



Review

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Mechanisms of action underlying the anti-inflammatory and immunomodulatory effects of propolis: a brief review

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Abstract: Many biological properties have been attributed to various types of propolis, including anti-inflammatory, antimicrobial, antioxidant, antitumor, wound healing, and immunomodulatory activities. This article reviewed studies published that investigated the anti-inflammatory activity of propolis of different origins and/or its isolated components, focusing on the mechanisms of action underlying this activity and also addressing some aspects of immunomodulatory effects. The search was performed of the following databases: PubMed, Science Direct, HighWire Press, Scielo, Google Academics, Research Gate and ISI Web of Knowledge. The anti-inflammatory activity was associated with propolis or compounds such as polyphenols (flavonoids, phenolic acids and their esters), terpenoids, steroids and amino acids. CAPE is the most studied compounds. The main mechanisms underlying the anti-inflammatory activity of propolis included the inhibition of cyclooxygenase and consequent inhibition of prostaglandin biosynthesis, free radical scavenging, inhibition of nitric oxide synthesis, reduction in the concentration of inflammatory cytokines and immunosuppressive activity. Propolis was found to exert an anti-inflammatory activity *in vivo* and *in vitro* models of acute and chronic inflammation and others studies, indicating its promising potential as anti-inflammatory agent of natural origin and as a source of chemical compounds for the development of new drugs.

Introduction

Propolis is the generic name for a complex mixture of resinous substances collected from plants by bees, which is used in the bee hive to coat the inner walls, to protect the entrance against intruders, and to inhibit the growth of fungi and bacteria (Ghisalberti, 1979; Burdock, 1998). For propolis production, bees add their salivary enzymes to the plant resin and this material is then partially digested, followed by the addition of wax also produced by the bees. This process is found in most bee species. An additional step is observed in the group of stingless bees of the subfamily Meliponinae, species that are native to South America. In this group, resins, saliva and wax are mixed with soil to form the so-called geopropolis (Bankova et al., 1998).

The chemical composition of propolis is strongly influenced by the type of vegetation visited by the bees and by the season of the year (Bankova et al., 2000; Majiene et al., 2004; Dausch et al., 2008; Teixeira et al., 2008). Propolis from temperate zones generally consists of 50-60% resins and balsams, 30-40% of wax, 5-10% of essential and aromatic oils, 5% of pollen, and 5% of

other substances (Mendoza et al., 1991). These substances comprise more than 210 different compounds identified so far, such as aliphatic acids, aromatic esters and acids, flavonoids, fatty acids, carbohydrates, aldehydes, amino acids, ketones, chalcones, dihydrochalcones, terpenoids, vitamins (B1, B2, B6, C, and E), and minerals (aluminum, antimonium, calcium, cesium, copper, iron, lithium, manganese, mercury, nickel, silver, vanadium, and zinc) (Ghisalberti, 1979; Moreira, 1990; Marcucci, 1995; Sousa et al., 2007; Chang et al., 2008; Lustosa et al., 2008). Therefore variation in propolis components could affect its properties (Nakamura et al., 2010).

Propolis has been used since ancient times for the treatment of many diseases, as well as in food products and cosmetics (Burdock, 1998). In fact, various biological properties have been demonstrated and attributed to different types of propolis, including antibacterial, antifungal, antiprotozoal, antioxidant, antitumor, anti-inflammatory, anesthetic, wound healing, immunomodulatory, antiproliferative and anticariogenic activities (Dobrowolski et al., 1991; Ivanovska et al., 1995; Moura et al., 1999; Kujumgiev et al., 1999; Isla et

al., 2001; Chen et al., 2004; Simões et al., 2004; Duran et al., 2006; Medic-Saric et al., 2009; Araujo et al., 2010; Sforzin, 2007; Libério et al., 2009; Pagliarone et al., 2009; Paulino et al., 2003).

