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Immunomodulatory Properties of Green Propolis

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Abstract: Propolis is a resinous material collected by honeybees from numerous plants and serves as a defense against intruders. Because of its relevant curative properties, it is now gaining popularity in health foods and in cosmetic products. Understanding the underlying molecular mechanisms of phytochemicals has become a good strategy in bioprospection for new anti-inflammatory compounds. The biological activity of propolis derives from its high levels of phenolic acids, while flavonoids are thought to account for the activity of propolis extracts. The comprehension of the relationship between propolis and the immune system has progressed in the last years, recent articles have provided important contributions to this investigation field. Studies have shown that propolis suppressed the "IL-6-induced phosphorylation of signal transducer and STAT3", an essential cytokine-activated transcription factor in Th17 development. Therefore, action mechanisms of "propolis on Th17 differentiation could be instrumental in controlling disturbed cytokine networks in inflammation, autoimmune diseases, and infections." The use of propolis has been proposed in some patents as: WO201363714; CN102885854, WO2013142936, US20130266521, and US20130129808, which are related to the treatment of dental diseases; adjuvant in anti-cancer treatment; in cosmetic products; as an anti-inflammatory agent and natural antibiotic. Although there are many publications regarding the propolis efficacy, its applicability to human health and mechanisms of action are not completely understood, creating opportunities for new studies.

Keywords: Cytokines, immunomodulation, interleukins, PAMPs, propolis, toll-like receptors.

1. INTRODUCTION

Propolis is a resinous material collected by honeybees in numerous plants as a defense against intruders [1, 2]. Because of its relevant therapeutic application, it has been used in folk medicine for centuries, and is now gaining popularity in health foods as well as in cosmetic products [1, 3, 4].

Also known as "bee glue", propolis plays an important role in ensuring bee colony health [5]. Honeybees exploit nectar and pollen from nature to fulfill their nutritional needs, and use propolis to maintain the antiseptic environment in the hive [1]. In fact, the expression *propolis* derives from the Greek *pro* (in defense of, or in front of) and *polis* (city or hive), and thus denotes a substance that is useful for the protection of the hive [6, 7].

Propolis is gathered by honeybees from resinous exudates of buds, leaves, branches, and barks found in the vicinity of the beehive [3, 8]. Propolis samples have shown many biological properties including, antimicrobial, anti-cancer, antioxidant, antiviral, anti-inflammatory, antiprotozoan, hepatoprotective, cytotoxic, antiulcer activity and protective of the heart [2, 4, 9-16].

Due to these health-promoting characteristics, propolis is regarded as a functional component, and thus can used in cosmetics, medicines, toothpastes, in the treatment of gingivitis, cheilitis and stomatitis. It can be presented in the form of gels, creams, beverages or foods to prevent diseases and improve health [1, 2, 17].

Though more than 400 different chemical constituents have been recognized in propolis during the past few years, these properties are primarily due to a few compounds including polyphenols, flavonoids, terpenes, essential oils, inorganic compounds, caffeic, ferulic and cumaric acids, aldehydes and esters [14, 18, 19]. Some organic constituents isolated from green propolis are presented in Fig. (**1**).

Green propolis is well known for its color [3, 9]. The plant *Baccharis dracunculifolia* DC (Asteraceae) is the primary subtract for it, a common species found in the Brazilian cerrado [2, 17]. The biological activity of propolis derives from its high levels of phenolic acids, while fla-

