır. Propolisin kimyasal bileşimi oldukça karmaşıktır. Propolis örneklerinde polifenoller, fenolik aldehitler, sekuiterpen kininler, kumarinler, amino asitler, steroid inorganik bileşikler gibi 300'den fazla bileşik tespit edilmiştir. İçerik, toplanma yerine, zamana ve bitki kaynağına göre değişebilir. Sonuç olarak, farklı fitocoğrafik bölgelerin farklı dönemlerinden toplanan propolisin biyolojik faaliyetleri büyük ölçüde değişir. Propolisin kimyasal bileşimi ve faydalı özellikleri, fitocoğrafik alanlara, mevsimlik toplama süresine ve botanik kaynağa bağlı olarak büyük ölçüde değişir. Meyve ve sebzelerde bulunan polifenoller, nöral hücrelerin oksidatif stres ve normal yaşlanmaya ve kronik alyuvar hastalıklarına bağlı nöroinflamasyona karşı korunmada yaşamsal rolü bulunur.*

Anahtar kelimeler: *Propolis, immun system, biyolojik aktiviteler,* ***Apis mellifera*** L.

INTRODUCTION

Natural products have been used for thousands of years in folk medicine for several purposes. Among them, propolis has attracted increased interest due to its antimicrobial activity against a wide range of pathogenic microorganisms. Propolis, sometimes also referred to 'bee glue', is the generic name for the resinous substance collected by honeybees (*Apis mellifera* ***L.***) from various plant sources (Burdock, 1998; Kujumgiev *et al*., 1999; Almas *et al*., 2001).

Propolis, also known as bee glue and bee propolis, is a brownish resinous substance collected by bees, mainly from poplar and conifer buds, and used to

seal their hives. Because of antimicrobial propertis of propolis, it helps keep hives free of germs. Propolis has a long history of use in folk medicine and was even used as an official drug in London in 1600s. Over time propolis has been used for many purposes and marketed as lozenges, cough syrups, tooth-pastes, mouth rinses, lipsticks, cosmetics and even for the varnishing of Stradivarius violins. It appears to have antimicrobial and anti-inflammatory activities (Ledon *et al.,* 1997; Hendler and Rorvik, 2008).

The composition of propolis is varable, depending on the locale and variety of trees and other plants used for the collection. For example, unique constituents have been identified in propolis collected in Cuba and Brazil. The primer chemical clases found in propolis are flavonoids, phenolics and terpenes. The flavonoids include quercetin, apegenin, galangin, kaempferol, luteolin, pinocembrin, pinostrobin and pinobanksin. The phenolic ester (caffeic acid phenethyl ester or CAPE) present in propolis are poorly soluble in water. In propolis structure found 180 different compounds. As pharmacological the most effective groups are; flavons, flavanols, flavanon, phenolic and aromatic. In structure propolis has 38 flavonoid; galangin, camferol, quersetin, pinosembrin, pinosambrin, pinobanksin. The phenolic compunds are sinnamic alcohol, sinnamic acid, benzyl alcohol, benzoic acid, caffeic acid, phenylacid acid (Yücel *et. al*., 2014).

Action and pharmacology

A list of possible actions of propolis includes: antibacterieal, antifungal, antiviral (includindg anti HIV-1 activity) antioxidant, anticarsinogenic, antitrombotic and immunomodulatory.

Mechanism of action

The mechanism of thr possible actions of propolis may be understood by reviewing research findings on some of the individual compounds found in it. It is the difficult to study the mechanism of actions of more than one compound at a time. Therefore the following descriptions apply only to single compound to the possible action of such a complex substance as propolis is diffucult to know.

Caffeic acid phenethyl ester (CAPE) inhibits the lipoxgenase pathway of arachidonic acid, resulting in anti-inflammatory activity. CAPE is also known to have anticarcinogenic, antimitogenic and immunomodulatory properties. CAPE has been found to completly inhibit the activation of the the nuclear transcription factor NF-Kappa B by tumor necrosis factor (TNF) as well as by the other pro-inflammatory agents. The inhibition of NF-Kappa B activation may provide the molecular basis for its immunomodulatory, anticarsinogenic, anti-inflammatory and antiviral activities. It is possible that CAPE exerts its effects by inhibiting reactive oxygen spesies (ROS) production. ROS are known to play a major role in the activation of NF-Kappa B (Natarajan *et al.,* 1996; Hendler and Rorvik, 2008).

Compounda in propolis found to have antibacterial activity include a polyisoprenylated benzophenone galangin, pinobanksin and pinocembrin. The exact mechanism of antimicrobial action of these compounds is not known (Grange and Davey 1990; Hendler and Rorvik, 2008).

Indications and usage

Propolis what defined as nature antibiotic was inhibitory effect on 21 bacteria, 9 mushrooms, 3 protozoa, and a large number of virusus. There is evidence that propolis has some broad antimicrobial activity and it may have anti-inflammatory effects that could make it useful in the treatment of some forms of arthritis among other disorders. There is also some evidence of anti-cancer activity (Hendler and Rorvik, 2008).