This article reviewed studies that investigated the anti-inflammatory and immunomodulatory activity of propolis, focusing on the mechanisms of action (already identified) underlying this activity and on the components identified in the different types of propolis. The following databases were searched: PubMed, Science Direct, HighWire Press, Scielo, Google Academics, Research Gate and ISI Web of Knowledge, for articles published between 1979 and 2011 using the key words propolis, inflammation, anti-inflammatory activity, bee products and propolis components.

Anti-inflammatory Activity

Chemical aspects of the inflammatory response

Inflammation is induced by the release of chemical mediators from damaged tissue and migratory cells. Mediators identified in the inflammatory process include vasoactive amines (histamine and serotonin), eicosanoids (metabolites of arachidonic acid, prostaglandins and leukotrienes), platelet aggregation factors, cytokines (interleukins and tumoral necrosis factor - TNF), kinins (bradykinin), and free oxygen radicals, among others (Czermak et al, 1998; Ohishi, 2000). These substances are produced by inflammatory cells such as polymorphonuclear leukocytes (neutrophils, eosinophils, basophils), endothelial cells, mast cells, macrophages, monocytes, and lymphocytes (Fiala et al., 2002).

It is well established in the literature that the main phenomenon activating the acute phase of inflammation is the local production of prostaglandins (especially PGE₂) and leukotrienes derived from arachidonic acid. These eicosanoids are relatively unstable and are notoriously non-selective in their interaction with various receptor subtypes as demonstrated in isolated tissue preparations (Coleman et al., 1994; Hata & Breyer, 2004).

Arachidonic acid is the precursor of eicosanoids such as prostaglandins. This fatty acid is stored as a phosphoglyceride in the cell membrane and is converted by cyclooxygenases or lipoxygenases. After tissue damage, conversion through cyclooxygenases leads to the synthesis of prostaglandins, which actively participate in the onset and progression of the inflammatory reaction. Studies have demonstrated that propolis acts as a potent anti-inflammatory agent in acute and chronic inflammation (Ledón et al., 1997; Uzel et al., 2005). Some of the substances present in propolis are able to inhibit cyclooxygenase and the consequent synthesis of prostaglandins (Sigal & Ron, 1994). This has been

suggested to be one of the mechanisms of action underlying the anti-inflammatory effect of propolis. Still, molecules that exert lipoxygenase (LOX) inhibitory and antioxidant activities also have potential anti-inflammatory activity (Polya, 2003).

Anti-inflammatory and immunomodulatory response to propolis extracts

The anti-inflammatory properties of propolis and its subproducts have been studied in different models of acute and chronic inflammation, such as formaldehyde-induced arthritis and paw edema induced by PGE₂, carrageenan or radiation (Dobrowolski et al, 1991; Park & Kang, 1999; El-Ghazaly & Khayyal, 1995), as well as in acute inflammation induced by zymosan (Ivanovska et al., 1995) and others (Table 1). In many of these studies propolis had an effect similar to that of anti-inflammatory drugs used as positive controls in the experiments.

In vitro and *in vivo* experiments using ethanol or aqueous extracts of propolis of different origins produced by different bee species are being conducted to confirm its anti-inflammatory activity. Some specific effects of the aqueous extract of propolis have been demonstrated, such as the inhibition of platelet aggregation, inhibition of prostaglandin biosynthesis *in vitro*, prevention of formaldehyde-induced paw edema and arthritis and inhibition of 5-lipoxygenase (5-LOX) activity (Dobrowolski et al., 1991; Khayyal et al, 1993; Massaro et al., 2011). In addition, propolis has shown *in vitro* free radical scavenging activity and a hepatoprotective effect on TNF- α -induced cell death (Banskota et al., 2000; Alencar et al., 2007). The ethanol extract of propolis has shown dose-dependent anti-inflammatory effects in models of carrageenan-induced paw edema, Freund's adjuvant-induced arthritis and foreign body-induced granuloma, effects on vascular permeability, and analgesic activity (Park et al., 1996). Additionally to its regenerative capacity, free radical scavenging is the main anti-inflammatory mechanism attributed to the ethanol extract of propolis (Krol et al., 1996; Pascual et al., 1994; Ichikawa et al., 2002).