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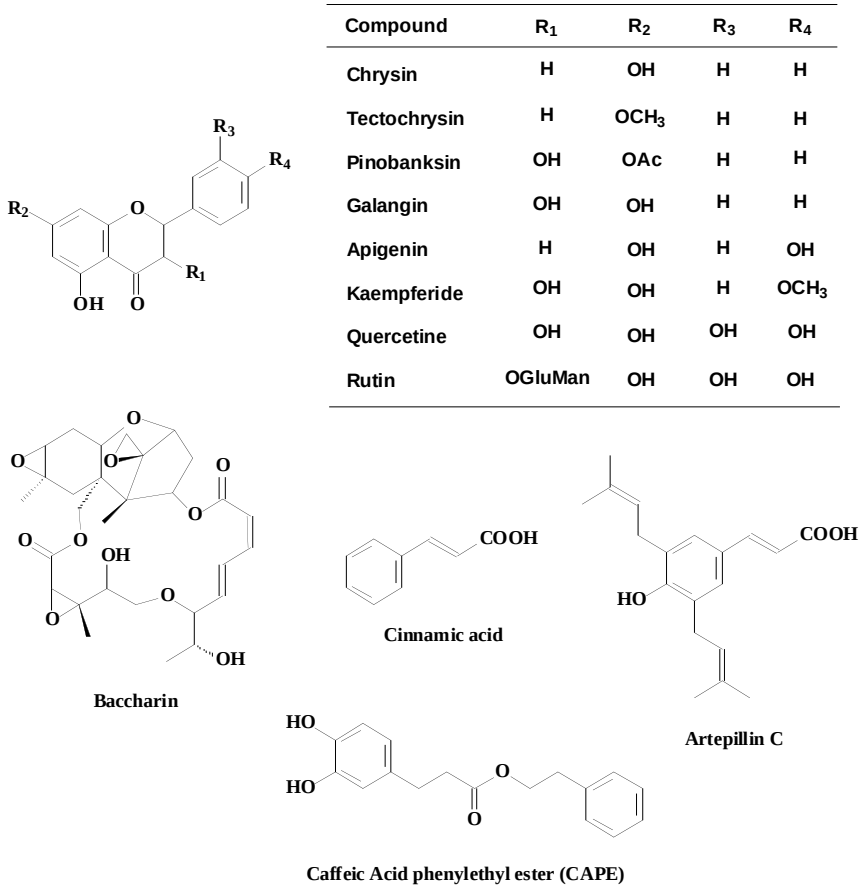

Fig. (1). Chemical structure of compounds isolated from green propolis.

vonoids are thought to account for the activity of propolis extracts [20, 21].

Wang *et al.* (2013) [15] reported that numerous varieties of propolis have a wide spectrum of pharmacological activity, and emphasized the fact that the main constituent of propolis varies widely when gathered from different geographic locations. Consequently, different aspects, such as the geographical origin, plant resources, collecting season, bee species, and solvents used in the extraction, have an influence on the chemical constitution of propolis [18, 22]. Therefore, it is necessary to distinguish between specific propolis types and their corresponding composition [2, 23].

Information on the underlying molecular mechanisms of phytochemicals has become a good strategy in the bioprospection of new anti-inflammatory compounds [24, 25]. Until the 1990s, the knowledge of the immunomodulatory action of propolis has been scarce [6]. But, in the last years, new articles have provided an important contribution to this investigation field, showing that the immunomodulatory properties of propolis are attributed to the flavonoids and phenolic acids [4, 26]. Regarding the Brazilian green propolis, the constituents are cinnamic acid, coumaric acid, quercetin, rutin, pinobanksin-3-acetate, kaempferide, apigenin, galangin, artepillin C, tectochrysin, baccharin, pinobanksin, chrysin, among others Fig. (**1**) [19, 24-29, 30].

Szliszka *et al.* (2013) [29] proposed that the immunomodulatory properties of propolis can be attributed to its flavonoids and phenolic acids. Among the flavonoids, the Artepilin C and the CAPE are associated in the immunomodulatory actions. Addictionally, the artepillin C presents several proven activities, such as antioxidant and antitumor [3] Caffeic acid phenethyl ester (CAPE) has a polyphenolic ring that networks with several molecules of the human body Fig. (**1**). This compound is known to have antitumoral, anti-inflammatory, antineoplastic and, to some extent, antioxidant properties [29].

In the present review, the role of propolis on immunomodulation and the signaling pathways associated with innate immunity is discussed [31]. In addition, the current literature and recent patents related to propolis effects on the immune system and metabolic signaling pathways are highlighted.

2. PROPOLIS AND IMMUNOMODULATION

According to some studies, the artepillin C that has demonstrated antitumor effects, antioxidant protection and exert an immunosuppressive function on T-lymphocyte subsets, while paradoxically activating macrophages [32]. Therefore, Chan *et al.* (2013) [33] and Ahn *et al.* (2009) [34] investigated a potential immunomodulatory properties of the cin-

namic acid, since these acids have a significant role in the mixture of compounds, among then the artepillin C [15, 32, 35].

Macrophages play an important role in the immune system as well as in the inflammation process. When stimulated by lipopolysaccharides (LPS), macrophages can secrete a variety of inflammatory mediators, including NO, IL-1β, and IL-6 [15, 36]. According to Wang (2013) [15], an increase of these mediators will break immune equilibrium and origin numerous inflammatory conditions, including septic shock, arteriosclerosis, and cancer and they suggest that the green propolis acts a suppressive influence on the expression of the inflammation-related genes at the transcriptional level.