Researches summary

In vitro and animal studies on propolis and derivative constituents have shown anti-bacterial, antiviral and antifungal effects. It shows activity in culture againsts a broad spectrum of pathogens, including influenza and herpes viruses, as well as HIV and various fungal and bacterial organisms (Harish *et al.,* 1997).

In a study of scool children an aqueous propolis extract was judget effectif in reducing the incidence and intensity of acute and chronic

rhinopharyngitis. ın another study involving 10 volunteers, it exerted activity against oral bacteria. A Cuban study concluded that propolis is more effective than tinidazole against giardia. In a comprehensive study on propolis of different geographic origin, Kujumgiev *et al.* (1999) have investigated the antibacterial activity on *Escherichia coli*, antifungal activity on *Candida albicans* and antiviral activity on Avian influenza. And he found that all samples were active against the fungal and gram positive bacterial test strains and most of them showed antiviral activity. Santos (2002) investigated the inhibitory activity of Brazilian propolis on a *Fusobacterium nucleatum*, *Porphyromonas gingivalis* and *Prevotella intermedia* and found out that all of the assayed bacterium species were susceptible to propolis extract. Koo (2000) compared the antimicrobial effects of *Arnica montana*, a perennial herbaceous plant, to propolis extract on 15 oral pathogen microorganism and stated that propolis extracts showed in vitro antibacterial activity and inhibition of cell adherence while *Arnica* extract was only slight active. The results of the aforementioned studies, the present study was designed to compare the antimicrobial effects of Turkish propolis, powder propolis from Sigma and two other propolis samples of far geographic regions (USA and Australia) on oral pathogen microorganisms and their cytotoxic effects on human gingival fibroblasts.

Propolis has a high concentration of caffeic acid esters that some believe may give it some antitumor properties. In two studies extracts of propolis fed to rats have inhibited azoxymethane - induced colonic tumors (Chopra *et al.,* 1995; Hendler and Rorvik, 2008).

In vitro studies have shown propolis-related anti-inflammatory effects. Various extracts of propolis have also shown anti-inflammatory activity in animal models, particularly against adjuvant-induced arthritis (Park and Kahng, 1999; Hendler and Rorvik, 2008).

Propolis (bee glue) is a natural resinous hive product collected by bees from plants, particularly from flowers and leaf buds. Propolis contains a variety of chemical compounds such as poly-phenols (flavonoid aglycones, phenolic acids and their esters, phenolic aldehydes, alcohols, and ketones), terpenoids, steroids, amino acids and inorganic compounds. Many biological properties, including anti-bacterial, antifungal, antiviral, antioxidant, hepatoprotective (Lin *et al.*, 1997) and immuno-stimulating activities of propolis have been reported. Modern herbalists recommend propolis for human use in medicine because of its antibacterial, anti-fungal, antiviral, hepatoprotective and anti-inflammatory properties to increase the body's natural resistance to infections and to treat gastro-duodenal ulcers.

Contraindications

Propolis is contraindicated in those who are allergic or hypersentitive to any of its components.

Precautions

Pregnant women and nursing mothers should avoid using propolis supplements (Hendler and Rorvik, 2008).

Advers reactions

There are reported adverse reactions in those using topical preperations of propolis. These reactions are manifestated as dermatitis. There are reports of hypersensitivity reactions to ingested propolis, including rhinitis, conjunctivitis (Oztürk *et al.,* 2000), skin rashes and bronchospasm (Hendler and Rorvik, 2008).

Overdosage

No reported overdosage of propolis.

Dosage and administration

No typical dose. Propolis is available in several different preparations, including lozenges, tablets, creams, gels, mouth rinses, toothpastes and cough syrups.

DISCUSSION

In some countries the bee pollen has been recognized as food and medicine. Bee pollen contains at least 22 amino acids, 18 vitamins, 25 minerals, 59 trace elements, 11 enzymes or

coenzymes, 14 fatty acids, 11 carbohydrates and approximately 25.00% protein. Bee pollen is extremely rich in carotenes, which are metabolic precursors of vitamin A. It is also high in vitamin B complex and vitamins C, D, E and lecithin. Bee pollen contains over 50.00% more protein than beef, yet its fat content is very low. Bee pollen contains digestive enzymes from the bees. Pollen may be used to improve the immune response, to reduce the effect of radiation (El-Ghazaly and Khayyal, 1995) and retards aging because of its antioxidant and flavonoid contents. Honey has been used since ancient times as part of traditional medicine (Castaldo and Capasso, 2002). Several functions such as antibacterial, antioxidant, antitumour, anti-inflamatory, antibrowning, and antiviral have been reported. Royal jelly contains considerable amounts of proteins, amino acids including eight essential amino acids, hormone rich substance (testosterone) has been identified in extremely small quantities in royal jelly about 12 mg g-1 fresh weight (Nagai *et al.,* 2004). Royal jelly also contains vitamins: A, C, D, E, minerals are in descending order: K, Ca, Na, Zn, Fe, Cu, Mn, enzymes and antibiotic components. It also has an abundance of nucleic acid DNA and RNA. Royal jelly has been determined to exhibit a variety of pharmacological activities including antitumor, antimicrobial, antioxidant activity, vasodilative and hypotensive activities, as well as growth stimulating and infection preventing, anti-hypercholesterolemic and anti-inflammatory activities (Mirzoeva and Calder, 1996; Matsuno *et al.,* 1997; Mirzoeva *et al.,* 1997).