In a study evaluating the anti-inflammatory activity of an ethanol extract of propolis on edema induced by carrageenan, dextran and histamine in mice, an oral dose of 650 mg/kg significantly inhibited the inflammatory process triggered by carrageenan and antagonized the edematogenic effect produced by histamine, but did not inhibit the inflammatory process induced by dextran. The dose administered had no toxic effects and the authors suggest that the extract exerted an anti-inflammatory effect similar to that of nonsteroidal anti-inflammatory drugs without causing damage to the gastric mucosa or other blood effects (Reis et al., 2000).

Fourteen commercial extracts of Brazilian

propolis originating from different regions of the country were tested using a rat model of arachidonic acid-induced ear edema. Four of the extracts tested showed anti-inflammatory effects similar to those produced by indomethacin, with these effects varying significantly depending on the origin of the propolis sample (Menezes et al., 1999).

The effects of propolis extracts were investigated in other rat models of inflammation. The arthritis indexes were suppressed by oral treatment with 50 and 100 mg/kg/day of the extract. In carrageenan-induced paw edema, the ethanol extract of propolis 200 mg/kg single dose showed a significant anti-inflammatory effect 3 to 4 h after carrageenan administration. The authors concluded that the extract presented marked anti-inflammatory effects in both chronic and acute inflammation and suggest that the anti-inflammatory effects of propolis might be due to its inhibitory effect on prostaglandin production (Park & Kahng, 1999).

Propolis has been shown to suppress the production of lipoxygenase and cyclooxygenase during acute zymosan-induced peritonitis and to inhibit *in vivo* the elevated production of leukotrienes B₄ (LTB₄) and leukotrienes C₄ (LTC₄). However, oral administration of the extracts did not affect the *ex vivo* production of PGE₂, but increased the production of leukotrienes and prostaglandins by peritoneal macrophages (Mirzoeva & Calder, 1996). Massaro et al. (2011) suggests a potential of cerumen (stingless bees propolis) for preventing the lipid oxidation of linoleic acid, thus protecting the integrity of cell membranes.

Propolis extracts can act on the nonspecific immune response by activating macrophages, inducing the release of hydrogen peroxide, and inhibiting the production of nitric oxide in a dose-dependent manner (Orsi et al., 2000). The latter it may be explained by the fact that propolis inhibits both inducible nitric oxide synthase (i-NOS) expression and the catalytic activity of i-NOS (Tam-no et al., 2006).

A significant inhibition of both the PGE₂ levels and in the nitric oxide effects it was demonstrated. There was also a reduction in enzymes activation and in the level of IL-6 and other inflammatory cytokines. Furthermore, inhibition of the activation and differentiation of macrophages has been suggested as one of the possible mechanisms underlying the anti-inflammatory and immunological effects of propolis extract and of its water-soluble derivatives. These effects are the result of the action of flavonoids and other components present in propolis (Krol et al., 1996; Hu et al., 2005).

It was suggested that propolis extract possess antioxidant capacity *in vitro* conditions (Rebiai et al., 2011). Propolis antiradical and protective abilities against lipid oxidation are related to its high levels of polyphenol and flavonoid total levels. According

Chaillou & Nazareno (2009) and Ikegaki et al. (1999), propolis showed high antioxidant activity by inhibiting the oxidation of the coupled reaction of β -carotene and linoleic acid. These last authors suggest that propolis also seems to inhibit hyaluronidase, an activity contributing to its anti-inflammatory and regenerative effects. Propolis with strong antioxidant activity also has high scavenging activity and contains large amounts of antioxidative compounds, such as caffeic acid, ferulic acid, caffeic acid phenethyl ester and kaempferol (Chen et al., 2004; Ahn et al., 2007; Kumazawa et al., 2004).