Researchers like Neiva *et al.* (2014) [36] verified that propolis decreased the LPS-induced cytokines and/or chemokines expression in odontoblast-like cells, in macrophages and in osteoclasts. Also, Bachiega *et al.* (2012) [37] researched the immunomodulatory effect of propolis on cytokine production (IL-6, IL-1b and IL-10) by peritoneal macrophages *in vitro* and verified that propolis may modulate the immune/inflammatory response, depending on its concentration, thanks to the synergic action of its constituents.

Propolis dose-dependently controls the immune/inflammatory response; its efficacy may be due to the synergistic effect of its compounds [38]. Marwaha *et al.* (2012) [39] suggested that depending on the environment T helper 17 cells (Th17 cells) can alter their differentiation program, ultimately giving rise to either protective or pro-inflammatory cells [39]. Okamoto *et al.* (2013) [40] also found that "Brazilian propolis restricts Th1 and Th17 differentiation and may prevent autoimmune and inflammatory diseases. The Brazilian propolis used in their study contained high levels of artepillin C as the major compound in the Brazilian green propolis from Baccharis dracunculifolia [9, 35]. Artepillin C has been reported to inhibit the expression of IFNγ and IL-17 in alloreactive human CD4+ T cells, and may be related to the inhibition of Th1 differentiation [39]. This finding is important to better understand the synergies of Th1-differentiation inhibition by propolis.

Tanaka (2013) [38] and Okamoto *et al.* (2013) [40] found that the protective effect of propolis on collagen-induced arthritis (CIA) was related to the suppression of interleukin-17 (IL-17) production in CIA mice. Okamoto *et al.* (2013) demonstrated that propolis inhibited IL-6 plus transforming growth factor-β induced for Th17 differentiation *in vitro* and reported that propolis suppressed the IL-6-induced phosphorylation of signal transducer - $STAT_3$, an essential cytokine-activated transcription factor in Th17 development [39].

Cheung *et al.* (2013) [41] indicated that Brazilian green propolis or the artepillin C isolated can suppress alloreactive CD4 T-cell responses *in vitro*, which suggests that artepillin C could be used as a potential immune suppressant, either alone or as an adjunct agent in treating graft versus host disease.

There are several studies around the antitumoral actions of propolis. In assays *in vivo*, Missima *et al.* (2010) [42] showed that propolis could be associated to immune regulation by stimulates IL-10 expression and production, and may be associated to its antitumoral action [42]. Regarding the anti-inflammatory action of propolis, Orsatti *et al.* (2010) [43] had previously found that propolis administration to mice for three consecutive days increased proinflammatory cytokines (IL-1β and IL-6) production and stimulated the expression of toll-like receptors (TLR-2 and TLR-4), which implies that propolis may balancing the components of the immune response [43, 44]. Additionally, propolis constituents could interact with diverse receptors in different cells, but further investigation is still needed to understand the involvement of isolated compounds [43].

Toll-like receptors (TLR) have a crucial role in the detection of microbial infection in mammals and insects [44]. TLR are capable to discriminate different domains of pathogen-associated molecular patterns (PAMPs) [44, 45] through pathogen recognition receptors (PRRs), and it is essential for microbial survival, thus playing an important function in host innate immunity with further activation of adaptive immunity [44]. TLR-2 and TLR-4 are transmembrane proteins that present a domain with a leucine-rich repetition in their extracellular region, which allows the recognition of diverse PAMPs [14, 44].

TLR-2 recognizes mechanism from Gram-positive bacteria and zymosan while TLR-4 recognizes Gram-negative bacteria LPS [44]. Human antigen-presenting cells (APCs) reveal both HLA-DR molecules, responsible for presenting peptides and CD80 (B7-1), which is a costimulatory molecule for T-cell activation [14]. In addition, subsequent to activation and signal transduction, signaling cascades might activate transcription factors and these in turn direct to the gene expression of cytokines, proinflammatory chemokines and antimicrobial peptides [14, 44].

In a study using chronically stressed mice, Orsatti and Sforcin (2012) [46] showed that propolis modulates the immune mechanisms, as it upregulates the TLR-2 and TLR-4 mRNA expression, promoting the recognition of microorganisms and the early stages of the immune response during stress [46].

