In: Beneficial Effects of Propolis on Human Health ... ISBN: 978-1- 62081-440-6
Editors: Tahira Farooqui and Akhlaq A. Farooqui © 2013 Nova Science Publishers, Inc.

Chapter 1

CHEMICAL PROFILES OF DIFFERENT PROPOLIS TYPES IN RELATION TO THEIR BIOLOGICAL ACTIVITY

Vassya Bankova and Boryana Trusheva*
Institute of Organic Chemistry with Centre of Phytochemistry,
Bulgarian Academy of Sciences, Sofia, Bulgaria

ABSTRACT

In the last decade, the paradigm shift in propolis research was completed: the awareness that propolis is a product of variable chemical composition and that there are many propolis types became common knowledge. For this reason and unlike previous review articles, the present review on propolis is organized in agreement with this concept. Recent findings in propolis research are summarized and discussed, concerning chemical profiles, new constituents, biological activity and active principles of different propolis types, as determined by their plant source(s). European poplar propolis, Brazilian green (*Baccharis*) propolis, Brazilian and Cuban red propolis (*Dalbergia*) and other recently discovered propolis types are considered.

1. INTRODUCTION

Propolis (bee glue) is a bee product with double application in the beehive. Bees make use of the sticky texture of this resinous material by applying it for blocking holes and cracks, repairing combs, strengthening the thin borders of the comb, etc. On the other hand, they make use also of its biological properties: propolis contains the putrefaction of "embalmed" intruders, killed in the hive and too large to be carried out, and it is responsible for the lower incidence of bacteria and moulds within the hive than in the atmosphere outside [1]. The

* Correspondence concerning this article should be addressed to: Vassya Bankova, Institute of Organic chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. B, Bonchev str. Bl.9, 1113 Sofia, Bulgaria. bankova@orgchm.bas.bg; Telephone: ++3592-9606-149; Fax: ++3592 8700 225.

property to fight and prevent infections is one of the most essential characteristics of propolis, which has been recognized and used by humans since ancient times. Nowadays, propolis is still among the most popular home made remedies in some regions of the world, and it is a valued ingredient of numerous health foods and drinks, food supplements, cosmetics and over-the-counter preparations [2,3]. For this reason, and inspired by the general interest in natural products, modern science took notice of propolis. The attention of researchers to this bee product has been constantly growing for the last 50 years. Over the period 2000 – 2010 the research articles on propolis increased from about 70 to over 200 per year (Scopus database). After the year 2000, many new propolis constituents have been isolated and structurally elucidated, and a lot of new data has been published concerning its beneficial biological properties. In the course of this research, numerous samples from different geographic origins have been studied and it has become obvious that the chemical composition of propolis is extremely variable. As propolis is a plant derived product, its chemistry depends on the source plant, respectively on the specificity of the local flora at the site of collection and the choice of plant resin for propolis production made by bees. It turned out that in a particular phytogeographic region honeybees demonstrate unambiguous and constant preference to particular plant source(s) and as a results, different propolis chemical types exist [4,5]. Basic information on the most widespread propolis types is represented in Table 1.

Table 1. Chemical profiles of the most widespread propolis types

Propolis type	Geographical distribution	Major plant source	Chemical profile (characteristic constituents)	References
Poplar type	Europe, Western Asia, China, South Africa, North America, New Zealand	Bud exudates of poplar trees, mainly Populus nigra	Pinocemnrin, galangin chrysin, pinobanksin 3-O-acetate, pentelyl caffeates, phenethyl caffeate (CAPE), caffeic acid, ferulic and isoferulic acid	[6-12]
Brazilian green	Brazil (Sao Paulo, Rio de Janeiro, Minas Gerais)	Leaf exudates of *Baccharis dracunculifolia*	Artepillin C, baccharin, drupanin, aromadendrine, caffeoylquinic acids	[13,14]
South American red	Brazil (North-East part), Cuba, Mexico	Exudates of *Dalbergia ecastophyllum*, other *Dalbergia* species	Medicarpin, vestitol, 3-O-methyl vestitol	[15-17]
Mediterranean	Southern Greece and Greek islands, Crete, Sicily, Malta, Adriatic Coast of Croatia	*Cupressus sempervirens* resin	isocupressic acid, pimaric acid, imbricataloic acid, totarol, ferruginol	[18-20]
Pacific	Okinawa, Taiwan, Indoinesia	Fruit exudates of *Macaranga tanarius*	Propolin C, propolin D, propolin F	[21,22]

The observed biological activities of bee glue are due to the plant-derived secondary metabolites but surprisingly, different chemical composition doesn't always result in drastic differences in pharmacological effects. However, there is some specificity, and for this reason

pharmacological studies must always be accompanied by chemical characterization of the propolis used in the experiments, or at least by determining the chemical type of this propolis. This was the paradigm shift in propolis research that was completed in the last decade: the awareness that propolis is a product of variable chemical composition and that there are many propolis types became common knowledge. Nevertheless, a significant number of pharmacological studies on propolis are yet published without any chemical analysis of the bee glue, and this makes them practically useless. This fact is most unfortunate because among them, there are investigations of high quality, regarding the pharmacological part, and also ones that report valuable activities.

In this chapter, we focus on the scientifically sound information about distinct propolis types, published in the years after 2000, grouped in accordance of the source plant and the respective chemical profiles, characteristic for the particular propolis type. The composition-activity relationship for these propolis types is discussed.

2. Poplar Type Propolis

Propolis has been a traditional European remedy since the times of Ancient Greece and Rome. For this reason the first studies on propolis chemistry and biological activity were performed in European laboratories and with European bee glue. In the 1970's and 1980's it became clear that in Europe the plant source of propolis are the bud exudates of poplar trees, mainly *Populus nigra* L. [7,23,24]. Hence, this propolis type contains the typical poplar bud constituents: flavonoid aglycones (flavanones, flavones and flavonols), phenolic acids (caffeic, ferulic, isoferulic, *p*-coumaric) and their esters. Most abundant are the flavonoids pinocembrin (Fig. 1), galangin and chrysin, and the esters phenethyl caffeate (CAPE) (Fig. 1), pentenyl caffeates, benzyl ferulate, etc. Over 150 individual constituents have been found in poplar type propolis so far [25].

There is an impressive number of articles dedicated to the pharmacological activities of poplar type propolis. The information (published after 2000) about pharmacological activities of this propolis type and the responsible constituents is summarized in Table 2.

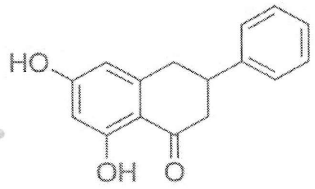
Of course, among the most studied ones is the most popular property of propolis: action against bacteria and fungi, and, to a lesser extent, against viruses. A long list of bacterial species and strains has been tested for their susceptibility towards poplar propolis extracts, including important human pathogens. Most often, ethanol propolis extracts have been used for the experiments. Numerous publications report that poplar bee glue is more active against Gram-positive bacteria than to Gram-negative ones [103-110]. Of practical importance are the observations that poplar propolis inhibits methicillin resistant *Staphylococcus aureus* (MRSA) [30], *Campylobacter jejuni* [111], *Helicobacter pylori* [112-114], *Listeria monocytogenes* [110]. The activity against oral pathogens, such as *Streptococcus mutans*, *Lactobacillus fermentum*, etc., is also of clinical interest and has been studied by many authors [26,106,115-118]. In general, the antibacterial activity of poplar propolis is attributed to its phenolic constituents [119,120], among them caffeic acid phenethyl ester (CAPE) [29,121], pinocembrin [30,122] and pinobanksin-3-O-acetate [26].

Table 2. Biological activities of poplar type propolis and responsible constituents

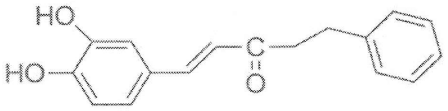
Type of activity	Responsible molecules	References
Antibacterial	Galangin, pinocembrin, pinobanksin-3-O-acetate, CAPE, quercetin	[26-30]
Antifungal	Galangin, pinocembrin, pinobanksin	[31,32]
Antiviral	Galangin, chrysin	[33-36]
Antioxidant	CAPE, tectochrysin, caffeic acid, ferulic acid, galangin	[37-43]
Antitumor, cytotoxic	CAPE, quercetin, chrysin, naringenin, caffeic acid, galangin; benzylcaffeate, cinnamyl caffeate; 2-acetyl-1,3-dicoumaroyl glycerol; 2-acetyl-1-coumaroyl-feruloyl glycerol	[44-62]
Antiinflammatory	Chrysin, kaempferol, CAPE, galangin, quercetin	[29,63-66]
Radioprotective	Quercetin, chrysin, naringenin, caffeic acid	[67-73]
Immunomodulatory	CAPE, quercetin, caffeic acid	[74-77]
UV-protecting	Not identified	[78]
Mitigaion of amnesia	Not identified	[79]
Clinical reports on use of topical preparation containing poplar propolis	Not identified	[80-86]
Prevention of hepatorenal injury	Not identified	[87]
Allergenic	Benzyl caffeate, 3-methyl-2-butenyl caffeate, CAPE	[88-100]
Inhibition of xanthine oxidase	CAPE, chrysin, galangin	[101]
Action against *Varroa destructor* (bee parasite)	Not identified	[102]

Poplar propolis extracts have been found capable of inhibiting the development of fungal human pathogens such as *Candida albicans* [123-125], but also of phytopathogenic fungi [31,32,126]. Filamentous fungi were generally less sensitive to poplar propolis than yeasts [105]. The active components were proved to be chrysin, pinocembrin and galangin [31,32].

Poplar type propolis demonstrated significant activity also against Herpes simplex virus type 1 and type 2 [33,35,36]. Alcohol extract was active against HSV-1 and HSV-2, of the tested individual compounds only galangin and chrysin exhibited antiviral activity. In both cases the extracts exhibited high anti-herpetic activity when viruses were pretreated with them prior to infection.

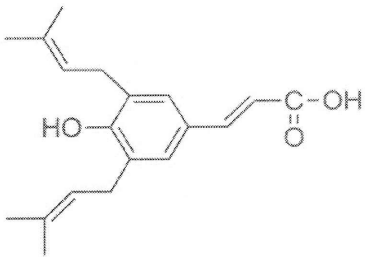


Pinocembrin

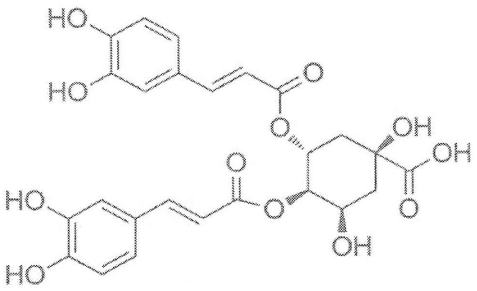


CAPE

POPLAR TYPE PROPOLIS

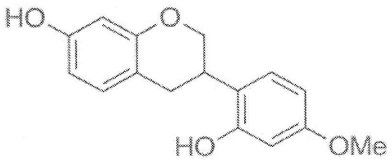


Artepillin C

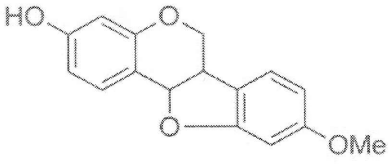


2,4-Dicaffeoylquinic acid

BRAZILIAN GREEN PROPOLIS



Vestitol



Medicarpin

RED SOUTH AMERICAL PROPOLIS

Figure 1. Important biologically active compounds in most widespread propolis types.

It is important to note that all investigations on the antibacterial action of individual substances, isolated from propolis, showed that not a single propolis component has an activity much higher than that of the total extract [121,127]. It seems that propolis has general antiinfective pharmacological value as a natural mixture and not as a source of new powerful antimicrobial, antifungal and antiviral individual compounds.

Antioxidant properties of propolis have attracted the attention of researchers and the general public especially during the last decade. Many studies confirm the radical scavenging potential of poplar propolis, using the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) and the 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation decolorization (ABTS) assays [39-42,128-135]. Evaluation of beta-carotene bleaching [39,128], of the ferric reduction antioxidant power (FRAP-assay) [135,136] and of the change of thiobarbituric acid reactive species (TBARS) [137] were also applied to poplar propolis, proving its antioxidant potential. Some further specialized tests have also confirmed this potential: microsomal lipid peroxidation test [138], test based on the modulation of ascorbate peroxidase activity of hemoglobin [139]. *In vivo* experiments proved that poplar propolis as food supplement modulated antioxidant enzymes and significantly decreased lipid peroxidation processes in mice [136]. Similar effects were observed also in an experiment with healthy humans [140]. The responsible constituents are again the poplar phenolics and flavonoids [131,135,137]. As individual antioxidant principles, CAPE [39,40,128], caffeic and ferulic acid [39,128] and galangin [42] were identified.

Since the beginning of the new Millennium, there has been a great number of publications considering the antitumor action of poplar propolis and its constituents. For example, poplar propolis and some isolated polyphenolic compounds (caffeic acid, CAPE and quercetin) decreased the number of tumor nodules in the lung; however, the antimetastatic effectiveness of poplar propolis was higher than that presented by its constituents [75]. The same authors found that poplar propolis, caffeic acid and CAPE modulate immune responses and increase host resistance to tumor cells [54,141]. Poplar propolis, caffeic acid and CAPE could be useful tools in the control of tumor growth according to Orsolic et al. [52], who reported that poplar propolis antitumor action could be the consequence of synergistic activities of its polyphenolic compounds.

The most important antitumor constituent of poplar propolis is the caffeic acid phenethyl ester (CAPE). This relatively simple compound is also the most studied propolis constituent of all, regardless the propolis type. Its popularity with researchers increased significantly after 1988, when it was identified as the main cytotoxic compound in propolis with preferential cytotoxicity on tumour cells [142]. Ever after, different aspects of the biological and pharmacological activities of CAPE have been studied, including the mechanism of its action. Many new aspects of its biological properties have been revealed, including anti-inflammatory, anti-HIV, antibacterial, antioxidant. CAPE has been shown to inhibit the ornithine decarboxylase, protein tyrosine kinase and lipoxygenase activities. It has also been reported that CAPE suppresses lipid peroxidation and inhibits the activation of nuclear transcription factor NF-kB, etc. [143,144]. The story of CAPE demonstrates the potential of propolis for identification of natural products with valuable activities [144].