The collection of antimicrobial resins from the environment by honey bees (Simone *et al*., 2009) and the deposition of these resins into the nest architecture is a fundamental component of bee social immunity. Resin is a plant exudate secreted prophylactically to protect young leaf buds from pathogen infection and herbivore attack. It is composed primarily of antimicrobial compounds (e.g. monoterpenes and flavonoids) that play a major defensive role in the survival of the plant (Langenheim, 2003). Honey bees deposit these plant resins in the nest as a form of cement, called propolis (Nicodema *et al.*, 2013). When honey bees nest in tree cavities, they use propolis to coat the entire inner surface of the nest cavity, constructing a propolis envelope (Seeley and Morse, 1976). However, honey bees do not construct a natural propolis envelope within standard beekeeping equipment because the inner walls of the wooden boxes are smooth and do not elicit propolis deposition behavior. Instead, bees deposit propolis only in dispersed cracks and crevices and not as a continuous envelope (Finstrom and Spivak, 2010).

Simone *et al.* (2009) first tested the benefits of a propolis envelope to the bees' immune system by experimentally coating the inside of boxes with a propolis extract solution (ethanolic solution of propolis) to simulate a propolis envelope surrounding small colonies of honey bees. After just 7 days of exposure to the propolis-enriched nest environment, the immune-related gene transcription of the bees was significantly lower than that of bees in boxes not enriched with the propolis extract. The bacterial load (eubacterial 16S gene expression, which measures internal and external bacteria carried by bees) was also significantly lower in bees in propolis-enriched colonies. These results suggested that the propolis reduced the level of immune elicitors in the nest, so that the bees were able to expend less energy on costly immune system activation (Simone *et al.,* 2009).

Other benefits of propolis to honey bee health have been documented. Numerous in vitro studies have demonstrated the inhibitory activity of propolis, and specific compounds within propolis, against the growth of the honey bee bacterial pathogen Paenibacillus larvae and Ascosphaera apis (Lindenfelser, 1968; Antúnez *et al*., 2008; Bastos *et al*., 2008; Bilikova *et al*., 2013; Wilson *et al*., 2013, 2015). It is not known whether honey bees actually consume propolis, but Johnson *et al*. (2012) demonstrated that when bees were experimentally fed propolis in sucrose syrup, the transcription of three cytochrome 450s, involved in pesticide detoxification, was induced (Johnson *et al*., 2006; Mao *et al*., 2011). The placement of natural propolis in the nest cavity has been positively correlated with brood viability, worker

lifespan, honey production, hygienic behavior and pollen stores (Nicodemo *et al*., 2013).

CONCLUSION

The insect immune system is composed of both humoral and cellular immune responses. The humoral immune response includes the biosynthesis of antimicrobial peptides (AMPs) via signaling pathways (Toll, IMD, Jak–STAT) (Evans *et al*., 2006). Cell-mediated immune responses involve hemocyte-associated defenses. These cellular defense mechanisms include phagocytosis, encapsulation and nodulation, which are often followed by a cell-associated response of melanization via the activation of the phenoloxidase cascade in hemocytes (Söderhäll and Cerenius, 1998; Strand, 2008). The study showed that 30% non-alcoholic-AU propolis and 20% non-alcoholic-USA propolis presented the best antibacterial activity on periodontal pathogens at 1/128 dilutions, but were found to be cytotoxic on gingival fibroblasts. 10% alcoholic propolis (Sigma), 10% PG-propolis (Sigma), 10% alcoholic Turkish propolis and 10% PG-Turkish propolis, which were prepared to use in this study, did not presented the same antibacterial activity on periodontal pathogens at 1/256 dilutions as the two foreign propolis solutions, but let the gingival fibroblasts stay alive. It is suggested that more trials are needed to reach the appropriate propolis solutions, which are less cytotoxic but present strong antibacterial effects (Sonmez, 2005).

SUGGESTIONS

Nowadays people are starting to use natural products from synthetic medicines. Propolis is also used as a natural antibiotic for complementary treatment of many diseases. On the other hand, in our country, there is also a need to carry out many researches in this regard.

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