Some studies indicated that propolis may reduce the risk of Atherosclerosis (AS) and it is potentially anti-AS [47-49]. Fang *et al.* (2013) [47], working with the administration of an ethanolic extract of propolis, observed significantly decreased levels of IL-6 and increased levels of IL-17 in ApoE−/− mice on a high-fat diet. Those authors [47], also noted that elevated levels of IL-17 were associated with a better outcome in patients with acute myocardial infarction a finding that supports a protective regulatory role of IL-17 in anti-Atherosclerosis effects [47].

Koya-Miyata *et al.* (2009) [48] reported that propolis extract avoids weight gain. In addition, reduced levels of glucose, triglycerides, cholesterol, non-esterified fatty acids serum in diet-induced obesity in C57BL/6 N mice. In another

study, Nader *et al.* (2010) [49] suggest that the extract of propolis produced the potential beneficial effects, inhibiting the development of AS in hypercholesterolemic rabbits [49].

Concerning the antimicrobial actions of propolis, Conti *et al.* (2013) [14] showed that TNF-α and IL-10 production by human monocytes was inhibited by high concentrations of cinnamic acid (Ci) while increased fungicidal activity was observed against *C. albicans*. Using a mouse model for vulvovaginal candidiasis, Castro *et al.* (2013) [19] showed that a propolis-based topical pharmaceutical preparation was able to control infections caused by *Candida albicans*, and the authors strongly indicate that propolis could be used as a strategy for controlling candidiasis.

The propolis immunomodulatory mechanisms described above, like the antitumoral, anti-inflammatory and antimicrobial are frequently attributed to the two main chemical constituents identified as Caffeic acid phenethyl ester (CAPE) and artepillin C, and are well-documented as NFκB inhibitor [2, 35, 50]. Previous reports have demonstrated that CAPE inhibits NFκB activation by suppressing nuclear translocation and DNA binding of p65, which may be dependent or independent of IκBα protein degradation in the cytosol [29]. Furthermore, the artepillin C, the major compound identified from Brazilian propolis, reduced NFκB expression during acute inflammation [50].

Ozturk *et al.* (2012) [51] reported that CAPE is a specific inhibitor of NFκB and can inhibit NFκB activation in prostatic cancer-3 (PC-3) cells by blocking the ability of paclitaxel and tumor necrosis factor-alpha (TNF-α) to activate NFκB. However, according Conti *et al.* (2014) [14], further investigations about molecular targets and structural analysis of CAPE, artepillin C and its inhibition of NFκB are necessary [14].

3. PATENTS

A large number of green propolis patents have been recorded, and multiple technical articles are available to describe biological profiles of propolis (Table **1**).

Table 1. Summary of Recent Patents Targeting Green Propolis.

Publication Number*	Description / Title	Inventors (Company)	Summary	Reference
WO2013163714	Green propolis pharmaceutical formulation for use in human odontology	Bastos, E.F., Alves, M., Fialho, S.L.	The present invention relates to the process for preparing a pharmaceutical formulation based on green propolis with antimicrobial properties, which can treat various odontological diseases. The formulation can be used via buccal administration	[50]
CN102885854	Taiwanese green propolis extractants used for the purpose of slowing down progression of patient disease	Huang, Y., Chen, J., Jane, Y., Huan, X., Qiao, H., Lin, J., Yang, Y.Z.	The invention provides a nutritious supplement which enhances life quality of a cancer patient. The nutritious supplement contains Taiwanese green propolis extractants and is used in combination with one or more anti-cancer drugs or components	[58]
CN102908287	Chinese and western medicine composite preparation toothpaste with propolis and preparation method thereof	Zhonghua, M.	The invention discloses a Chinese and Western medicine composite preparation toothpaste with propolis and a preparation method of the Chinese and western medicine composite preparation toothpaste with the propolis	[59]
WO2013042932	Food production method capable of reducing the time required for radiation detoxification	Kim, J.T., Kim, J.-T.	The food production method capable of reducing the time required for radiation detoxification comprises obtaining fine powders of propolis, seaweeds, or other useful plants; extracting effective ingredients from said plants, and mixing the effective ingredients	[60]
CN203111738	Propolis antioxidant package	Li, H., In, E.	The utility model relates to the field of agricultural product deep processing, and particularly relates to the field of propolis capsules	[61]
WO2013142936	Scalp cleansing and treating composition	Dios, M.	Invention patent to cosmetics, shampoos, nutrients, moisturisers; special customised conditioners with propolis	[62]
WO2013147409	Natural extract for preventing and treating oral disease	Oh, M.H., Kim, W.H., Kim, G.J., Choi, H.A., Kim, Y.K.	The present invention relates to an extract having the activity of preventing and treating oral disease, wherein the extract is isolated from natural substances	[63]

Table (1) contd….