Propolis in general is regarded as non-toxic but it is known to cause allergic reactions, mainly contact dermatitis. Practically all reports concerning propolis allergy involve poplar type propolis [90,95-97,99]. The main contact allergens in poplar propolis were identified as benzyl caffeate and 3-methyl-2-butenyl caffeate [90]. It is not clear whether other propolis types might cause allergic reactions as well.

Speaking of poplar propolis, it is important to mention a variety of poplar propolis which is encountered in locations of high altitude (over 1200 – 1500 m) and in the Northern regions of Europe. Its major plant source is the common aspen *Populus tremula* and it contains higher amounts of phenolic acids and less flavonoids, compared to the one coming from *P. nigra.*

This propolis type contains also phenolic glycerides (dicoumaroyl acetyl glycerol, diferuloyl acetyl glycerol, feruloyl coumaroyl acetyl glycerol, caffeoyl coumaroyl acetyl glycerol) [46,145]. The latter compounds contribute to the biological activity of the corresponding propolis, they have been proved to possess antiproliferative activity against different cell lines, antiradical and hepatoprotective action [44,46].

Available information about the abovementioned and about further biological activities of poplar type propolis and the responsible molecules is represented in Table 2.

Obviously, poplar propolis possesses valuable activities that have been well documented. In many cases, the active principles have also been identified. This knowledge gives the reason for a standardization of poplar propolis, based on the concentration of active principles. However, it has been demonstrated in many cases that the activity of propolis of any type is the result of simultaneous and synergistic action of several active molecules. For this reason it seems that, for the purposes of standardization and quality control, measuring the concentration of only one (or a couple of) individual constituent(s) could be inappropriate. A combination of three spectrophotometric methods has been proposed to quantify total phenolics, total flavones/flavonols and total flavanones/dihydroflavonols in poplar propolis [146]. This procedure is simple, easy to perform, gives results with good repeatability and accuracy, and provides reliable characterization of the chemical profile of poplar type propolis for the purposes of its use in different preparations and health foods.

3. Green Brazilian Propolis

In the last two decades, Brazilian propolis has become a subject of increasing commercial and scientific interest, because Brazil exports large amounts of propolis at the international market. Brazil is a large country comprising diverse phyto-geographical regions and therefore 12 distinct chemical types of Brazilian propolis have been described according to their botanical origin [5]. Without any doubt, green Brazilian propolis (GBP) is the most commercialized and most widely used Brazilian propolis type, greatly popular also in Japan. This propolis type is collected by bees from the shoot apices of *Baccharis dracunculifolia* (alecrim), an asteracean plant commonly found in the states Minas Gerais, Parana, Sao Paulo and Rio de Janeiro [14,147]. Its chemical composition differs significantly from the one of poplar type propolis. Most characteristic chemical constituents of green Brazilian propolis are prenylated phenylpropanoids, mostly prenylated coumaric acid derivatives (artepillin C, baccharin, drupanin), some flavonoid aglycones (although different from the ones in poplar propolis and in much lower concentration), diterpenic acids and caffeoylquinic acids [148].

Despite the impressive chemical difference, green Brazilian propolis has demonstrated biological activity which is similar to a great extent to that of poplar propolis. Expectedly, GBP is active against different bacteria, fungi and viruses. Among the susceptible microorganisms are the bacteria *Staphylococcus aureus* [149-153], *Streptococcus pneumoniae* [150], *Sterptococcus pyogenes* [152], *Klebsiela pneumoniae* [150], *Listeria monocytogenes* [153], the pathogenic fungi *Candida albicans* [150,154], *Trichophyton* species [155], *Paracoccidioides brasiliensis* [150], *Criptococcus neophormans* [156], the moulds *Cladosporium cladosporioides* and *C. sphaeroides* [157]. The activity *in vitro* against *Helicobacter pylori* is comparable to the one of poplar propolis [158] but the results of a pilot

clinical study were inconclusive [159]. A series of studies deal with the activity of GBP against oral pathogens, causing caries and periodontitis [160-163] and with the use of GBP preparations in treatment of root canals, periodontitis and stomatitis [164-167]. Significant inhibition of the important bee pathogen *Paenibacillus larvae* has also been documented [168].

Active antimicrobial substances of GBP were found to be mainly phenolic compounds, details are displayed in Table 3.

Table 3. Biological activities of green Brazilian propolis and responsible constituents

Type of activity	Responsible molecules	References
Antibacterial	artepillin C, drupanin, 3-hydroxy-2,2-dimethyl-8-prenylchromane-6-propenoic acid, (*E*)-3-[2,3-Dihydro-2-(1-methylethenyl)-7-prenyl-5-benzofuranyl]- 2-propenoic acid, 15-acetoxyisocupressic acid, caffeoylquinic acids	[149-153,158-163,168-172]
Antifungal	Artepillin C, drupanin	[150,154-157,164,173-175]
Antiviral	3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 3,4,5-tricaffeoylquinic acid	[34,176-179]
Antiparasitic	Not identified	[180-183]
Antitumor, cytotoxic	3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 3,4,5-tricaffeoylquinic acid, 3-[2-dimethyl-8(3-m3thyl-2-butehyl)benzopyran]-6-propenoic acid, baccharin, drupanin, aromadendrin-4-methyl ether	[184-208]
Antioxidant	Artepillin C, baccharin; chlorogenic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, kaempferid	[44,170,209-222]
Antiinflammatory	Artepillin C; baccharin, kaempferid	[223-228]
Wound-healing	Not identified	[229-231]
UV-protecting	phenolics	[232,233]
Immunomodulatory	phenolics	[234-239]
Antihypertensive	3,4-dicaffeoylquinic acid 3,5-dicaffeoylquinic acid 3,4,5-tricaffeoylquinic acid, dihydroquercetin, isosakuranetin	[240-242]
Antihypercholesterolemic and antihyperlipidemic	Not identified	[243-246]
Suppressive effect on toxicity of different toxic agents	Baccharin	[247-252]
Neuroprotective	Not identified	[253-255]
Antiulcer	Caffeic, ferulic, *p*-coumaric, cinnamic acids	[256-259]
Inhibition of xanthine oxidase	Artepillin C, *p*-coumaric acid	[101]
Anti-emetic	(E)- and (Z)-3-(2,2-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenoic acid, dihydrocinnamic acid; dihydrohautriwaic aicd	[260]
Relaxant action of guinea-pig trachea *in vitro*	Not identified	[261]

The antiviral action of GBP has been studied in the last decade much more that the one of poplar propolis. GBP demonstrated efficacy against herpes simplex virus type 1 [178] but also against influenza virus (H1N1) ([176,179], poliovirus type 1 [177], and anti-HIV-1 activity in CD4(+) lymphocyte and microglial cell cultures [34]. Caffeoylquinic acids have been identified as major antiinfluenza agents in GBP [179].

GBP has also potential to be used against two parasitic diseases which are of importance in tropical countries. Activity against *Leishmania braziliensis* [180,181] and activity *in vitro* and *in vivo* against *Tripanozoma cruzi* (causing Shaga's disease) have been reported [182,183].

GBP contains significant amounts of phenolic substances, so it is not surprising that it possesses antioxidant activity. Radical scavenging activity against DPPH radicals has been repeatedly demonstrated [215-218,221,222]. Da Silva et al. (2006) found correlation between the antiradical activity and the total phenolic and flavonoid levels in GBP [170]. Other authors demonstrated the anti-lipid peroxidation potential of GBP [209,214]. In addition, GBP was able to inhibit the oxidative stress in neutrophiles [211,219]. Its potential to act as UV-photoprotector was found promising [232,233].

The antioxidant activity is believed to be related to the anti-inflammatory properties in general [262] and GBP was found to exert anti-inflammatory action in several models [224,228,230]. Individual compounds with antiinflammatory properties are artepillin C, baccharin and kaempferid [225,227]. The anti-inflammatory and antibacterial properties contribute to the positive effect of GBP on tissue repair of cutaneous wounds in rats [229,231].

Research on the antitumor and cytotoxic activity of GBP has received much attention since the year 2000 (See Table 3). Cytotoxicity of GBP against different tumor cell lines has been demonstrated [184,194,197,202]. Apoptosis induced by GBP and its constituents artepillin C and caffeoylquinic acids was observed by several research groups [186,189,190,206-208]. GBP and artepillin C can play a cancer-preventing role against chemically induced carcinogenesis in rats and mice [185,187,192,196,205].

Many of the pharmacological properties of GBP have been connected, at least partly, to the *p*-coumaric acid derivative artepillin C. Analogously to CAPE in poplar propolis, this compound has been the subject of numerous pharmacological studies and has demonstrated diverse and valuable activities. A comprehensive review on its synthesis, biological activities and pharmacokinetics has been published recently [263].

Unlike poplar propolis, there is no publication claiming allergy toward GBP. There is only one communication reporting on acute renal failure in a patient with cholangiocarcinoma due to ingestion of GBP [264]. The allergenic properties of GBP haven't been studied so far. In a study aimed to search for side effects of GBP after long-term administration (30 days), no significant changes in the serum biochemical parameters of rats were observed [265].

Further data concerning the abovementioned and further biological activities of green Brazilian (alecrim) propolis, and the corresponding active constituents, are represented in Table 3.

Concerning standardization and quality control of GBP, a combination of spectrophotometric methods has been proposed [266,267] to quantify total phenolics and total flavonoids. This approach is similar but not identical to the one used for poplar type propolis. It is important to note that the content of flavonoids in GBP is much lower than the one in poplar propolis. Another important point is the need to use different standards for calibration

for the measurements in case of GBP and in case of poplar propolis, because of the difference in their chemical composition.

3. Red South American Propolis

The first communications about red propolis and its biological activities came from Cuba and appeared in the 1990's. [268]. The major constituents in Cuban red propolis were identified as isoflavonoids [269-271]. With the beginning of the 21 century, red propolis has been detected also in the North-Eastern parts of Brazil, in the states of Alagoas, Bahia and Paraiba [272,273]. Red Brazilian propolis attracted the attention of propolis researchers and it turned out that isoflavonoids and pterocarpans were its major constituents [272]. Their plant source was identified as the red resinous exudates of *Dalbergia ecasophyllum* [15,274,275]. A comparative study of Brazilian and Cuban red propolis showed their similar chemical profiles and confirmed that they both originated from *Dalbergia* spp. [17]. However, Brazilian samples contained also prenylated benzophenones, typical for *Clusia* species, and this makes them specific [17,272]. Recently, a red-type propolis from the Southern region of Mexico was studied and found to contain *Dalbergia* isoflavonoids and pterocarpans, too [16]. Obviously, there is a red propolis type (RP), typical for South America. The published research papers concerning this propolis type are increasing from year to year, and the communicated results on its biological activity are encouraging, so we believe it deserves a more detailed overview.

Brazilian RP and some of its constituents (see Table 4) possess antimicrobial activity against *S. aureus* ([272,276-280], *Streptococcus mutans* [280,286], *Candida albicans* [272], *Trichophyton rubrum, T. tonsurans* and *T. mentagrophytes* [155]. Potent cytotoxic activity of Brazilian RP and isolated compounds against different cancer cell lines has been reported [276,281,283]. Atheroprotecive properties of Brazilian RP are described, and attributed to its phenolic constituents [287]; it also improved dermal wound healing in a rodent model [284]. Red propolis contains isoflavonoids and its radical scavenging activity against DPPH radicals [272,276,288], as well as its high antioxidant activity by β-carotene/linoleic acid test [288] are not surprising. But maybe the most attractive and promising property of Brazilian red propolis is its ability to promote adypocite differentiation through PPARγ activation, which suggests that it has the potential, when used as food additive, to prevent obesity and obesity associated disorders [285].

The data concerning biological activities and active constituents of red South American propolis are summarized in Table 4.

4. Other Propolis Types from Tropical and Subtropical Regions

The remarkable chemical variability of propolis is, of course, due to its' plant origin and to the fact that at different geographic locations the source plants might vary with respect to the local flora at the site of collection. The chemical composition of propolis is directly dependant on the availability of resinous plant materials in different geographic regions. This

is especially true for tropical and subtropical regions, with their huge biodiversity. However, there is another important but often neglected factor: the choices bees make. In any environment, bees tend to choose as propolis sources plants with pronounced antimicrobial, antioxidant and cytotoxic properties, because propolis is very important as chemical defense of the hive [144]. Moreover, in environments with similar flora, as a rule, they choose the same source material, which leads to the existence of specific propolis types.

In the last decade, several new propolis types "emerged" in the scientific literature and in this chapter we are going to discuss briefly the most important ones of them.

The oldest known tropical propolis type, different from Green Brazilian and Red South-American ones, is the *Clusia*-type propolis. It was first noticed by the group of Tomas-Barberan in 1993, when they studies Venezuelan bee glue: they found in it (by LC-MS) polyprenylated benzophenones, and the propolis chemical profile coincided with the profile of the resins exuded by the flowers of *Clusia major* (autograph tree) [289]. The prenylated benzophenones exuded from the flowers of *Clusia* species were isolated later from propolis from Venezuela [290], Cuba [291,292] and Brazil [293,294]. The biological activities of the *Clusia*-type propolis are due to the properties of the prenylated benzophenones. Nevertheless, they are typical for propolis in general: antibacterial, antioxidant, cytotoxic (see Table 5). Propolis rich in prenylated benzophenones was active against *Staphylococccus aureus* [290,293], *Streptococcus mutans* [293-295], *S. sorbinus*, *S. oralis, S. mitis, S. salivarius* and *Actinomycetes aeslundii* [293,294]. In addition, it suppressed the formation of mutans streptococci biofilms [295,296]. Of interest is the antiretroviral activity against HIV-1, displayed by two prenylated benzophenones isolated from Caribbean propolis [298]. Antioxidant potential of *Clusia*-type propolis has also been reported [291,333], as well as cytotoxic activity against human tumor cell lines [299-301].