Studies investigating an aqueous extract of rosemary propolis in an *in vivo* model of chronic inflammation demonstrated that the extract suppresses the cell migration. However, the deposition of collagen was not affected, suggesting that the aqueous extract of propolis can be used to control the inflammatory response without compromising the tissue repair process. This activity was attributed to the high content of caffeic acid in the propolis extract (Moura et al., 2009).

In vivo pre-activation of macrophages by green propolis extract administered to rodents has been suggested to increase the production of nitric oxide after activation with interferon gamma (INF- γ) and, consequently, to reduce the proliferation of lymphocytes (Sá-Nunes et al., 2003). The inhibitory effect of propolis on lymphoproliferation might be associated with the production of regulatory cytokines such as IL-10 and TGF- β (Sforcin, 2007), as well as the anti-inflammatory/anti-angiogenic effects of propolis could be also associated with modulation of cytokine TGF- β 1 (Moura et al., 2011). Recent works has demonstrate that the propolis administration over a short-term to mice affected both basal and stimulated INF- γ production, what may be related to its anti-inflammatory properties (Pagliarone et al., 2009; Orsatti et al., 2010; Missima et al., 2010).

The activation of macrophages and release rates of nitric oxide and hydrogen peroxide have been studied using an ethanol extract of propolis in stressed mice to evaluate the effects of propolis on stress-related immunosuppression. The results showed that propolis reduced nitric oxide production and potentiated hydrogen peroxide formation. The histological characteristics of the thymus, bone marrow and adrenal gland were found to be altered, but no histological alterations were observed in the spleen. The authors concluded that propolis-based products might be used for the treatment of stress (Missima & Sforcin, 2008). Thus, it was shown that ethanol extract of propolis inhibits the inducible nitric oxide synthase (iNOS) gene transcription through action on the NF- κ B sites in the iNOS promoter in a concentration-dependent manner (Song et al., 2002).

An *in vivo* study has been conducted on healthy humans, for the first time reporting the effects of prolonged propolis supplementation on redox-status of

human organism. The benefit of propolis use was shown in male population demonstrating reduction in free-radical-induced lipid peroxidation as well as increase in activity of superoxide dismutase. Further a decrease in malonaldehyde (degradation product of peroxidation of polyunsaturated fatty acids) concentration and increase in superoxide dismutase activity (first and most important line of antioxidant enzyme defense) were observed (Jasprica et al., 2007).

The antiulcer activity of Brazilian green propolis was demonstrated by the administration of hydroalcoholic extracts to animals with gastric ulcers induced by ethanol, by a nonsteroidal anti-inflammatory drug (indomethacin) and by stress. A reduction in gastric secretion was also observed. The results obtained were attributed to the presence of phenolic acids (caffeic acid, cinnamic acid, p-coumaric acid and ferulic acid) in the extracts. However, the mechanisms of action still need to be established (Barros et al., 2007; 2008). The alcoholic extract of propolis has been shown to promote the acceleration of ulcer healing in the oral cavity of rats, by reducing the time of ulcer epithelization and interfering with the quality and quantity of inflammatory cells (Gregio et al., 2005). Still, propolis increases the wound healing rate and reepithelialization of diabetic wounds in rodents. It also has additional roles in decreasing neutrophil infiltration and normalizing wound tissue macrophage influx (McLennan et al., 2008).

Recent studies show that the ethanol extract of propolis is also able to interfere with others mechanisms underlying on the inflammatory response like the activity of phosphatidylcholine-specific phospholipase C (PC-PLC), that plays critical roles in controls of vascular endothelial cell function, as well as in the p53 - a key protein in apoptosis signal transductions of this cells - and further levels of reactive oxygen species (ROS) (Xuan et al., 2011). The propolis is responsible for ERK1/2 (extracellular signal-regulated kinase 1/2) inactivation in endothelial cells that ultimately leads to angiogenesis suppression (Kunimasa et al., 2009).