Publication Number*	Description / Title	Inventors (Company)	Summary	Reference
US20130266521	Oral compositions comprising propolis	Fetissova, N., Blanvalet, C., Lambert, P.	Oral compositions are provided that comprise a propolis extract	[64]
CN102994296	Propolis ginger juice no-alcohol wine	Wang, R.	The invention provides a bee glue ginger juice no-alcohol wine beverage, which comprises natural bee glue, fresh ginger juice and no-alcohol wine	[65]
CN103300372	Propolis capsules wolfberry	Wang, J.	The invention discloses a capsule propolis wolfberry, wolfberry extracts from, almond powder, propolis, pine pollen, dextrin is made, characterized in that: the weight ratio of raw material: 20-40 wolfberry extract, almond powder 20 -30, propolis 10-15, pine pollen 20-30, dextrin 6-15	[66]
CN101361757	Combination containing brown alga polysaccharide sulfuric ester and propolis and use thereof	Hao, S.Z.	The present invention discloses a composition of fucoidan and the application in the regulation of the immune system, said composition comprising fucoidan or flavonoids and propolis extract as an active ingredient adjusted	[67]
EP2633862	Compositions based on propolis nanocapsules which can be used as carriers for substances of interest, methods for producing same and use thereof	Brandão, H.M.	The present invention relates to a process for obtaining compositions constituted by propolis nanoparticles and to the use thereof. Said nanoparticles being optionally associated to one or more substances of interest such as active ingredients, as well as, optionally, substances of secondary effect such as synergists and adjuvants	[68]
US20130129808	Medical product containing active component of propolis or grapefruit seed extract and manufacturing method thereof	Chang, J.H, Lee, H.S., Lee, J.H.	A medical product containing either an active ingredient of propolis which is a natural antibiotic or a grapefruit seed extract, and a manufacturing method thereof are provided	[69
US20130280183	Anticariogenic dentifrice composition comprising propolis as anticariogenic active ingredient	Navarrete, L.A.S., Rizzardinni, G.D.C.M.	From these 3 components, propolis is the major component, which is reinforced in its activity for a smaller amount of methylparaben and propylparaben obtaining a composition with a high anticariogenic composition without side effects	[70]
WO2013091053	Polymer composition containing natural bioactive principles for use in pharmaceutical and cosmetic formulations	Cabrera, W.I.R., Nakajima, K., Bendo, L.	The present invention refers to a polymer composition containing natural bioactive principles, in particular Propolis extract	[71]
CN302509436	Bottle (Propolis)	Xiao, Y.	Name of the product design: bottle (propolis); design uses of products: transportation of goods, loading or unloading of packaging and containers used to hold propolis; design features: the product's overall shape; points that best describe the design drawings or photographs: three-dimensional map	[72]
CN102356799	Propolis Sugar	Gao, Y.L., Zhao, L., Zhao, P., Zhao, Q.D., Europe, Y., Zhao, Q.-C., Wang, R.Z., Fan, K.	The present invention discloses a sugar propolis containing propolis extract, ganoderma extract, sugar, Vitamin C	[73]

Table (1) contd….