Table 4. Biological activities of South American red propolis and responsible constituents

Type of activity	Responsible molecules	References
Antibacterial	Isosativan, medicarpin, vestitol, neovestitol,isoliquiritgenin	[272,276-280]
Antifungal	Isosativan, medicarpin	[155,272]
Antitumor, cytotoxic	3,8-dihydroxi-9-methoxypterocarpan, 7-hydroxy-6-methoxyflavanon, mucronulatol	[276,281-283]
Antioxidant	Vestitol, neovestitol, Isosativan, medicarpin	[272,280]
Against *Leishmania*	Not identified	[180]
Wound healing	Not identified	[284]
Anti-obesity	Not identified	[285]

Bees in the Pacific islands in the Far East have been reported to collect a specific propolis type of bright green colour. From this propolis type from Okinawa [334] and Taiwan [312], prenylated flavanones (propolins) with radical scavenging activity were isolated. Further studies on chemical profiles and bee behaviour revealed the corresponding plant source: the resinous material on the surface of the fruits of *Macaranga tanarius* [22]. This propolis type

and its major constituents the propolins, possess antibacterial activity [307,308], including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [311]. Its antiradical and antioxidant properties [309,313] are similar to the ones demonstrated by other propolis types. Pacific propolis and propolins have attracted the attention of researchers mainly with their cytotoxic and anticancer effect [21,61,314,315,335]. Details about the active constituents are displayed in Table 5. Recently, propolins have been identified in propolis from the Solomon Islands [311] and Indonesia [332], confirming the appropriateness of the term "Pacific propolis". Interestingly, prenylated *Macaranga* flavonoids were found also in some African propolis samples [310,331].

Table 5. New propolis types, some of them possibly with limited distribution

Propolis type	Geographical distribution	Plant source(s)	Biological activity	Responsible molecules	References
Clusia type	**South America (Cuba, Brazil, Venezuela)**	**Frower resin of *Clusia species***			
			Antibacterial	Prenylated benzophenones: hyperibone A; 7-*epi*-nemorosone, 7-*epi*-clusianone, xanthochymol, gambogenone	[293-297]
			Antiretroviral	7-*epi*-nemorosone, plukenetione A	[298]
			Antitumor, cytotoxic	Nemorosone, plukenetione A	[291,299-301]
Mediterranean type	**Southern Greece, Krete, Sicily, Malta**	***Cupressus sempervirens* resin**			
			Antibacterial	Totarol, totarolone, 14,15-dinor-13-oxo-8(17)-labden-19-oic acid, epi-manool, unicedric acid	[19,302-305]
			Antioxidant		[303]
			Antiproliferative	Diterpenes	[306]
Pacific type	**Okinawa, Taiwan, Indonesia**	**Fruit resin of *Macaranga tanarius***			
			Antibacterial	Nymphaeol B, isonymphaeol B; propolisns C, G, D and H	[307-311]
			Antioxidant	Propolins	[22,309,312, 313]
			Anticancer	Nymphaeols A, B and C, propolin A, propolin B, propolin H, propolin G	[21,61,312,314,315]
		Other propolis t ypes			
Argentinean Andean	San Juan Province, Argentina	*Larrea nitida* resinous exudates	Antifungal	3´methyl-nordihydroguaiaretic acid,,nordihydroguaiaretic acid; (4-[4-(4-hydroxy-phenyl)-2,3-dimethyl-butyl]-benzene-1,2-diol	[316]

Propolis type	Geographical distribution	Plant source(s)	Biological activity	Responsible molecules	References
Zuccagnia type	Tucuman Province, Argentina	*Zuccagnia punctata*	Cytotoxic, Antifungal	2',4'-dihydroxy-3'-methoxychalcone, 2',4'-dihydroxychalcone, pinocembrin, galangin, 7-hydroxy-8-methoxyflavanone	[317,318]
Unknown Argentinean	Catamarca Province, Argentina	Unknown	Antibacterial, antioxidant	2',4'-dihydroxy-3'-methoxychalcone, 2',4'-dihydroxychalcone, 2',4',4-trihydroxy-6'- methoxychalcone, 5-hydroxy-4',7-dimethoxyflavone, 4',5-dihydroxy-3,7,8-trimethoxyflavone and 7-hydroxy- 5,8-dimethoxyflavone	[319]
Nepalese	Nepal	*Dalbergia sissoo*	Inhibitory activity on nitric oxide production	Neoflavonoids	[320]
Unknown	Mexico	Unknown	cytotoxic	(2*R*,3*S*)-8-[4-phenylprop-2-en-1-one]-4',7-dihydroxy-3',5-dimethoxyflavan-3-ol	[321]
Rhus type	Okayama, Japan	*Rhus javanica* var. *chinensis* sap	antioxidant	Unidentifed flavonoids	[322]
Unknown	Piaui State, Brazil	*Anacardium occidentale ??*	Antimicrobial	Cardanols, cardols, anacardic acid	[323]
Unknown	Brazil	Unknown	Ani-HIV	Moronic acid	[324]
Unknown	Myanmar	Unknown	Cytotxic	3α,27-dihydroxycycloart-24E-en-26-oic acid, (22*Z*,24*E*)-3-oxocycloart-22,24-dien-26-oic acid, (24*E*)-3-oxo-27,28-dihydroxycycloart-24-en-26-oic acid	[325,326]
Unknown	Algeria	Unknown	Stromelysin-1 inhibition	(+)-chickoric acid and its methyl ester, caffeic acid	[327]
Unknown	Henan Province, China	Unknown	Cytotoxic	8-C-Cinnamoyl flavan-3-ols	[328]
Unknown	Jeju Island, Korea	Unknown	Inhibition of soybean lipoxygenase	4'-Methoxy-bavachromanol	[329]
Unknown	Nigeria	Unknown	Antibacterial	Unknown	[330]
Africna Macaranga	Kenya	*Macaranga schweinfurthii* ??	Antibacterial, antioxidant	Macarangin, schweinfurthins A and B	[331]
Unknown	Kenya	Unknown	Antibacterial	Tetrahydrojusticidin B, phyllamyricinC	[331]
Mixed type	Malta	*Cupressus sempervirens* + *Ferula communis*	Antifungal	Dierpenic acids, ferutin, teferin, jaeschkeanadiol, 2-acetoxy-6-p-hydroxybenzoyl jaeschkeanadiol	[305]
Mixed type	Indonesia	*Mangifera indica* + *Macaranga tanarius*	Antioxidant	Alkylresorcinols	[332]

Recent studies have revealed a new type of European propolis: Mediterranean propolis, distinguished by a high concentration of diterpenoids. This propolis type was found in the South of Greece, in Sicily and in some Croatian Adriatic islands and Malta [18,20,304,305]. Its chemical profile is characterized by the presence of substantial amounts of diterpene acids:

isocupressic, communic, pimaric and imbricatoloic acid, together with totarol and 13-epitorulosal. It also possesses antibacterial [18,19,303-305] and antiproliferative activity [306]. A separate chapter in this book is dealing with this propolis type, so it will not be discussed further in this chapter.

There are numerous research papers reporting on the biological activity and chemical composition of propolis types, different from the already discussed. Maybe some of these propolis types will become as popular and important in propolis research as the red-type propolis or the Pacific type propolis. The available data of these propolis types are collected and represented in Table 5.

CONCLUSION

There is no doubt that in further specific ecosystems, for example such in Sub-Saharan Africa, Australia, etc.; propolis plant sources and respectively the chemical composition of propolis will continue to surprise scientists. The search for new active propolis constituents in samples from unexplored regions is a promising direction for further propolis research, especially in the search for new antimicrobial, antioxidant and anticancer agents. The results summarized in this chapter demonstrate once again that propolis remains a fascinating subject for further studies and we can expect further exciting findings, further surprises that bees have prepared for us.

REFERENCES

[1] Ghisalberti E. L. Propolis: a review. *Bee World*. 1979;60:59-84.

[2] Burdock G. A. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chemistry and Toxicology*. 1998;36:347-363.

[3] Pietta P. G., Gardana C., Pietta A. M. Analytical methods for quality control of propolis. *Fitoterapia*. 2002;73 Suppl 1:S7-20.

[4] Bankova V. Chemical diversity of propolis and the problem of standardization. *Journal of Ethnopharmacology*. 2005;100:114-117.

[5] Park Y. K., Alencar S. M., Aguiar C. L. Botanical origin and chemical composition of Brazilian propolis. *Journal of Agricultural and Food Chemistry*. 2002;50:2502-2506.

[6] Bankova V. S., Popov S. S., Marekov N. L. A study on flavonoids of propolis. *Journal of Natural Products*. 1983;46:471-474.

[7] Nagy E., Papay V., Litkei G., Dinya Z. Investigation of the chemical constituents, particularly the flavonoid components of propolis and *Populi gemma* by the GC/MS method. In: Farkas L, Gabor M, Kallay F, eds. Flavonoids and bioflavonoids. Amsterdam: *Elsevier*. 1985:233-240.

[8] Greenaway W., Scaysbrook T., Whatley F..R. Composition of propolis of Oxfordshire, UK and its relation to poplar bud exudate. *Zeitschrift fur Naturforschung*. 1988;43c:301-304.

[9] Bankova V., Dyulgerov A., Popov S., Evstatieva L., Kuleva L., Pureb O., Zamjansan Z. Propolis produced in Bulgaria and Mongolia: phenolic compounds and plant origin. *Apidologie*. 1992;23:79-85.

[10] Markham K. R., Mitchell K. A., Wilkins A. L., Daldy J. A., Lu Y. HPLC and GC-MS identification of the major organic constituents in New Zealand propolis. *Phytochemistry*. 1996;42:205-211.

[11] Sawaya A. C. H. F., Tomazela D. M., Cunha I. B. S., Bankova V. S., Marcucci M. C., Custodio A. R., Eberlin M. N. Electrospray ionization mass spectrometry fingerprinting of propolis. *Analyst*. 2004;129:739-744.

[12] Cao W., Fu J., Suo Z., Chen W., Zheng J. A comparative study on chemical compositions of Chinese propolis and poplar resin. *Food and Fermentation Industries*. 2007;33:162-166.

[13] Bankova V., Boudourova- Krasteva G., Sforcin J. M., Frete X., Kujumgiev A., Maimoni-Rodella R., Popov S. Phytochemical evidence for the plant origin of Brazilian propolis from Sao Paulo state. *Zeitschrift fur Naturforschung C*. 1999;54:401-405.

[14] Teixeira E. W., Negri G., Meira R. M. S. A., Message D., Salatino A. Plant origin of green propolis: bee behavior, plant anatomy and chemistry. *Evidence-Based Complementary and Alternative Medicine*. 2005;2:85-92.

[15] Daugsch A., Moraes C. S., Fort P., Park Y. K. Brazilian red propolis—chemical composition and botanical origin. *Evidence-Based Complementary and Alternative Medicine*. 2008;5:435–441.

[16] Lotti C., Fernandez M. C., Piccinelli A. L., Cuesta-Rubio O., Hernandez I. M., Rastrelli L. Chemical constituents. *Journal of Agricultural and Food Chemistry*. 2010;58:2209-2213.

[17] Piccinelli A. L., Lotti C., Campone L., Cuesta-Rubio O., Fernandez M. C., Rastrelli L. Cuban and Brazilian red propolis: botanical origin and comparative analysis by high-performance liquid chromatography-photodiode array detection/electrospray ionization tandem mass spectrometry. *Journal of Agricultural and Food Chemistry*. 2011;59:6484-6491.

[18] Trusheva B., Popova M., Bankova V., Tsvetkova I., Naydenski C., Sabatini A. G. A new type of European propolis, containing bioactive labdanes. *Rivista Italiana EPPOS*. 2003;13:3-8.

[19] Melliou E, Chinou I. Chemical analysis and antimicrobial activity of Greek propolis. *Planta Medica*. 2004;70:1-5.

[20] Popova M. P., Graikou K., Chinou I., Bankova V. S. GC-MS profiling of diterpene compounds in Mediterranean propolis from Greece. *Journal of Agricultural and Food Chemistry*. 2010;58:3167-3176.

[21] Chen C. N., Wu C. L., Lin J. K. Apoptosis of human melanoma cells induced by the novel compounds propolin A and propolin B from Taiwenese propolis. *Cancer Letters*. 2007;245:218-231.

[22] Kumazawa S., Nakamura J, Murase M, Miyagawa M., Ahn M. R., Fukumoto S. Plant origin of Okinawan propolis: honeybee behavior observation and phytochemical analysis. *Naturwissenschaften*. 2008;95:781-786.

[23] Lavie P. The relationship between propolis, poplar buds (*Populus* spp.) and castor. In: Lavie P, ed. *Proceedings of the XXVth International Beekeeping Congress, Grenoble 1975*. Bucharest: Apimondia Publishing House. 1976:227–231.

[24] Greenaway W., Scaysbrook T., Whatley F. R., The analysis of bud exudate of *Populus x euramericana* and of propolis by gas chromatography-mass spectrometry. *Proceedings of the Royal Society B*. 1987;232:249-272.

[25] Greenaway W., May J., Scaysbrook T., Whatley F. R. Identification by gas-chromatography mass-spectrometry of 150 compounds in propolis. *Zeitschrift fur Naturforschung C*. 1991;46:111-121.

[26] Koo H., Rosalen P. L., Cury J. A., Park Y. K., Bowen W. H. Effects of compounds found in propolis on *Streptococcus mutans* growth and on glucosyltransferase activity. *Antimicrobial Agents and Chemotherapy*. 2002;46:1302-1309.

[27] Pepeljnjak S., Kosalec I. Galangin expresses bactericidal activity against multiple-resistant bacteria: MRSA, *Enterococcus* spp. and *Pseudomonas aeruginosa*. *FEMS*. 2004;240:111-116.

[28] Cushnie T. P., Lamb A. J. Detection of galangin-induced cytoplasmic membrane damage in *Staphylococcus aureus* by measuring potassium loss. *Journal of Ethnopharmacology*. 2005;101:243-248.

[29] Du Toit K., Buthelezi S., Bodenstein J. Anti-inflammatory and antibacterial profiles of selected compounds found in South African propolis. *South African Journal of Science*. 2009;105:470-472.