Anti-inflammatory and immunomodulatory response to isolated propolis components

Different components of propolis have been studied to evaluate their therapeutic application. Flavonoids, phenolic acids like caffeic acid phenethyl ester (CAPE), and esters are the most biologically active compounds (Table 2) (Burdock, 1998; Dausch et al., 2008; Baumann et al., 1980; Silva et al., 2007). These compounds exert multiple effects on bacteria, fungi and viruses and also present anti-inflammatory, antioxidant, immunomodulatory, wound healing, antiproliferative and antitumor activities (Machado et al., 2008; Pagliarone et al., 2009; Buyukberber et al., 2009; Jaganathan &

Mandal, 2009; Medic-Saric et al., 2009; Pillai et al., 2010; Moreira et al., 2011; Lotfy, 2006).

The anti-inflammatory activity of propolis seems to be associated with the presence of flavonoids, especially galangin and quercetin. This flavonoids has been shown to inhibit the activity of cyclooxygenase and lipoxygenase and to reduce the levels of PGE₂ and the release and expression of the induced isoform cyclooxygenase-2 (COX-2) (Shimoi et al., 2000; Raso et al., 2001). Studies using animal models of acute and chronic inflammation showed that caffeic acid is essential for the anti-inflammatory activity of propolis since it inhibits the synthesis of arachidonic acid and suppresses the enzymatic activity of COX-1 and COX-2 (Borrelli, 2002). In addition, caffeic acid inhibits the gene expression of COX-2 (Michaluart et al., 1999) and the enzymatic activity of myeloperoxidase (Frenkel et al., 1993), ornithine decarboxylase, lipoxygenase, and tyrosine kinase (Rao et al., 1993). Caffeic acid also presents immunosuppressive activity, inhibiting the early and late events of T cell activation and the consequent release of cytokines such as IL-2 (Marquez et al., 2004) in an unspecific way of inhibition of ion channels (Nam et al., 2009). Chrysin, a flavonoid isolated from propolis, also seems to suppress the expression of COX-2 by inhibiting a nuclear factor for IL-6 (Woo et al., 2005).

In vivo studies on artepillin C, the main component present in propolis from south and southeast of Brazil, have shown that this substance inhibits the production of PGE₂ during peritoneal inflammation. This activity may explain, at least in part, the anti-inflammatory and antiedematogenic effects of artepillin C observed in carrageenan-induced paw edema and peritonitis. Inhibition of the production of nitric oxide and TNF has also been reported (Paulino et al., 2008). Further artepillin C was found to have strong antioxidant effects may be accounted for by additional effects of caffeoylquinic acid and other prenyl analogues (Nakajima et al., 2009; Mishima et al., 2005).

Caffeic acid phenethyl ester (CAPE), the most extensively studied and biological active component in propolis, inhibit cytokine and chemokine production, proliferation of T cells and lymphokine production, and thus results in a decrease in inflammatory process. The mechanism is through to be related to NF- κ B signaling pathway (Natarajan et al., 1996; Wang et al., 2009; 2010). CAPE is a potent inhibitor of nuclear factor - κ B (NF κ B) activation (Shvarzbeyn & Huleihel, 2011) and NF- κ B inhibition may result in a reduced expression of COX-2, whose gene is NF- κ B-regulated (Maffia et al., 2002) and in a potent NO inhibition by blocking the activation of INOS (Nagaoka et al., 2003).

Other studies have investigated the effects of propolis and of its polyphenolic components (*e.g.*, flavonoids) on LPS-induced production of nitric oxide

Table 1. Anti-inflammatory activity of different types of propolis.