Publication Number*	Description / Title	Inventors (Company)	Summary	Reference
EP2646041	Extraction and formation of inclusion complexes of propolis active components with hydroxypropyl-beta-cyclodextrin	Mourtzinos, I., Koutsianas, N., Dragani, A.P.	The extraction of propolis is effected at room temperature, without the use of ultrasound or microwaves, by adding hydroxypropyl-β-cyclodextrin in the extraction solvent system	[74]
CN102961410	Oral spray of propolis	Liu, M.W., Sunde, G.	The invention relates to an oral spray of propolis, aims at providing an oral spray product of the propolis, and provides the oral spray of the propolis for playing an inhibitional role on coliform and *Staphylococcus aureus*	[75]
CN102940648	Bee propolis soft capsule and manufacturing process thereof	Liu, M.W., Sunde, G.	The invention aims to overcome the defect that polyethylene glycol is added into bee propolis to influence an effective component in the bee propolis	[76]
EP2612667	Anticaries dentifrice composition that includes anticaries propolis as an active principle	Navarrete, L.A.S., Rizzardinni, G.D.C.M.	The invention is referred to a new dentifrice composition with anticariogenic properties, which has as active anticariogenic ingredients a combination of propolis, methylparaben and propylparaben	[77]
WO2013132456	Prebiotic mixture	Mercati, V., Mercati, V., Lugli, A., Maidecchi, A.	The present invention refers to a prebiotic mixture comprising at least one plant polysaccharide fibre and at least one of Propolis and/or *Olea europaea* and/or *Aloe vera* extracts, optionally comprising also *Thymus vulgaris* and/or *Agrimoniaeupatoria* extracts	[78]
CN102894246	Water-soluble propolis liquid and preparation method thereof	Liu, M.W., Sunde, G.	The invention aims to provide a water-soluble propolis liquid product. According to the water-soluble propolis liquid, capryliccapric triglyceride is used as a cosolvent originally	[79]
CN103054906	Propolis ethanol extract for alleviating hangover and preparation method thereof, and application of propolis ethanol extract in producing buccal tablets	Zhou, B., Ji, F., Ji, J.	The invention relates to a propolis ethanol extract for alleviating a hangover and a preparation method thereof, and application of the propolis ethanol extract in producing buccal tablets, belonging to the technical field of techniques for extracting effective substances from propolis	[80]
CN102283794	Toothpaste including radix notoginseng and propolis and preparation method thereof	Li, J., Luo, S., Susa, Y.L.	The invention is a propolis toothpaste containing thirty-seven and its preparation method	[81]
US8455007	Method to treat propolis	Flurin, C.B.	The method applies to the production of extracts of propolis for use in the fabrication of hygiene, cosmetic products, food supplements and others	[82]
CN102824371	Propolis lycopene composition and preparation method	Estrela W. H., Jingjing L., Xuan Z., Passou L., Huan Z., Gang L.	The invention is propolis lycopene soft capsule and its preparation	[83] .
US20130309218	Process for producing aqueous solution containing fat-soluble substance	Terao, K., Fukumi, H., Nakata, D., Uekaji, Y., Jo, A.	The purpose of the present invention is to provide a process for producing an aqueous solution containing a fat-soluble substance	[84]

Table (1) contd….

Publication Number*	Description / Title	Inventors (Company)	Summary	Reference
CN102499338	Hydrophilic propolis powder capsule composition and production method thereof	Zhou, P.	The present invention relates to a hydrophilic capsule composition of propolis powder and its production method	[85]
WO2013155715	Stomach health-preserving capsule	Chen, H., Chen, H., Zheng, H., Zheng, H., Chen, Y., Chen, Y., Lu, H., Luhan, P., Chen, C.N., Weijie, W.U., Wu, W.	Disclosed is a stomach health-preserving capsule, consisting of components in the following weight ratios: 16% *Ganoderma lucidum* extract, 12% milk vetch root extract, 42.2% *Hericium erinaceus* extract, 7% propolis and 22.8% *Lentinus edodes* extract	[86]
CN102961314	Propolis cutin removal paste for lips	Liu, H.S.	The invention relates to a propolis cutin removal paste for lips, belonging to the field of cosmetics	[87]
WO2013012477	Propolis and caffeic acid phenethyl ester and uses thereof	Omene, C., O'Connor, O., Frenkel, K.	Methods for treating a subject with cancer using a combined therapeutic regimen comprising administering propolis or caffeic acid phenethyl ester (CAPE) in conjunction with other cancer therapeutics are described herein	[88]
US20120004389	Method for extracting propolis using far-infrared rays from earthenware	Lee, Y.K.	A method for extracting propolis by using far infrared ray from pottery	[89]
CN101669556	Method for preparing blueberry green tea granules	Week, Z.	The granule mainly comprises the following raw materials: green tea, blueberries, propolis, vitamin E, vitamin C, and dextrin	[90]
WO2012057291	Process for production of phenolic polymerizable compound having physiological activity	Kishi, A., Doi, S., Matsukawa, T., Matsui, T., Yamada, Y., Yamada, I.	The present invention relates to a process for producing a phenolic polymerizable compound	[91]
WO2011114291	Process for obtaining non-allergic propolis	Ricchiuto, G.M., Gardana, C.S., Guglielmetti, S.D.	The present invention also relates to a method of purifying semisolid propolis derivative to obtain a hydroalcoholic hydrodispersible propolis derivative	[92]
WO2011141007	Propolis and method of its production	Saroch, J., Holub, M., Krupickova, J.	The invention relates to propolis containing active substances, whose composition is specific according to the season of harvesting and according to the origin and method of production of such propolis	[93]
EUA20120004389	Method for extracting propolis using far-infrared rays from earthenware	Kwang, Y.L.	The described methodology for extracting propolis using far-infrared rays from earthenware, make possible to avoid microorganisms proliferation and so, the consequent oxidation and deterioration of the propolis	[94]