[30] Darwish R. M., Abu Fares R. J., Abu Zarga M. H., Nazer I. K. Antibacterial effect of Jordanian propolis and isolated flavonoids against human pathogenic bacteria. *African Journal of Biotechnology*. 2010;9:5966-5974.

[31] Quiroga E. N., Sampietro D. A., Soberon J. R., Sgariglia M. A., Vattuone M. A. Propolis from the northwest of Argentina as a source of antifungal principles. *Journal of Applied Microbiology*. 2006;101:103-110.

[32] Yang S. Z., Peng L. T., Su X. J., Chen F., Cheng Y. J., Fan G., Pan S. Y. Bioassay-guided isolation and identification of antifungal components from propolis against *Penicillium italicum*. *Food Chemistry*. 2011;127:210-215.

[33] Huleihel M., Isanu V. Anti-herpes simplex virus effect of an aqueous extract of propolis. *The Israel Medical Association Journal*. 2002;4 Suppl:923-927.

[34] Gekker G., Hu S., Spivak M., Lokensgard J. R., Peterson P. K. Anti-HIV-1 activity of propolis in $CD4^+$ lymphocyte and microglial cell cultures. *Journal of Ethnopharmacology*. 2005;102:158–163.

[35] Nolkemper S., Reichling J., Sensch K. H., Schnitzler P. Mechanism of herpes simplex virus type 2 suppression by propolis extracts. *Phytomedicine*. 2010;17:132-138.

[36] Schnitzler P., Neuner A., Nolkemper S., Zundel C., Nowack H., Sensch K. H., Reichling J. Antiviral activity and mode of action of propolis extracts and selected compounds. *Phytotherapy Research*. 2010;24 Suppl 1:S20-S28.

[37] Lee S., Kim K. S., Park Y., Shin K. H., Kim B. K. In vivo anti-oxidant activities of tectochrysin. *Archives of Pharmacal Research*. 2003;26:43-46.

[38] Okutan H., Ozcelik N., Ramazan Yilmaz H., Uz E. Effects of caffeic acid phenethyl ester on lipid peroxidation and antioxidant enzymes in diabetic rat heart. *Clinical Biochemistry*. 2005;38:191-196.

[39] Ahn M. R., Kumazawa S., Usui Y., Nakamura J., Matsuka M., Zhu F., Nakayama T. Antioxidant activity and constituents of propolis collected in various areas of China. *Food Chemistry*. 2007;101:1383-1392.

[40] Velazquez C., Navarro M., Acosta A., Angulo A., Dominguez Z., Robles R., Robles-Zepeda R., Lugo E., Goycoolea F. M., Velazquez E. F., Astiazaran H., Velazquez J. H. C. Antibacterial and free-radical scavenging activities of Sonoran propolis. *Journal of Applied Microbiology*. 2007;103:1747-1756.

[41] Kumazawa S., Ahn M. R., Fujimoto T., Kato M. Radical-scavenging activity and phenolic constituents of propolis from different regions of Argentina. *Natural Product Research*. 2010;24:804-812.

[42] Laskar R. A., Sk I., Roy N., Begum N. A. Antioxidant activity of Indian propolis and its chemical constituents. *Food Chemistry*. 2010;122:233-237.

[43] Gocer H., Gulcin I. Caffeic acid phenethyl ester (CAPE): correlation of structure and antioxidant properties. *International Journal of Food Sciences and Nutrition*. 2011; doi:10.3109/09637486.2011.585963.

[44] Banskota A. H., Tezuka Y., Adnyana I. K., Midorikawa K., Matsushige K., Message D., Huertas A. A. G., Kadota S. Cytotoxic, hepatoprotective and free radical scavenging effects of propolis from Brazil, Peru, the Netherlands and China. *Journal of Ethnopharmacology*. 2000;72:239-246.

[45] Heo M. Y., Sohn S. J., Au W. W. Anti-genotoxicity of galangin as a cancer chemopreventive agent candidate. *Mutation Research*. 2001;488:135-150.

[46] Banskota A. H., Nagaoka T., Sumioka L. Y., Tezuka Y., Awale S., Midorikawa K., Matsushige K., Kadota S. Antiproliferative activity of the Netherlands propolis and its active principles in cancer cell lines. *Journal of Ethnopharmacology*. 2002;80:67-73.

[47] Usia T., Banskota A. H., Tezuka Y., Midorikawa K., Matsushige K., Kadota S. Constituents of Chinese propolis and their antiproliferative activities. *Journal of Natural Products*. 2002;65:673-676.

[48] Liao H. F., Chen Y. Y., Liu J. J., Hsu M. L., Shieh H. J., Liao H. J., Shieh C. J., Shiao M. S., Chen Y. J. Inhibitory effect of caffeic acid phenethyl ester on angiogenesis, tumor invasion, and metastasis. *Journal of Agricultural and Food Chemistry*. 2003;51:7907–7912.

[49] Lee K. W., Chun K. S., Lee J. S., Kang K. S., Surh Y. J., Lee H. J. Inhibition of Cyclooxygenase-2 expression and restoration of gap junction intercellular communication in H-ras-transformed rat liver epithelial cells by caffeic acid phenethyl ester. *Annals of the New York Academy of Sciences*. 2004;1030:501-507.

[50] Woo K. J., Jeong Y. J., Park J. W., Kwon T. K. Chrysin-induced apoptosis is mediated through caspase activation and Akt inactivation in U937 leukemia cells. *Biochemical and Biophysical Research Communications*. 2004;325:1215-1222.

[51] Orsolic N., Terzic S., Mihaljevic Z., Sver L., Basic I. Effects of local administration of propolis and its polyphenolic compounds on tumor formation and growth. *Biological and Pharmaceutical Bulletin*. 2005;28:1928-1933.

[52] Orsolic N., Sver L., Terzic S., Basic I. Peroral application of water-soluble derivative of propolis (WSDP) and its related polyphenolic compounds and their influence on immunological and antitumour activity. *Veterinary Research Communications*. 2005;29:575-593.

[53] Orsolic N., Terzic S., Sver L., Basic T. Honey-bee products in prevention and/or therapy of murine transplantable tumours. *Journal of the Science of Food and Agriculture*. 2005;85:363-370.

[54] Orsolic N., Saranovic A. B., Basic I. Direct and indirect mechanism(s) of antitumour activity of propolis and its polyphenolic compounds. *Planta Medica*. 2006;72:20-27.

[55] Benkovic V., Knezevic A. H., Brozovic G., Knezevic F., Dikic D., Bevanda M., Basic I., Orsolic N. Enhanced antitumor activity of irinotecan combined with propolis and its polyphenolic compounds on Ehrlich ascites tumor in mice. *Biomedicine and Pharmacotherapy*. 2007;61:292-297.

[56] Orsolic N., Basic I. Suppression of tumor growth by water-soluble derivative of propolis and related polyphenolic compounds. *Periodicum Biologorum*. 2007;109:181-187.

[57] Draganova-Filipova M. N., Georgieva M. G., Peycheva E. N., Miloshev G. A., Sarafian V. S., Peychev L. P. Effects of propolis and CAPE on proliferation and apoptosis of McCoy-Plovdiv cell line. *Folia Medica*. 2008;50:53-59.

[58] Demestre M., Messerli S. M., Celli N., Shahhossini M., Kluwe L., Mautner V., Maruta H. CAPE (Caffeic acid phenethyl ester)-based propolis extract (Bio 30) suppresses the growth of human neurofibromatosis (NF) tumor xenografts in mice. *Phytotherapy Research*. 2009;23:226-230.

[59] Orsolic N., Stajcar D., Basic I. Propolis and its flavonoid compounds cause cytotoxicity on human urinary bladder transitional cell carcinoma in primary culture. *Periodicum Biologorum*. 2009;111:113-121.

[60] Szliszka E., Czuba Z. P., Domino M., Mazur B., Zydowicz G., Krol W. Ethanolic extract of propolis (EEP) enhances the apoptosis- inducing potential of TRAIL in cancer cells. *Molecules*. 2009;14:738-754.

[61] Chen C. N., Hsiao C. J., Lee S. S., Guh J. H., Chiang P. C., Huang C. C., Huang W. J. Chemical modification and anticancer effect of prenylated flavanones from Taiwanese propolis. *Natural Product Research*. 2011. doi:10.1080/14786419.2010.535146.

[62] Shvarzbeyn J., Huleihel M. Effect of propolis and caffeic acid phenethyl ester (CAPE) on NFκB activation by HTLV-1 Tax. *Antiviral Research*. 2011;90:108-115.

[63] Rossi A., Longo R., Russo A., Borrelli F., Sautebin L. The role of the phenethyl ester of caffeic acid (CAPE) in the inhibition of rat lung cyclooxygenase activity by propolis. *Fitoterapia*. 2002;73 Suppl 1:S30-S37.

[64] Beyer G., Melzig M. F. Effects of propolis on hypoxanthine-xanthine oxidase-induced toxicity in cultivated human cells and on neutrophil elastase activity. *Biological and Pharmaceutical Bulletin*. 2005;28:1183-1186.

[65] Woo K. J., Jeong Y. J., Inoue H., Park J. W., Kwon T. K. Chrysin suppresses lipopolysaccharide- induced cyclooxygenase-2 expression through the inhibition of nuclear factor for IL-6 (NF-IL6) DNA-binding activity. *FEBS Letters*. 2005;579:705-711.

[66] Xuan H., Zhu R., Li Y., Hu F. Inhibitory effect of chinese propolis on phosphatidylcholine-specific phospholipase C activity in vascular endothelial cells. *Evidence- Based Complementary and Alternative Medicine*. 2011;2011:985278.

[67] Orsolic N., Tadic Z., Benkovic V., Horvat A., Lojkic M., Basic I. Radioprotective effect of a water-soluble derivative of propolis in mice. *Mellifera*. 2004;4:45-52.

[68] Orsolic N., Basic I. Antitumor, hematostimulative and radioprotective action of water-soluble derivative of propolis (WSDP). *Biomedicine and Pharmacotherapy*. 2005;59:561-570.

[69] Orsolic N., Benkovic V., Horvat- Knezevic A., Kopjar N., Kosalec I., Bakmaz M., Mihaljevic Z., Bendelja K., Basic I. Assessment by survival analysis of the radioprotective properties of propolis and its polyphenolic compounds. *Biological and Pharmaceutical Bulletin*. 2007;30:946—951.

[70] Benkovic V., Orsolic N., Horvat-Knezevic A., Ramic S., Dikic D., Basic I., Kopjar N. Evaluation of the radioprotective effects of propolis and flavonoids in gamma-irradiated mice: the alkaline comet assay study. *Biological and Pharmaceutical Bulletin*. 2008;31:167-172.

[71] Benkovic V., Horvat-Knezevic A., Dikic D., Lisicic D., Orsolic N., Basic I., Kosalec I., Kopjar N. Radioprotective effects of propolis and quercetin in γ-irradiated mice evaluated by the alkaline comet assay. *Phytomedicine*. 2008;15:851-858.

[72] Benkovic V., Knezevic A. H., Dikic D., Lisicic D., Orsolic N., Basic I., Kopjar N. Radioprotective effects of quercetin and ethanolic extract of propolis in gamma-irradiated mice. *Archives of Industrial Hygiene and Toxicology*. 2009;60:129-138.

[73] Benkovic V., Knezevic A. H., Orsolic N., Basic I., Ramic S., Viculin T., Knezevic F., Kopjar N. Evaluation of radioprotective effects of propolis and its flavonoid constituents: in vitro study on human white blood cells. *Phytotherapy Research*. 2009;23:1159-1168.

[74] Ansorge S., Reinhold D., Lendeckel U. Propolis and some of its constituents down-regulate DNA synthesis and inflammatory cytokine production but induce TGF-β1 production of human immune cells. *Zeitschrift für Naturforschung*. 2003;58c:580-589.

[75] Orsolic N., Knezevic A. H., Sver L., Terzic S., Basic I I. Immunomodulatory and antimetastatic action of propolis and related polyphenolic compounds. *Journal of Ethnopharmacology*. 2004;94:307-315.

[76] Park J. H., Lee J. K., Kim H. S., Chung S. T., Eom J. H., Kim K. A., Chung S. J., Paik S. Y., Oh H. Y. Immunomodulatory effect of caffeic acid phenethyl ester in Balb/c mice. *International Immunopharmacology*. 2004;4:429-436.

[77] Draganova-Filipova M., Nikolova M., Mihova A., Peychev L., Sarafian V. A pilot study on the immunomodulatory effect of Bulgarian propolis. *Biotechnology and Biotechnological Equipment*. 2010;24:119-124.

[78] Gregoris E., Fabris S., Bertelle M., Grassato L., Stevanato R. Propolis as potential cosmeceutical sunscreen agent for its combined photoprotective and antioxidant properties. *International Journal of Pharmaceutics*. 2011;405:97-101.

[79] Chen J., Long Y., Han M., Wang T., Chen Q., Wang R. Water-soluble derivative of propolis mitigates scopolamine-induced learning and memory impairment in mice. *Pharmacology Biochemistry and Behavior*. 2008;90:441-446.

[80] Hartwich A., Legutko J., Wszołek J. Propolis: its properties and administration to patients treated for some surgical diseases. *Przeglad Lekarski*. 2000;57:191-194.

[81] Holcova S., Schmidt M. Showering gel and shampoo with a special concentrate from propolis for the treatment of seborrhoic eczema, psoriasis and atopic eczema- An observational study. *Haut*. 2005;16:311-315.

[82] Holcova S., Hladicova M. Effect and local tolerability of a shampoo containing the propolis special extract GH 2002 in dermatitis seborrhoica with distinct dandruff formation. *Kosmetische Medizin*. 2007;28:76-80.

[83] Sosa S., Bornancin A., Tubaro A., Loggia R. D. Topical antiinflammatory activity of an innovative aqueous formulation of Actichelated® propolis vs two commercial propolis formulations. *Phytotherapy Research*. 2007;21:823–826.