Material studied	Origin (Type)	Activity	Method	Region	Biological material	Administration route	Reference
Propolis (AE + tablets)	NS	Anti-inflammatory	Arthritis; Paw edema; Granuloma	Poland	albino Wistar rats	Oral	Dobrowolski et al., 1991
Propolis (HAE)	NS	Anti-inflammatory	Damage caused by gamma irradiation; Paw edema (carrageenan); Induced arthritis		Rats	Oral	El-Chazaly & Khayyal, 1995
Propolis (AE)	NS	Anti-edema Increase in complement activity	Paw edema (zymosan); Serum complement activity	NS	ICR	Intravenous, oral and intraperitoneal	Ivanovska et al., 1995
Propolis (EE)	NS	Anti-inflammatory Analgesic	Paw edema; Granuloma; Arthritis; Vascular permeability	Chungju (Korea)	ICR Sprague-Dawley rats	Oral	Park et al., 1996
Propolis (EE)	NS	Anti-inflammatory	Paw edema induced by carrageenan, dextran and histamine; Toxicity	Oliveira and Bambui, Minas Gerais (Brazil)	Wistar rats and albino Swiss mice	Oral	Reis et al., 2000
Propolis (EE)	Commercial extracts	Anti-inflammatory	Ear edema	Various (Brazil)	Balb/c	Topic	Menezes et al., 1999
Propolis (HAE)	Africanized	Immunomodulatory	Macrophage activation	Lageado, São Paulo (Brazil)	Balb	<i>In vivo</i> (Intraperitoneal) <i>In vitro</i>	Orsi et al., 2000
Propolis (AE, EE)	NS	Anti-inflammatory	Paw edema (carrageenan); Peritonitis (carrageenan) Capillarity; Arthritis (method NS);	North China	ICR mice Wistar rats	<i>Intragastric</i>	Hu et al., 2005
Propolis (AE)	Green (rosemary) <i>Apis mellifera</i>	Healing Anti-inflammatory	Chronic inflammation (fibrovascular tissue growth induced by murine sponge disks)	Jaguaraçu, Minas Gerais (Brazil)	Swiss	Oral	Moura et al., 2009
Propolis (EE)	NS	Anti-inflammatory Antioxidant	iNOS promoter activity induced by LPS plus IFN- γ ; iNOS mRNA expression and nuclear factor-kappa B (NF-kB)	Namyangju (Korea)	<i>In vitro</i>	<i>In vitro</i>	Song et al., 2002
Propolis (EE)	NS	Antioxidant Immunomodulatory	Determination of glucose and corticosterone; Peritoneal macrophages Determination of NO and peroxides	Botucatu, São Paulo (Brazil)	Balb	Oral	Missima & Sforcin, 2008
Propolis (EE)	Rosemary	Immunomodulatory	Stimulation of immune complexes by zymosan	Oliveira, Minas Gerais (Brazil)	Rabbits	<i>In vitro</i>	Simões et al., 2004
Propolis (EE)	NS	Antioxidant Anti-inflammatory	Coupled oxidation of beta-carotene and linoleic acid Inhibition of hyaluronidase activity	NS	NS	NS	Park et al. (2000)
Propolis (HAE)	<i>Apis mellifera</i> L.	Immunomodulatory Action on cytokines	Spleen cell culture; Determination of cytokines Confinement stress	Botucatu, São Paulo (Brazil)	BALB/c	Oral	Pagliarone et al., 2009

Propolis (EE)	Red	Anti-inflammatory	Granuloma, Peritoneal capillary permeability Ear edema	Cuba	Sprague-Dawley rats	Intragastric topical	Ledón et al., 1997
Cerumen (Stingless bees propolis)(ME)	<i>T. Carbonaria</i>	Anti-inflammatory Antioxidant	Inhibition of 5-LOX activity	Australia	NS	<i>In vitro</i>	Massaro et al., 2011
Propolis (AE)	<i>Apis mellifera</i>	Anti-inflammatory Anti-Angiogenic	Granuloma (Sponge Disks, Implantation), Hemoglobin extraction; VEGF, TNF- α and TGF- β 1 Production in the Sponge Implants	Minas Gerais (Brazil)	Swiss	Oral	Moura et al., 2011
Propolis (EE)	NS	Anti-inflammatory	Carrageenin-induced mouse paw edema	Brazil	ddY-strain mice	Oral	Tam-no et al., 2006