*This survey was conducted with patents related to the use of green propolis, its use in cancer treatment, and other propolis-related products; the consultation was performed from January 2011 to November 2013.

Those works focus on the relevant compiled results on the properties of propolis, its potential mechanisms and its active constituents. The inventions are related to the processes for preparing green propolis-based pharmaceutical formulations and propolis capsules with antimicrobial properties, which can treat various dental diseases such as mucositis, cancer, and buccal peri-implantitis [52].

Propolis is a cationic antibacterial agent as well as an anti-attachment, anti-inflammatory, and biofilm disruption agent [2]. Processes for obtaining standardized extracts or isolated substances from green propolis; standardized extracts formulations, fractions and isolated substances of propolis are used as sanitizer, antiseptic and/or disinfecting products for microbiological control in alimentary and similar industries, fixed surfaces and dairy products [2].

There are different commercial formulations [52-94], already patented, that are used as antisepsis of hands and skin, nutritional supplements that enhances the quality of life of cancer patients. Since the first Romanian patent in 1965 until 1999, 239 propolis-related patents had been filed. Until the late 1980s, the patents were dominated by the former USSR and its satellite countries, especially Romania [53]. According to data obtained from the LATIPAT database on the Instituto Nacional de Propriedade Industrial - INPI [54]. (National Institute of Industrial Property) website, by January 2014, approximately 2452 patent applications could be found in worldwide records of propolis-related patents. Of these, 110 were Japanese and the first patent from Japan was filed in 1987 [55].

Among Japanese patents are those on the isolation and application of an antitumor compound from Brazilian propolis produced in the states of Minas Gerais and São Paulo, Artepillin C [56]; the application of Artepillin C alone and/or its salt as an agent for apoptosis [57].

Thousands of patents are mentioned in the literature but only those associated to effects on the immune system were analyzed (2,452). Thus, we can infer that the propolis is still treated as a functional food, even though we observed a general description of its many properties regarding human health.

4. CURRENT & FUTURE DEVELOPMENTS

The present review highlights the potential application of propolis as a natural alternative 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 activity.

The information on the biological properties and biochemical interactions of propolis on the immune system has advanced a lot in the last years on account of a number of *in vitro* and *in vivo* studies. However, there is not much information about the clinical efficacy of propolis and its impact in human treatment so clinical studies are necessary in order to evaluate this potential application.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

CAPE	=	Caffeic acid phenethyl ester
Ci	=	Cinnamic acid
Artepillin C	=	3, 5-Diprenyl-4-hydroxycinnamic acid
CIA	=	Collagen-induced arthritis
IL-17	=	Interleukin-17
STAT3	=	Activator of transcription 3
Th17 cells	=	T Helper cells 17
Th1 cells	=	T Helper cell (redirect from Th1 cell)
IFNγ	=	Interferon gamma
CD4+ T cells	=	CD4+T helper cells
IL-1β	=	Interleucina 1β
IL-6	=	Interleukin 6
TLR	=	Toll-like receptors
PAMPs	=	Pathogen-associated molecular patterns
APCs	=	Human antigen-presenting cells
HLA-DR	=	MHC class II cell surface receptor
CD80 (B7-1)	=	Cluster of Differentiation 80
LPS	=	Lipopolysaccharide
mRNA	=	Messenger RNA
EEP	=	Ethanolic extract of propolis
NFκB	=	Factor nuclear kappa B
IL-10	=	Interleukin-10
IκBα protein	=	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
p65	=	Transcription factor p65
IKK	=	IκB kinase complex
PC-3	=	Prostatic cancer-3
TNF-α	=	Necrosis factor-alpha
AS	=	Atherosclerosis
LATIPAT	=	Database on the Instituto Nacional de Propriedade Industrial-INPI

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