[84] Lozina L. A., Peichoto M. E., Boehringer S. I., Koscinczuk P., Granero G. E., Acosta O. C. Efficacy of Argentine propolis formulation for topical treatment of canine otitis externa. *Arquivo Brasileiro de Medicina Veterinaria e Zootecnia*. 2010;62:1359-1366.

[85] Marchisio P., Esposito S., Bianchini S., Desantis C., Galeone C., Nazzari E., Pignataro L., Principi N. Effectiveness of a propolis and zinc solution in preventing acute otitis media in children with a history of recurrent acute otitis media. *International Journal of Immunopathology and Pharmacology*. 2010;23:567-575.

[86] Akyol S., Armutcu F., Yigitoglu M. R. The medical usage of caffeic acid phenethyl ester (CAPE), an active compound of propolis, in neurological disorders and emergencies. *Spatula DD*. 2011;1:37-42.

[87] Zhu W., Li Y. H., Chen M. L., Hu F. L. Protective effects of Chinese and Brazilian propolis treatment against hepatorenal lesion in diabetic rats. *Human and Experimental Toxicology*. 2011;30:1246-1255.

[88] Kiec-Swierczynska M., Krecisz B., Swierczynska-Machura D. Most frequent causes of allergic contact dermatitis in farmers: based on material collected in the Nofer Institute of Occupational Medicine, Lodz. *Medycyna Pracy*. 2003;54:237-243.

[89] Giusti F., Miglietta R., Pepe P., Seidenari S. Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis*. 2004;51:255-258.

[90] Hausen B. M. Evaluation of the main contact allergens in propolis (1995 to 2005). *Dermatitis*. 2005;16:127-129.

[91] Maria Y. Rhinitis and asthma triggered by nasal inhalation of a spray containing propolis in a beekeeper. *Revue Francaise d'Allergologie et d'Immunologie Clinique*. 2005;45:426-427.

[92] Seidenari S., Giusti F., Pepe P., Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. *Pediatric Dermatology*. 2005;22:1-5.

[93] Walgrave S. E., Warshaw E. M., Glesne L. A. Allergic contact dermatitis from propolis. *Dermatitis*. 2005;16:209-215.

[94] Brailo V., Boras V. V., Alajbeg I., Juras V. Delayed contact sensitivity on the lips and oral mucosa due to propolis-case report. *Medicina Oral, Patología Oral y Cirugía Bucal*. 2006;11:E303-304.

[95] Munstedt K., Hellner M., Hackethal A., Winter D., von Georgi R. Contact allergy to propolis in beekeepers. *Allergologia et Immunopathologia*. 2007;35:95-100.

[96] Menniti-Ippolito F., Mazzanti G., Vitalone A., Firenzuoli F., Santuccio C. Surveillance of suspected adverse reactions to natural health products: the case of propolis. *Drug Safety*. 2008;31:419-423.

[97] Rajpara S., Wilkinson M. S., King C. M., Gawkrodger D. J., English J. S., Statham B. N., Green C., Sansom J. E., Chowdhury M. M., Horne H. L., Ormerod A. D. The importance of propolis in patch testing-a multicentre survey. *Contact Dermatitis*. 2009;61:287-290.

[98] Wagner E., Becker D., Dickel H., Geier J., John S. M., Lessmann H., Mahler V., Rogosky E., Skudlik C., Weisshaar E., Diepgen T. L. Impact of an occupational contact allergy to propolis in cases of occupational skin disease. *Dermatologie in Beruf und Umwelt*. 2009;57:77–80.

[99] Necas M., Dastychova E. Contact sensitization in patients with lower extremity dermatitis in the South Moravian region, Czech Republic. *Phlebology*. 2010;25:132-137.

[100] Holcova S., Hladikova M. Efficacy and tolerability of propolis special extract GH 2002 as a lip balm against *Herpes labialis*: a randomized, double-blind three-arm dose finding study Treatment of *Herpes labialis* by propolis lip balm. *Health*. 2011;3:49-56.

[101] Yoshizumi K., Nishioka N., Tsuji T. The xanthine oxidase inhibitory activity and hypouricemia effect of the propolis in rats. *Yakugaku Zasshi*. 2005;125:315-321.

[102] Garedew A., Lamprecht I., Schmolz E., Schricker B. The varroacidal action of propolis: a laboratory assay. *Apidologie*. 2002;33:41–50.

[103] El-Fadaly H., El-Badrawy E. E. Y. Flavonoids of propolis and their antibacterial activities. *Pakistan Journal of Biological Sciences*. 2001;4:204-207.

[104] Stepanovic S., Antic N., Dakic I., Svabic-Vlahovic M. In vitro antimicrobial activity of propolis and synergism between propolis and antimicrobial drugs. *Microbiological Research*. 2003;158:353-357.

[105] Garedew A., Schmolz E., Lamprecht I. Microbiological and calorimetric investigations on the antimicrobial actions of different propolis extracts: an *in vitro* approach. *Thermochimica Acta*. 2004;422:115-124.

[106] Boyanova L., Kolarov R., Gergova G., Mitov I. In vitro activity of Bulgarian propolis against 94 clinical isolates of anaerobic bacteria. *Anaerobe*. 2006;12:173-177.

[107] Scazzocchio F., D'Auria F. D., Alessandrini D., Pantanella F. Multifactorial aspects of antimicrobial activity of propolis. *Microbiological Research*. 2006;161:327-333.

[108] Silici S., Unlu M., Vardar-Unlu G. Antibacterial activity and phytochemical evidence for the plant origin of Turkish propolis from different regions. *World Journal of Microbiology and Biotechnology*. 2007;23:1797-1803.

[109] Yaghoubi M. J., Ghorbani G., Zad S. S., Satari R. Antimicrobial activity of Iranian propolis and its chemical composition. *DARU Journal of Pharmaceutical Sciences*. 2007;15:45-48.

[110] Marghitas L. A., Mihai C. M., Chirila F., Dezmirean D. S., Fit N. The study of the antimicrobial activity of Transylvanian (Romanian) propolis. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*. 2010;38:40-44.

[111] Campana R., Patrone V., Franzini I. T., Diamantini G., Vittoria E., Baffone W. Antimicrobial activity of two propolis samples against human *Campylobacter jejuni*. *Journal of Medicinal Food*. 2009;12:1050-1056.

[112] Boyanova L., Derejian S., Koumanova R., Katsarov N., Gergova G., Mitov I., Nikolov R., Krastev Z. Inhibition of *Helicobacter pylori* growth *in vitro* by Bulgarian propolis: preliminary report. *Journal of Medical Microbiology*. 2003;52:417–419.

[113] Boyanova L., Gergova G., Nikolov R., Derejian S., Lazarova E., Katsarov N., Mitov I., Krastev Z. Activity of Bulgarian propolis against 94 *Helicobacter pylori* strains *in vitro* by agar-well diffusion, agar dilution and disc diffusion methods. *Journal of Medical Microbiology*. 2005;54:481-483.

[114] Nostro A., Cellini L., Di Bartolomeo S., Di Campli E., Grande R., Cannatelli M. A., Marzio L., Alonzo V. Antibacterial effect of plant extracts against *Helicobacter pylori*. *Phytotherapy Research*. 2005;19:198-202.

[115] Uzel A., Sorkun K., Oncag O., Cogulu D., Gencay O., Salih B. Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. *Microbiological Research*. 2005;160:189-195.

[116] Koru O., Toksoy F., Acikel C. H., Tunca Y. M., Baysallar M., Guclu A. U., Akca E., Tuylu A. O., Sorkun K., Tanyuksel M., Salih B. *In vitro* antimicrobial activity of propolis samples from different geographical origins against certain oral pathogens. *Anaerobe*. 2007;13:140-145.

[117] Liberio S. A., Pereira A. L. A., Araujo M. J. A. M., Dutra R. P., Nascimento F. R. F., Monteiro-Neto V., Ribeiro M. N. S., Goncalves A. G., Guerra R. N. M. The potential use of propolis as a cariostatic agent and its actions on mutans group streptococci. *Journal of Ethnopharmacology*. 2009;125:1-9.

[118] Saavedra N., Barrientos L., Herrera C. L., Alvear M., Montenegro G., Salazar L. A. Effect of Chilean propolis on cariogenic bacteria *Lactobacillus fermentum*. *Ciencia e Investigacion Agraria*. 2011;38:117-125.

[119] Kosalec I., Pepeljnjak S., Bakmaz M., Vladimir-Knezevic S. Flavonoid analysis and antimicrobial activity of commercially available propolis products. *Acta Pharmaceutica*. 2005;55:423-430.

[120] Popova M., Silici S., Kaftanoglu O., Bankova V. Antibacterial activity of Turkish propolis and its qualitative and quantitative chemical composition. *Phytomedicine*. 2005;12:221-228.

[121] Kujumgiev A., Bankova V., Ignatova A., Popov S. Antibacterial activity of propolis, some of its components and their analogues. *Pharmazie*. 1993;48:785-786.

[122] Chaillou L. L., Nazareno M. A. Bioactivity of propolis from Santiago del Estero, Argentina, related to their chemical composition. *LWT- Food Science and Technology*. 2009;42:1422-1427.

[123] Kacaniova M., Melich M., Knazovicka V., Felsociova S., Sudzinova J. The antimicrobial activity of honey and propolis against yeasts *Candida* species. *Lucrari Stiintifice Zootehnie si Biotehnologii*. 2009;42:167-173.

[124] Herrera C. L., Alvear M., Barrientos L., Montenegro G., Salazar L. A. The antifungal effect of six commercial extracts of Chilean propolis on *Candida* spp. *Ciencia e Investigacion Agraria*. 2010;37:75-84.

[125] Buchta V., Cerny J., Opletalova V. In vitro antifungal activity of propolis samples of Czech and Slovak origin. *Central Europe*. 2011;6:160-166.

[126] Yang S., Peng L., Cheng Y., Chen F., Pan S. Control of Citrus green and blue molds by Chinese propolis. *Food Science and Biotechnology*. 2010;19:1303-1308.

[127] Bonvehi J. S., Coll F. V. Phenolic composition of propolis from China and from South America. Zeitschrift für Naturforschung. 1994;49c:712–718.

[128] Ahn M. R., Kumazawa S., Hamasaka T., Bang K. S., Nakayama T. Antioxidant activity and constituents of propolis collected in various areas of Korea. *Journal of Agricultural and Food Chemistry*. 2004;52:7286–7292.

[129] Jasprica I., Bojic M., Mornar A., Besic E., Bucan K., Medic-Saric M. Evaluation of antioxidative activity of Croatian propolis samples using $DPPH^{\cdot}$ and $ABTS^{\cdot+}$ stable free radical assays. *Molecules*. 2007;12:1006-1021.

[130] Rzepecka-Stojko A., Kurek-Gorecka A., Maciejewska-Paszek I., Stec M., Pawlowska-Goral K., Gastolek-Soltysik K. The determination of flavonoid content of ethanol

extracts of propolis and the antioxidant capacity of flavonoids. *Farmaceutyczny Przeglad Naukowy*. 2009;11:33-36.

[131] Gregoris E., Stevanato R. Correlations between polyphenolic composition and antioxidant activity of Venetian propolis. *Food and Chemical Toxicology*. 2010;48:76-82.

[132] Savickas A., Ramanauskiene K., Pukalskas A., Kasparaviciene G., Briedis V., Inkeniene A., Zilius M., Kasparavicius S. The influence of solvent on the quantity and antioxidant activity of ethanolic extracts of Lithuanian propolis. *Chemija*. 2010;21:118-122.

[133] Mot A. C., Silaghi-Dumitrescu R., Sarbu C. Rapid and effective evaluation of the antioxidant capacity of propolis extracts using DPPH bleaching kinetic profiles, FT-IR and UV—vis spectroscopic data. *Journal of Food Composition and Analysis*. 2011;24:516-522.

[134] Sulaiman G. M., Al Sammarrae K. W., Ad'hiah A. H., Zucchetti M., Frapolli R., Bello E., Erba E., D'Incalci M., Bagnati R. Chemical characterization of Iraqi propolis samples and assessing their antioxidant potentials. *Food and Chemical Toxicology*. 2011;49:2415-2421.

[135] Yang H, Dong Y, Du H, Shi H, Peng Y, Li X. Antioxidant compounds from propolis collected in Anhui, China. *Molecules*. 2011;16:3444-3455.

[136] Sobocanec S., Sverko V., Balog T., Saric A., Rusak G., Likic S., Kusic B., Katalinic V., Radic S., Marotti T. Oxidant/antioxidant properties of Croatian native propolis. *Journal of Agricultural and Food Chemistry*. 2006;54:8018–8026.

[137] Katalinic V., Radic S., Ropac D., Mulic R., Katalinic A. Antioxidative activity of propolis from Dalmatia (Croatia). *Acta Medica Croatica*. 2004;58:373-376.

[138] Zunini M. P., Rojas C., de Paula S., Elingold I., Migliaro E. A., Casanova M. B., Restuccia F. I., Morales S. A., Dubin M. Phenolic contents and antioxidant activity in Central-Southern Uruguayan propolis extracts. *Journal of the Chilean Chemical Society*. 2010;55:141-146.

[139] Mot A. C., Damian G., Sarbu C., Silaghi-Dumitrescu R. Redox reactivity in propolis: direct detection of free radicals in basic medium and interaction with hemoglobin. *Redox Report*. 2009;14:267-274.

[140] Jasprica I., Mornar A., Debeljak Z., Smolcic-Bubalo A., Medic-Saric M., Mayer L., Romic Z., Bucan K., Balog T., Sobocanec S., Sverko V. *In vivo* study of propolis supplementation effects on antioxidative status and red blood cells. *Journal of Ethnopharmacology*. 2007;110:548-554.

[141] Orsolic N., Terzic S., Sver L., Basic I. Polyphenolic compounds from propolis modulate immune responses and increase host resistance to tumour cells. *Food and Agricultural Immunology*. 2005;16:165-179.

[142] Grunberger D., Banerjee R., Eisinger K., Oltz E. M., Efros L., Caldwell M., Estevez V., Nakanishi K. Preferential cytotoxicity on tumor cells by caffeic acid phenethyl ester isolated from propolis. *Cellular and Molecular Life Sciences*. 1988;44:230-232.