EE: ethanol extract; AE: aqueous extract; HAE: hydroalcoholic extract; ME: methanol extract; NS: not specified.

and on the expression of inducible nitric oxide synthase (iNOS) by activated macrophages (Song et al., 2002; Hämäläinen et al., 2007). The most effective classes of polyphenolic compounds were flavonoids, especially isoflavones and flavones. In addition, eight compounds that were able to inhibit the production of nitric oxide and expression of iNOS were identified. Four compounds (genistein, kaempferol, quercetin, and daidzein) inhibited the activation of two important gene transcription factors for iNOS, *i.e.*, signal transducer and activator of transcription 1 (STAT-1) and NF- κ B, whereas four other compounds (flavone, isorhamnetin, naringenin, and pelargonidin) only inhibited NF- κ B (Hämäläinen et al., 2007). Another study showed that selected flavonoids, including fisetin, kaempferol, morin, myricetin, and quercetin, exhibited distinct antioxidant properties against different types of free radicals (Wang et al., 2006). These results indicate that flavonoids have different antioxidant and anti-inflammatory effects despite their structural similarity (Hämäläinen et al., 2007; Wang et al., 2006). Some flavonoids stimulate macrophages stop further production of eicosanoids and destroy excess oxidants (Havsteen, 2002).

Ansorge et al. (2003) studied the effects of propolis and some of its components on basic functions of mitogen-activated immune cells of human blood, as well as on DNA synthesis and cytokines production *in vitro*. The authors detected the production of IL-1 β and IL-12 by macrophages, as well as the production of IL-2, IL-4, IL-10 and transforming growth factor beta (TGF- β). The results showed that propolis, caffeic acid, quercetin, hesperidin and other flavonoids strongly inhibited DNA synthesis and the production of inflammatory cytokines in a concentration-dependent manner. On the other hand, the production of TGF- β , a mediator of immunosuppression, was increased. These findings demonstrate that propolis and a number of its constituents exerts a direct regulatory effect on basic immune cell functions and can be considered an alternative natural anti-inflammatory agent.

Recently, studies have been published on the known biological activities of CAPE as well as on the activities of other compounds as well studied as Artepillin C than the discovery of new components isolated from propolis from different regions, showing perspectives on propolis and its individual components for medicine (Aviello et al., 2010; Salatino et al., 2011).

Conclusions

The anti-inflammatory activity attributed to propolis has been confirmed in numerous *in vitro* and *in vivo* animal studies using models of acute and chronic inflammation. These studies attributed this biological activity to different mechanisms according to the results

Table 2. Anti-inflammatory activity of different isolated components of propolis.