[143] Borrelli F., Capasso F. CAPE, a constituent of propolis: a mini review. *Honeybee Science*. 2003;24:67-70.

[144] Bankova V. Chemical diversity of propolis makes it a valuable source of new biologically active compounds. *Journal of ApiProduct and ApiMedical Science*. 2009;1:23-28.

[145] Bankova V., Popova M., Bogdanov S., Sabatini A. G. Chemical composition of European propolis: expected and unexpected results. *Zeitschrift für Naturforschung*. 2002;57c:530-533.

[146] Popova M., Bankova V., Butovska D., Petkov V., Nikolova-Damyanova B., Sabatini A. G., Marcazzan G. L., Bogdanov S. Validated methods for the quantification of biologically active constituents of poplar type propolis. *Phytochemical Analysis*. 2004;15:235-240.

[147] Marostica Junior M. R., Daugsch A., Moraes C. S., Queiroga C. L., Pastore G. M., Park Y. K. Comparison of volatile and polyphenolic compounds in Brazilian green propolis and its botanical origin *Baccharis dracunculifolia*. *Ciencia e Tecnologia de Alimentos*. 2008;28:178-181.

[148] Marcucci M. C., Bankova V. S. Chemical composition, plant origin and biological activity of Brazilian propolis. *Current Topics in Phytochemistry*. 1999;2:115-123.

[149] Jorge R., Furtado N. A. J. C., Sousa J. P. B., da Silva A. A., Gregorio Jr. L. E., Martins C. H. G., Soares A. E. E., Bastos J. K., Cunha W. R., Silva M. L. A. Brazilian propolis: seasonal variation of the prenylated p-coumaric acids and antimicrobial activity. *Pharmaceutical Biology*. 2008;46:889-893.

[150] Salomao K., Pereira P. R. S., Campos L. C., Borba C. M., Cabello P. H., Marcucci M. C., de Castro S. L. Brazilian propolis: correlation between chemical composition and antimicrobial activity. *Evidence-Based Complementary and Alternative Medicine*. 2008;5:317–324.

[151] Neto T. M. S., Mota R. A., Silva L. B. G., Viana D. A., Lima-Filho J. Susceptibility of *Staphylococcus* spp. isolated from milk of goats with mastitis to antibiotics and green propolis extracts. *Letters in Drug Design and Discovery*. 2009;6:63-68.

[152] Oliveira A. P., Franca H. S., Kuster R. M., Teixeira L. A., Rocha L. M. Chemical composition and antibacterial activity of Brazilian propolis essential oil. *Journal of Venomous Animals and Toxins Including Tropical Diseases*. 2010;16:121-130.

[153] da Silva K. R., Mathias F. T., Dutra K. A., Kleinubing S. D., Santa H. S. D., da Rosa M. R., Buriol L., Torres Y. R., Monteiro M. C. Antimicrobial activity from a brazilian propolis oily extract compared with other propolis extracts. *Revista Ciencias Exatas e Naturais*. 2010;12: http://revistas.unicentro.br/index.php/RECEN/article/view/964/1099.

[154] Mello A. M., Gomes R. T., Lara S. R., Silva L. G., Alves J. B., Cortés M. E., Abreu S. L., Santos V. R. The effect of Brazilian propolis on the germ tube formation and cell wall of *Candida albicans*. *Pharmacologyonline*. 2006;3:352-358.

[155] Siqueira A. B. S., Gomes B. S., Cambuim I., Maia R., Abreu S., Souza-Motta C. M., de Queiroz L. A., Porto A. L. F. Trichophyton species susceptibility to green and red propolis from Brazil. *Letters in Applied Microbiology*. 2009;48:90-96.

[156] Fernandes F. F., Dias A. L., Ramos C. L., Ikegaki M., Siqueira A. M., Franco M. C. The "in vitro" antifungal activity evaluation of propolis G12 ethanol extract on *Cryptococcus neoformans*. *Revista do Instituto de Medicina Tropical de Sao Paulo*. 2007;49:93-95.

[157] Ioshida M. D. M., Young M. C. M., Lago J. H. G. Chemical composition and antifungal activity of essential oil from Brazilian propolis. *Journal of Essential Oil-Bearing Plants*. 2010;13:633-637.

[158] Banskota A. H., Tezuka Y., Adnyana I. K., Ishii E., Midorikawa K., Matsushige K., Kadota S. Hepatoprotective and anti-*Helicobacter pylori* activities of constituents from Brazilian propolis. *Phytomedicine*. 2001;8:16-23.

[159] Coelho L. G. V., Bastos E. M. F., Resende C. C., e Silva C. M. P., Sanches B. S. F., de Castro F. J., Moretzsohn L. D., Vieira W. L. D. S., Trindade O. R. Brazilian green propolis on *Helicobacter pylori* infection. A pilot clinical study. *Helicobacter*. 2007;12:572-574.

[160] Santos F. A., Bastos E. M. A., Uzeda M., Carvalho M. A. R., Farias L. M., Moreira E. S. A., Braga F. C. Antibacterial activity of Brazilian propolis and fractions against oral anaerobic bacteria. *Journal of Ethnopharmacology*. 2002;80:1-7.

[161] Santos. F. A., Bastos E. M. A. F., Maia A. B. R. A., Uzeda M., Carvalho M. A. R., Farias L. M., Moreira E. S. A. Brazilian propolis: physicochemical properties, plant origin and antibacterial activity on periodontopathogens. *Phytotherapy Research*. 2003;17:285–289.

[162] Hayacibara M. F., Koo H., Rosalen P. L., Duarte S., Franco E. M., Bowen W. H., Ikegaki M., Cury J. A. *In vitro* and *in vivo* effects of isolated fractions of Brazilian propolis on caries development. *Journal of Ethnopharmacology*. 2005;101:110-115.

[163] Costa E. M. M. B., Esmeraldo M. R. A., de Carvalho M. G. F., Daniel R. L. D. P., Pastro M. F., da Silva Jr. F. L. Evaluation of the antimicrobial action of propolis and substances used in endodontics against *Enterococcus faecalis*. *Pesquisa Brasileira em Odontopediatria e Clinica Integrada*. 2008;8:21-25.

[164] Santos VR, Pimenta FJ, Aguiar MC, do Carmo MA, Naves MD, Mesquita RA. Oral candidiasis treatment with Brazilian ethanol propolis extract. *Phytotherapy Research*. 2005;19:652-654.

[165] Do Amaral RC, Gomes RT, Rocha WMS, Abreu SLR, Santos VR. Periodontitis treatment with Brazilian green propolis gel. *Pharmacologyonline*. 2006;3:336-341.

[166] Santos V. R., Gomes R. T., Mesquita R. A., Moura M. D., França E. C., Aguiar E. G., Naves M. D., Abreu J. A., Abreu S. R. Efficacy of Brazilian propolis gel for the management of denture stomatitis: a pilot study. *Phytotherapy Research*. 2008;22:1544-1547.

[167] Valera M. C., da Rosa J. A., Maekawa L. E., de Oliveira L. D., Carvalho C. A., Koga-Ito C. Y., Jorge A. O. Action of propolis and medications against *Escherichia coli* and endotoxin in root canals. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics*. 2010;110:70-74.

[168] Bastos E. M., Simone M., Jorge D. M., Soares A. E., Spivak M. *In vitro* study of the antimicrobial activity of Brazilian propolis against *Paenibacillus larvae*. *Journal of Invertebrate Pathology*. 2008;97:273-281.

[169] Pinto M. S., de Faria J. E., Message D., Cassini S. T. A., Pereira C. S., Gioso M. M. Effect of green propolis extracts on patogenic bacteria isolated from milk of cows with mastitis. *Brazilian Journal of Veterinary Research and Animal Science*. 2001;38:278-283.

[170] Da Silva J. F. M., De Souza M. C., Matta S. R., De Andrade M. R., Vidal F. V. N. Correlation analysis between phenolic levels of Brazilian propolis extracts and their antimicrobial and antioxidant activities. *Food Chemistry*. 2006;99:431-435.

[171] Nogueira M. A., Diaz M. G., Tagami P. M., Lorscheide J. Antimicrobial activity of essential oils and propolis against oral pathogens. *Journal of Basic and Applied Pharmaceutical Sciences*. 2007;28:93-97.

[172] Farnesi A. P., Aquino-Ferreira R., De Jong D., Bastos J. K., Soares A. E. Effects of stingless bee and honey bee propolis on four species of bacteria. *Genetics and Molecular Research*. 2009;8:635-640.

[173] Feresin G. E., Tapia A., Gimenez A., Ravelo A. G., Zacchino S., Sortino M., Schmeda-Hirschmann G. Constituents of the Argentinian medicinal plant *Baccharis grisebachii* and their antimicrobial activity. *Journal of Ethnopharmacology*. 2003;89:73-80.

[174] Dota K. F. D., Faria M. G., Bruschi M. L., Pelloso S. M., Lopes-Consolaro M. E., Svidzinski T. I. Antifungal activity of propolis extract against yeasts isolated from vaginal exudates. *Journal of Alternative and Complementary Medicine*. 2010;16:285-290.

[175] Dota K. F., Consolaro M. E., Svidzinski T. I., Bruschi M. L. Antifungal activity of Brazilian propolis microparticles against yeasts isolated from vulvovaginal candidiasis. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:201953.

[176] Shimizu T., Hino A., Tsutsumi A., Park Y. K., Watanabe W., Kurokawa M. Anti-influenza virus activity of propolis *in vitro* and its efficacy against influenza infection in mice. *Antiviral Chemistry and Chemotherapy*. 2008;19:7-13.

[177] Bufalo M. C., Figueiredo A. S., de Sousa J. P. B., Candeias J. M. G., Bastos J. K., Sforcin J. M. Anti-poliovirus activity of *Baccharis dracunculifolia* and propolis by cell viability determination and real-time PCR. *Journal of Applied Microbiology*. 2009;107:1669-1680.

[178] Shimizu T., Takeshita Y., Takamori Y., Kai H., Sawamura R., Yoshida H., Watanabe W., Tsutsumi A., Park Y.. K., Yasukawa K., Matsuno K., Shiraki K., Kurokawa M. Efficacy of Brazilian propolis against Herpes Simplex Virus Type 1 infection in mice and their modes of antiherpetic efficacies. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:976196.

[179] Urushisaki T., Takemura T., Tazawa S., Fukuoka M., Hosokawa-Muto J., Araki Y., Kuwata K. Caffeoylquinic acids are major constituents with potent anti-influenza effects in Brazilian green propolis water extract. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:254914.

[180] Ayres D. C., Marcucci M. C., Giorgio S. Effects of Brazilian propolis on *Leishmania amazonensis*. *Memorias do Instituto Oswaldo Cruz*. 2007;102:215-220.

[181] Pontin K., Filho A. A. S., Santos F. F., Silva M. L., Cunha W. R., Nanayakkara N. P., Bastos J. K., de Albuquerque S. *In vitro* and *in vivo* antileishmanial activities of a Brazilian green propolis extract. *Parasitology Research*. 2008;103:487-492.

[182] Salomao K., de Souza E. M., Barbosa H. S., de Castro S. L. Propolis and derivatives of megazol: *In vitro* and *in vivo* activity on *Trypanosoma cruzi*, mechanism of action and selectivity. *International Journal of Infectious Diseases*. 2010;14 Suppl 1:e441-e442.

[183] De Castro S. L., Salomao K., de Souza E. M., Henriques-Pons A., Barbosa H. S. Brazilian green propolis: effects *in vitro* and *in vivo* on *Trypanosoma cruzi*. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:185918.

[184] Banskota A. H., Tezuka Y., Midorikawa K., Matsushige K., Kadota S. Two novel cytotoxic benzofuran derivatives from Brazilian propolis. *Journal of Natural Products*. 2000;63:1277-1279.

[185] Kimoto T., Koya S., Hino K., Yamamoto Y., Nomura Y., Micallef M. J., Hanaya T., Arai S., Ikeda M., Kurimoto M. Renal carcinogenesis induced by ferric nitrilotriacetate in mice, and protection from it by Brazilian propolis and Artepillin C. *Pathology International*. 2000;50:679–689.

[186] Kimoto T., Aga M., Hino K., Koya-Miyata S., Yamamoto Y., Micallef M. J., Hanaya T., Arai S., Ikeda M., Kurimoto M. Apoptosis of human leukemia cells induced by Artepillin C, an active ingredient of Brazilian propolis. *Anticancer Research*. 2001;21:221-228.

[187] Kimoto T., Koya-Miyata S., Hino K., Micallef M. J., Hanaya T., Arai S., Ikeda M., Kurimoto M. Pulmonary carcinogenesis induced by ferric nitrilotriacetate in mice and protection from it by Brazilian propolis and artepillin C. *Virchows Archiv*. 2001;438:259-270.

[188] Luo J., Soh J. W., Xing W. Q., Mao Y., Matsuno T., Weinstein I. B. PM-3, a benzo-gamma-pyran derivative isolated from propolis, inhibits growth of MCF-7 human breast cancer cells. *Anticancer Research*. 2001;21:1665-1671.

[189] Mishima S., Inoh Y., Narita Y., Ohta S., Sakamoto T., Araki Y., Suzuki K. M., Akao Y., Nozawa Y. Identification of caffeoylquinic acid derivatives from Brazilian propolis as constituents involved in induction of granulocytic differentiation of HL-60 cells. *Bioorganic and Medicinal Chemistry*. 2005;13:5814-5818.

[190] Mishima S., Narita Y., Chikamatsu S., Inoh Y., Ohta S., Yoshida C., Araki Y., Akao Y., Suzuki K., Nozawa Y. Effects of propolis on cell growth and gene expression in HL-60 cells. *Journal of Ethnopharmacology*. 2005;99:5-11.

[191] Mishima S., Ono Y., Araki Y., Akao Y., Nozawa Y. Two related cinnamic acid derivatives from Brazilian honey bee propolis, baccharin and drupanin, induce growth inhibition in allografted sarcoma S-180 in mice. *Biological and Pharmaceutical Bulletin*. 2005;28:1025-1030.

[192] Shimizu K., Suzuki Y., Hashiguchi M., Hashiguchi T. Anti-tumor cell activity of water-dispersible propolis. *Journal of Tokyo Medical University*. 2006;64:153-158.

[193] Ahn M. R., Kunimasa K., Ohta T., Kumazawa S., Kamihira M., Kaji K., Uto Y., Hori H., Nagasawa H., Nakayama T. Suppression of tumor-induced angiogenesis by Brazilian propolis: Major component artepillin C inhibits in vitro tube formation and endothelial cell proliferation. *Cancer Letters*. 2007;252:235-243.

[194] Chen C. R., Lee Y. N., Chang C. M. J., Lee M. R., Wei I. C. Hot-pressurized fluid extraction of flavonoids and phenolic acids from Brazilian propolis and their cytotoxic assay in vitro. *Journal of the Chinese Institute of Chemical Engineers*. 2007;38:191-196.

[195] Li H., Kapur A., Yang J. X., Srivastava S., McLeod D. G., Paredes-Guzman J. F., Daugsch A., Park Y. K., Rhim J. S. Antiproliferation of human prostate cancer cells by ethanolic extracts of Brazilian propolis and its botanical origin. *International Journal of Oncology*. 2007;31:601-606.

[196] Yasui Y, Miyamoto S, Kim M, Kohno H, Sugie S, Tanaka T. Aqueous and ethanolic extract fractions from the Brazilian propolis suppress azoxymethane-induced aberrant crypt foci in rats. *Oncology Reports*. 2008;20:493-499.

[197] Buriol L., Finger D., Schmidt E. S., dos Santos J. M. T., da Rosa M. R., Quinaia S. P., Torres Y. R., Santa H. S. D., Pessoa C., de Moraes M. O., Costa-Lotufo L. V., Ferreira P. M. P., Sawaya A. C. H. F., Eberlin M. N. Chemical composition and biological

activity of oil propolis extract: an alternative to ethanolic extract. *Quimica Nova*. 2009;32:296-302.

[198] Chen C. R., Lee Y. N., Lee M. R., Chang C. M. J. Supercritical fluids extraction of cinnamic acid derivatives from Brazilian propolis and the effect on growth inhibition of colon cancer cells. *Journal of the Taiwan*. 2009;40:130-135.

[199] Messerli S. M., Ahn M. R., Kunimasa K., Yanagihara M., Tatefuji T., Hashimoto K., Mautner V., Uto Y., Hori H., Kumazawa S., Kaji K., Ohta T., Maruta H. Artepillin C (ARC) in Brazilian green propolis selectively blocks oncogenic PAK1 signaling and suppresses the growth of NF tumors in mice. *Phytotherapy Research*. 2009;23:423-427.

[200] Paulino N., Abreu S. R. L., Machado G., Silveira E. Scientific evidences to pharmacological anticancer action of *Baccharis dracunculifolia* Brazilian propolis. *Revista de Pesquisa e Inovacao Farmaceutica*. 2009;1:15-26.

[201] Wu J. J., Shen C. T., Jong T. T., Young, C. C., Yang H. L., Hsu S. L., Chang C. M. J., Shieh CJ. Supercritical carbon dioxide anti-solvent process for purification of micronized propolis particulates and associated anti-cancer activity. *Separation and Purification Technology*. 2009;70:190-198.

[202] Bufalo M. C., Candeias J. M., Sousa J. P., Bastos J. K., Sforcin J. M. In vitro cytotoxic activity of *Baccharis dracunculifolia* and propolis against HEp-2 cells. *Natural Products Research*. 2010;24:1710-1718.

[203] Moraes C. S., Daugsch A., Li H., Rhim J. S., Park Y. K. Comparative antiproliferation of human prostate cancer cells by ethanolic extracts of two groups of Brazilian propolis. *Ciencia e Tecnologia de Alimentos*. 2010;30:539-543.

[204] Carvalho A. A., Finger D., Machado C. S., Schmidt E. M., Costa P. M., Alves A. P. N. N., Morais T. M. F., Queiroz M. G. R., Quináia S. P., Rosa M. R., Santos J. M. T., Pessoa C., Moraes M.O., Costa-Lotufo L. V., Sawaya A. C. H. F., Eberlin M. N., Torres Y. R. *In vivo* antitumoural activity and composition of an oil extract of Brazilian propolis. *Food Chemistry*. 2011;126:1239-1245.

[205] Cavalcante D. R. R., de Oliveira P. S., Gois S. M., Soares A. F., Cardoso J. C., Padilha F. F., de Albuquerque Júnior RLC. Effect of green propolis on oral epithelial dysplasia in rats. *Brazilian Journal of Otorhynolaryngology*. 2011;77:278-284.

[206] Kunimasa K., Ahn M. R., Kobayashi T., Eguchi R., Kumazawa S., Fujimori Y., Nakano T., Nakayama T., Kaji K., Ohta T. Brazilian propolis suppresses angiogenesis by inducing apoptosis in tube-forming endothelial cells through inactivation of survival signal ERK1/2. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:870753.

[207] Szliszka E., Zydowicz G., Janoszka B., Dobosz C., Kowalczyk-Ziomek G., Krol W. Ethanolic extract of Brazilian green propolis sensitizes prostate cancer cells to TRAIL-induced apoptosis. *International Journal of Oncology*. 2011;38:941-953.

[208] Xuan H., Zhao J., Miao J., Li Y., Chu Y., Hu F. Effect of Brazilian propolis on human umbilical vein endothelial cell apoptosis. *Food and Chemical Toxicology*. 2011;49:78-85.

[209] Shinohara R., Ohta Y., Hayashi T., Ikeno T. Evaluation of antilipid peroxidative action of propolis ethanol extract. *Phytotherapy Research*. 2002;16:340–347.

[210] Nakanishi I., Uto Y., Ohkubo K., Miyazaki K., Yakumaru H., Urano S., Okuda H., Ueda J. I., Ozawa T., Fukuhara K., Fukuzumi S., Nagasawa H., Hori H., Ikota N.

Efficient radical scavenging ability of artepillin C, a major component of Brazilian propolis, and the mechanism. *Organic and Biomolecular Chemistry*. 2003;1:1452-1454.

[211] Simoes L. M., Gregorio L. E., Filho A. A. S., De Souza M. L., Azzolini A. E. C. S., Bastos J. K., Lucisano-Valim Y. M. Effect of Brazilian green propolis on the production of reactive oxygen species by stimulated neutrophils. *Journal of Ethnopharmacology*. 2004;94:59-65.

[212] Shimizu K., Ashida H., Matsuura Y., Kanazawa K. Antioxidative bioavailability of artepillin C in Brazilian propolis. *Archives of Biochemistry and Biophysics*. 2004;424:181-188.

[213] Marquele F. D., Di Mambro V. M., Georgetti S. R., Casagrande R., Valim Y. M. L., Fonseca M. J. V. Assessment of the antioxidant activities of Brazilian extracts of propolis alone and in topical pharmaceutical formulations. *Journal of Pharmaceutical and Biomedical Analysis*. 2005;39:455-462.

[214] Nakajima Y., Shimazawa M., Mishima S., Hara H. Water extract of propolis and its main constituents, caffeoylquinic acid derivatives, exert neuroprotective effects via antioxidant actions. *Life Sciences*. 2006;80:370-377.

[215] Sheng J., Zhou J., Wang L., Xu J., Hu Q. Antioxidant activity of ethanol and petroleum ether extracts from Brazilian propolis. *European Food Research and Technology*. 2007;225:249-253.

[216] Souza J. P. B., Tacon L. A., Correia C. C., Bastos J. K., Freitas L. A. P. Spray-dried propolis extract, II: Prenylated components of green propolis. *Pharmazie*. 2007;62:488–492.

[217] Nakanishi I., Uto Y., Ohkubo K., Kawashima T., Manda S., Matsumoto K., Hori H., Fukuhara K., Okuda H., Ikota N., Fukuzumi S., Ozawa T., Anzai K. Structure-activity relationship in radical-scavenging reactions of naturally-oriented Artepillin C derivatives. In: *Proceedings of the 14th Biennial Meeting of the Society for Free Radical Research International*. Beijing, China, 18-22 Oct 2008. 2008:125-128.

[218] Izuta H., Narahara Y., Shimazawa M., Mishima S., Kondo S., Hara H. 1,1-Diphenyl-2-picrylhydrazyl radical scavenging activity of bee products and their constituents determined by ESR. *Biological and Pharmaceutical Bulletin*. 2009;32:1947-1951.

[219] Simoes- Ambrosio L. M., Gregorio L. E., Sousa J. P., Figueiredo A. S., Azzolini A. E., Bastos J. K., Lucisano-Valim Y. M. The role of seasonality on the inhibitory effect of Brazilian green propolis on the oxidative metabolism of neutrophils. *Fitoterapia*. 2010;81:1102-1108.

[220] Teixeira E. W., Message D., Negri G., Salatino A., Stringheta P. C. Seasonal variation, chemical composition and antioxidant activity of Brazilian propolis samples. *Evidence-Based Complementary and Alternative Medicine*. 2010;7:307-315.

[221] Cottica S. M., Sawaya A. C. H. F., Eberlin M. N., Franco S. L., Zeoula L. M., Visentainer J. V. Antioxidant activity and composition of propolis obtained by different methods of extraction. *Journal of the Brazilian Chemical Society*. 2011;22:929-935.

[222] Rocha B. A., Rodrigues M. R., Bueno P. C. P., Costa-Machado A. R. M., Vaz M. M. O. L. L., Nascimento A. P., Barud H. S., Berretta-Silva A. A. Preparation and thermal characterization of inclusion complex of Brazilian green propolis and hydroxypropyl-β-cyclodextrin- Increased water solubility of the chemical constituents and antioxidant activity. *Journal of Thermal Analysis and Calorimetry*. 2011; DOI 10.1007/s10973-011-1713-4.

[223] Orsi RO, Sforcin JM, Funari SRC, Gomes JC. Effect of propolis extract on guinea pig lung mast cell. *Journal of Venomous Animals and Toxins including Tropical Deseases*. 2005;11:76-83.

[224] Paulino N., Teixeira C., Martins R., Scremin A,. Dirsch V. M., Vollmar A. M., Abreu S. R., de Castro S. L., Marcucci M. C. Evaluation of the analgesic and anti-inflammatory effects of a Brazilian green propolis. *Planta Medica*. 2006;72:899-906.

[225] Paulino N., Abreu S. R., Uto Y., Koyama D., Nagasawa H., Hori H., Dirsch V. M., Vollmar A. M., Scremin A., Bretz W. A. Anti-inflammatory effects of a bioavailable compound, Artepillin C, in Brazilian propolis. *European Journal of Pharmacology*. 2008;587:296-301.

[226] Orsatti C. L., Missima F., Pagliarone A. C., Sforcin J. M. Th1/Th 2 cytokines' expression and production by propolis-treated mice. *Journal of Ethnopharmacology*. 2010;129:314-318.

[227] Tani H., Hasumi K., Tatefuji T., Hashimoto K., Koshino H., Takahashi S. Inhibitory activity of Brazilian green propolis components and their derivatives on the release of cys-leukotrienes. *Bioorganic and Medicinal Chemistry*. 2010;18:151-157.

[228] Moura S. A. L., Ferreira M. A. N. D., Andrade S. P., Reis M. L. C., Noviello M. L., Cara D. C. Brazilian green propolis inhibits inflammatory angiogenesis in a murine sponge model. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:182703.

[229] Mezadri T. J., Leite M. F., Staack Jr. M. C., Colchon P. H., Balan A. B., Zanatta M. L., Costa I. C., Perin C., Tames D. R., Sousa J. P. B., Bastos J. K., Andrade S. F. Evaluation of the contraction of cutaneous wounds in Wistar rats treated with Brazilian green propolis gel. *Latin America*. 2009;28:762-767.

[230] Moura S. A. L., Negri G., Salatino A., Lima L. D. C., Dourado L. P. A., Mendes J. B., Andrade S. P., Ferreira M. A. N. D., Cara D. C. Aqueous extract of Brazilian green propolis: primary components, evaluation of inflammation and wound healing by using subcutaneous implanted sponges. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:748283.

[231] Staak Jr. M. C., Colchon P. H., Portes A. G., Mezadri T. J., Tames D. R., Andrade S. F. Histological evaluation on Brazilian green propolis effect in tissue repair of Wistar rats cutaneous wounds. *Latin American Journal of Pharmacy*. 2011;30:383-387.

[232] Reis G. S., Valadao A. F., Lima L. R. P., Moreira M. L. Preparation of a sunscreen and evaluation of the photoprotective action of the green propolis from Vale do Aço, Minas Gerais, Brazil. *Boletin Latinoamericano y del Caribe de Plantas Medicinales y Aromaticas*. 2009;8:282-288.

[233] Fonseca Y. M., Marquele-Oliveira F., Vicentini F. T., Furtado N. A., Sousa J. P., Lucisano-Valim Y. M., Fonseca M. J. Evaluation of the potential of Brazilian propolis against UV-induced oxidative stress. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:863917.

[234] Sa-Nunes A., Faccioli L. H., Sforcin J. M. Propolis: lymphocyte proliferation and IFN-γ production. *Journal of Ethnopharmacology*. 2003;87:93-97.

[235]Missima F., Sforcin J. M. Green Brazilian propolis action on macrophages and lymphoid organs of chronically stressed mice. *Evidence-Based Complementary and Alternative Medicine*. 2008;5:71-75.

[236] Pagliarone A. C., Missima F., Orsatti C. L., Bachiega T. F., Sforcin J. M. Propolis effect on Th1/Th2 cytokines production by acutely stressed mice. *Journal of Ethnopharmacology*. 2009;125:230-233.

[237] Pagliarone A. C., Orsatti C. L., Bufalo M. C., Missima F., Bachiega T. F., Junior J. P., Sforcin J. M. Propolis effects on pro-inflammatory cytokines production and Toll-like receptors 2 and 4 expression in stressed mice. *International Immunopharmacology*. 2009;9:1352-1356.