Material studied	Origin (Type)	Activity	Method	Region	Biological material	Administration route	Reference
Propolis (EE) Caffeic acid	NS	Anti-edema Anti-inflammatory Immunomodulatory	Paw edema (carrageenan); Peritonitis (carrageenan) Arthritis (Mycobacterium tuberculosis in Freund suspension); T cell proliferation	Milan (Italy)	Wistar rats Lewis rats	Intraperitoneal, oral	Borrelli et al., 2002
Flavonoids	Synthetic	Anti-inflammatory	Cell culture, Nitrite determinations	NS	Murine macrophages	<i>In vitro</i>	Hämäläinen et al., 2007
Propolis (EE) Quercetin Hesperidin Caffeic acid	NS	Suppression of DNA synthesis Antiproliferative Immunomodulatory	Cell proliferation; DNA synthesis; Induction of cytokines (IL-2, IL-4, IL-10, IL-12 and TGF-β1)	Neichen (Germany)	Human cells	<i>In vitro</i>	Ansorge et al., 2003
Artepillin C	Synthetic	Anti-edematogenic Analgesic Anti-inflammatory	Paw edema; Peritonitis; Quantification of NO	South and southeast Brazil	Swiss, Raw 264.7 cells, HEK 293 cells	Intraperitoneal, <i>In vitro</i>	Paulino et al. (2008)
Caffeic acid (CAPE)	Synthetic	Anti-inflammatory Anticancer	Tissue Culture, PGE2 Production, Cox Enzyme Assay <i>in Vitro</i> , Arachidonic Acid Release, Air Pouch Model	NS	Human Oral Epithelial Cells, Lewis	<i>In vitro</i> , Intraperitoneal	Michaluart et al., 1999
Chrysin	Synthetic	Anti-inflammatory Anti-carcinogenic	Expression of COX-2 in lipopolysaccharide (LPS)-activated cells	NS	Macrophage Raw 264.7	<i>In vitro</i>	Woo et al., 2005
Caffeic acid esters	Synthetic	Antitumor	Lipoxygenase and Cyclooxygenase Activities, induced ornithine decarboxylase (ODC), l-rosine protein kinase (TPK),	New York (USA)	F344 rats, liver and colonic mucosa	<i>Oral</i> , <i>subcutaneous</i> , <i>In vitro</i>	Rao et al., 1993
Caffeic acid phenethyl ester (CAPE)	NS	Antitumor	TPA-induced ear edema, MPO, H ₂ O ₂ , and Oxidized DNA Bases	NS	SENCAR and CD-1 mice, Human PMNs., Bovine Lens	Topically, <i>In vitro</i>	Frenkel et al., 1993
Caffeic acid, ferulic acid, p-coumaric acid and cinnamic acid	Belgium	Antiulcer	Alcohol-, NSAID- and stress-induced ulcer	Belgium	Wistar	Oral	Barros et al., 2008
Propolis (EE) Caffeic acid	NS Germany	Inhibition of neutrophils	Chromatography, chemoluminescence	NS	Guinea pigs	Intraperitoneal	Krol et al., 1996
Caffeic acid (CAPE)	NS	Immunomodulatory	TCell Proliferation Assays, Measurement of IL-2 Synthesis, NF-κB Transcriptional Activity, antigen-induced proliferation	NS	Jurkat cells, NFAT-Luc plasmid, PBMC	<i>In vitro</i>	Marquez et al., 2004
Flavonols	Synthetic	Antioxidant Anti-inflammatory	Free radical scavenging, iNOS mRNA expression, Nitric and PGE2 measurement, induced ROS production	NS	Cell culture (RAW264.7), Human PMN	<i>In vitro</i>	Wang et al., 2006
CAPE	Synthetic	Antioxidant Anti-inflammatory	Acute edematous pancreatitis	NS	Wistar albino	Subcutaneous	Buyukberber et al., 2009

EE: ethanol extract; NS: not specified.

obtained. Most researchers reported an action of propolis extracts on the enzyme cyclooxygenase, a trigger of the inflammatory process. Furthermore, effective anti-inflammatory activity of propolis was attributed to the inhibition of prostanoids, especially PGE₂, and to the reduction of cytokines. Other mechanisms were also reported, such as an effect on inflammatory cell activity (cell migration, macrophage activation), reduction in nitric oxide synthesis, reduced enzymatic activity during the healing process, and inhibition of TNF.

This review highlights the potential use of propolis as an alternative natural anti-inflammatory agent in acute and chronic inflammation. It is believed that propolis acts through different mechanisms and that its polyphenolic components are responsible for this action. However, the biological properties of the propolis should not be considered a synergic effect among the various compounds, suggesting the need for isolation and identification of the various bioactive compounds responsible for its effects, and to better understand their mechanisms of action.

As stated here, there is increasing scientific evidence confirming the anti-inflammatory properties of propolis and/or its components. In this respect, most of the studies analyzed here leave something to be desired since they do not specify the type and origin of the propolis sample studied or even the compound isolated, nor do they report the genus of the producing bee species, since propolis may have very different chemical composition and actions according to these factors.

Disclosure statement

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