[238] Fischer G., Paulino N., Marcucci M. C., Siedler B. S., Munhoz L. S., Finger P. F., Vargas G. D., Hubner S. O., Vidor T., Roehe P. M. Green propolis phenolic compounds act as vaccine adjuvants, improving humoral and cellular responses in mice inoculated with inactivated vaccines. *Memorias do Instituto Oswaldo Cruz*. 2010;105:908-913.

[239] Orsatti C. L., Sforcin J. M. Propolis immunomodulatory activity on TLR-2 and TLR-4 expression by chronically stressed mice. *Natural Product Research*. 2011; DOI: 10.1080/14786419.2010.482049.

[240] Kubota Y., Umegaki K., Kobayashi K., Tanaka N., Kagota S., Nakamura K., Kunitomo M., Shinozuka K. Anti-hypertensive effects of brazilian propolis in spontaneously hypertensive rats. *Clinical and Experimental Pharmacology and Physiology*. 2004;31 Suppl 2:S29-30.

[241] Mishima S., Yoshida C., Akino S., Sakamoto T. Antihypertensive effects of Brazilian propolis: identification of caffeoylquinic acids as constituents involved in the hypotension in spontaneously hypertensive rats. *Biological and Pharmaceutical Bulletin*. 2005;28:1909-1914.

[242] Maruyama H., Sumitou Y., Sakamoto T., Araki Y., Hara H. Antihypertensive effects of flavonoids isolated from Brazilian green propolis in spontaneously hypertensive rats. *Biological and Pharmaceutical Bulletin*. 2009;32:1244-1250.

[243] Mesquita F. F., Rueda B. Z., Tardivo A. C., Alves M. J. Q. F. Effects of propolis flavonoids fraction on the cholesterol metabolism of rabbits with experimental hypercholesterolemia. *Revista Brasileira de Plantas Medicinais*. 2007;9:44-50.

[244] Alves M. J. Q. F., Mesquita F. F., Sakaguti M., Tardivo A. C. Hypocholesterolemic effect of propolis' caffeic acids. *Revista Brasileira de Plantas Medicinais*. 2008;10:100-105.

[245] Koya-Miyata S., Arai N., Mizote A., Taniguchi Y., Ushio S., Iwaki K., Fukuda S. Propolis prevents diet-induced hyperlipidemia and mitigates weight gain in diet-induced obesity in mice. *Biological and Pharmaceutical Bulletin*. 2009;32:2022-2028.

[246] El-Sayed S. M., Abo-Salem O. M., Aly H. A., Mansour A. M. Potential antidiabetic and hypolipidemic effects of propolis extract in streptozotocin-induced diabetic rats. *Pakistan Journal of Pharmaceutical Sciences*. 2009;22:168-174.

[247] Araki H., Jin C., Gomita Y., Doi S., Sugimoto H., Yamada H. The effect of Alecrim propolis on cyanide intoxication in mice. *Honeybee Science*. 2001;22:62-66.

[248] Fernandes A. A. H., Fernandes Jr. A., Novelli E. L. B. Effect of Brazilian propolis on experimental hepatotoxicity in rats. *Revista de Ciencias Farmaceuticas*. 2004;25:85-89.

[249] Park Y. K., Fukuda I., Ashida H., Nishiumi S., Yoshida K., Daugsch A., Sato H. H., Pastore G. M. Suppressive effects of ethanolic extracts from propolis and its main botanical origin on dioxin toxicity. *Journal of Agricultural and Food Chemistry*. 2005;53:10306-10309.

[250] Tavares D. C., Lira W. M., Santini C. B., Takahashi C. S., Bastos J..K. Effects of propolis crude hydroalcoholic extract on chromosomal aberrations induced by doxorubicin in rats. *Planta Medica*. 2007;73:1531-1536.

[251] Valadares B. L. B., Graf U., Spanó M. A. Inhibitory effects of water extract of propolis on doxorubicin-induced somatic mutation and recombination in *Drosophila melanogaster*. *Food and Chemical Toxicology*. 2008;46:1103-1110.

[252] Oliveira P. F., Neto M. A. B. M., Leandro L. F., Bastos J. K., Filho A. A. S., Tavares D. C. *In vivo* antigenotoxicity of baccharin, an important constituent of *Baccharis Dracunculifolia* DC (Asteraceae). *Basic and Clinical Pharmacology and Toxicology*. 2011;109:35-41.

[253] Shimazawa M., Chikamatsu S., Morimoto N., Mishima S., Nagai H., Hara H. Neuroprotection by Brazilian green propolis against *in vitro* and *in vivo* ischemic neuronal damage. *Evidence-Based Complementary and Alternative Medicine*. 2005;2:201-207.

[254] Inokuchi Y., Shimazawa M., Nakajima Y., Suemori S., Mishima S., Hara H. Brazilian green propolis protects against retinal damage *in vitro* and *in vivo*. *Evidence-Based Complementary and Alternative Medicicne*. 2006;3:71-77.

[255] Nakajima Y., Shimazawa M., Mishima S., Hara H. Neuroprotective effects of Brazilian green propolis and its main constituents against oxygen-glucose deprivation stress, with a gene-expression analysis. *Phytotherapy Research*. 2009;23:1431-1438.

[256] Barros M. P., Sousa J. P., Bastos J. K., de Andrade S. F. Effect of Brazilian green propolis on experimental gastric ulcers in rats. *Journal of Ethnopharmacology*. 2007;110:567-571.

[257] Lemos M., de Barros M. P., Sousa J. P., Filho A. A. S., Bastos J. K., de Andrade S. F. *Baccharis dracunculifolia*, the main botanical source of Brazilian green propolis, displays antiulcer activity. *Journal of Pharmacy and Pharmacology*. 2007;59:603-608.

[258] Barros M. P., Lemos M., Maistro E. L., Leite M. F., Sousa J. P., Bastos J. K., Andrade S. F. Evaluation of antiulcer activity of the main phenolic acids found in Brazilian green propolis. *Journal of Ethnopharmacology*. 2008;120:372-377.

[259] Nakamura T., Ohta Y., Tada M., Teruya A., Ohashi K., Ikeno K., Watanabe R., Tokunaga K., Harada N. Protective effect of Brazilian propolis ethanol extract against stress-induced gastric mucosal lesions in rats. Its evaluation using oxidative stress markers. *Journal of Analytical BioScience*. 2011;34:135–146.

[260] Eda M., Hayashi Y., Kinoshita K., Koyama K., Takahashi K., Akutu K. Anti-emetic principles of water extract of Brazilian propolis. *Pharmaceutical Biology*. 2005;43:184-185.

[261] Paulino N., Scremin F. M., Raichaski L. B., Marcucci M. C., Scremin A., Calixto J. B. Mechanisms involved in the relaxant action of the ethanolic extract of propolis in the guinea-pig trachea in-vitro. *Journal of Pharmacy and Pharmacology*. 2002;54:845–852.

[262] Cestari S. H., Bastos J. K., Di Stasi L. C. Intestinal anti-inflammatory activity of *Baccharis dracunculifolia* in the trinitrobenzenesulphonic acid model of rat colitis. *Evidence-Based Complementary and Alternative Medicine*. 2011;2011:524349.

[263] Estrada G. O. D., da Silva J. F. M., Antunes O. A. C. Artepillin C: a review. *Letters in Drug Design and Discovery*. 2008;5:88-92.

[264] Li Y. J., Lin J. L., Yang C. W., Yu C. C. Acute renal failure induced by a Brazilian variety of propolis. *American Journal of Kidney Diseases*. 2005;46:125-129.

[265] Mani F., Damasceno H. C., Novelli E. L., Martins E. A., Sforcin J. M. Propolis: Effect of different concentrations, extracts and intake period on seric biochemical variables. *Journal of Ethnopharmacology*. 2006;105:95-98.

[266] Woisky R. G., Salatino A. Analysis of propolis: some parameters and procedures for chemical quality control. *Journal of Apicultural Research*. 1998;37:99-105.

[267] Funari C. S., Ferro V. O. Propolis analysis. *Ciencia e Tecnologia de Alimentos*. 2006;26:171-178.

[268] Ledon N., Casaco A., Gonzalez R., Merino N., Gonzalez A., Tolon Z. Efectos antipsoriásico, antiinflamatorio y analgésico del propoleo rojo colectado en Cuba. *Revista Cubana de Farmacia*. [online]. 1996;30:http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0034-75151996000100008&lng=pt.

[269] Questa-Rubio O., Frontana-Uriba B., Perez J. C. Isoflavonoides en propoleos Cubanos. *Revista Cubana de Farmacia*. 2001;35 Suppl:58–61.

[270] Piccinelli A. L., Fernandez M. C., Cuesta-Rubio O., Hernandez I. M., De Simone F., Rastrelli L. Isoflavonoids isolated from Cuban propolis. *Journal of Agricultural and Food Chemistry*. 2005;53:9010-9016.

[271] Cuesta-Rubio O., Piccinelli A. L., Fernandez M. C., Hernandez I. M., Rosado A, Rastrelli L. Chemical characterization of Cuban propolis by HPLC-PDA, HPLC-MS, and NMR: the brown, red, and yellow Cuban varieties of propolis. *Journal of Agricultural & Food Chemistry*. 2007;55:7502-7509.

[273] Trusheva B., Popova M., Bankova V., Simova S., Marcucci M. C., Miorin P. L., Pasin F. D., Tsvetkova I. Bioactive constituents of Brazilian red propolis. *Evidence-Based Complementary and Alternative Medicine*. 2006;3:249-254.

[274] Da Luz CFP, Barth OM, Bacha Junior GL. Analise palinologica de propolis vermelha do Brasil: subsidios para a certificacao de sua origem botanica e geografica. *Mensagem Doce*. 2009;102:art. No 2.

[275] Daugsch A., Moraes C. S., Fort P., Park Y.K. Botanical origin of Brazilian reddish propolis and its major chemical constituents. *Honeybee Science*. 2007;27:55-62.

[276] Silva B. B., Rosalen P. L., Cury J. A., Ikegaki M., Souza V. C., Esteves A., Alencar S. M. Chemical composition and botanical origin of red propolis, a new type of Brazilian propolis. *Evidence-Based Complementary and Alternative Medicine*. 2008;5:313–316.

[277] Alencar S. M., Oldoni T. L. C., Castro M. L., Cabral I. S. R., Costa-Neto C. M., Cury J. A., Rosalen P. L., Ikegaki M. Chemical composition and biological activity of a new type of Brazilian propolis: Red propolis. *Journal of Ethnopharmacology*. 2007;113:278-283.

[278] Moraes C. S., Daugsch A., Fort P., Park Y. K. Extrações de própolis vermelha do nordeste brasileiro em diferentes concentrações alcoólicas, com diferentes solventes e suas atividades contra *Staphylococcus aureus*. *Mensagem Doce*. 2008;99:art. No 1.

[278] Cabral I. S. R., Oldoni T. L. C., Prado A., Bezerra R. M. N., Alencar S. M., Ikegaki M., Rosalen P. L. Phenolic composition, antibacterial and antioxidant activities of Brazilian red propolis. *Quimica Nova*. 2009;32:1523-1527.

[279] Maia-Araujo YLF, Mendonca LS, Orellana SC, Araujo ED. Comparação entre duas técnicas utilizadas no teste de sensibilidade antibacteriana do extrato hidroalcoólico de própolis vermelha. *Scientia Plena*. 2011;7:046201.

[280] Oldoni T. L. C., Cabral I. S. R., d'Arce M. A. B. R., Rosalen P. L., Ikegaki M., Nascimento A. M., Alencar S. M. Isolation and analysis of bioactive isoflavonoids and chalcone from a new type of Brazilian propolis. *Separation and Purification Technology*. 2011;77:208-213.

[281] Awale S., Li F., Onozuka H., Esumi H., Tezuka Y., Kadota S. Constituents of Brazilian red propolis and their preferential cytotoxic activity against human pancreatic PANC-1 cancer cell line in nutrient-deprived condition. *Bioorganic and Medicinal Chemistry*. 2008;16:181-189.

[282] Diaz-Carballo D., Freistuhler M., Malak S., Bardenheuer W., Reusch H. P. Mucronulatol from Caribbean propolis exerts cytotoxic effects on human tumor cell lines. *International Journal of Clinical Pharmacology and Therapeutics*. 2008;46:226-235.

[283] Li F., Awale S., Tezuka Y., Kadota S. Cytotoxic constituents from Brazilian red propolis and their structure-activity relationship. *Bioorganic and Medicinal Chemistry*. 2008;16:5434-5440.

[284] Albuquerque-Junior R. L. C., Barreto A. L. S., Pires J. A., Reis F. P., Lima S. O., Ribeiro M. A. G., Cardoso J. C. Effect of bovine type-I collagen-based films containing red propolis on dermal wound healing in rodent model. *International Journal of Morphology*. 2009;27:1105-1110.

[285] Iio A., Ohguchi K., Inoue H., Maruyama H., Araki Y., Nozawa Y., Ito M. Ethanolic extracts of Brazilian red propolis promote adipocyte differentiation through PPARγ activation. *Phytomedicine*. 2010;17:974-979.

[286] Rosalen P. L., Silva B. B., Falsetta M., Ikegaki M., Alencar S. M., Koo H. Influences of red propolis on *S. mutans*-transcriptome responses within biofilms (poster). On: *89th General Session and Exhibition of the IADR*. San Diego, USA: No 2772.

[287] Daleprane J. B., Dehne N., Ong T. P., Brune B., Abdalla D. S. P. Antiangiogenic properties of natural polyphenols from red propolis. *The FASEB Journal*. 2011;25:lb236.

[288] Righi A. A., Alves T. R., Negri G., Marques L. M., Breyer H., Salatino A. Brazilian red propolis: unreported substances, antioxidant and antimicrobial activities. *Journal of the Science of Food and Agriculture*. 2011;91:2363–2370.

[289] Tomas-Barberan F. A., Garcia-Viguera C., Vit-Olivier P., Ferreres F., Tomas-Lorente F. Phytochemical evidence for the botanical origin of tropical propolis from Venezuela. *Phytochemistry*. 1993;34:191-196.

[290] Trusheva B., Popova M., Naydenski H., Tsvetkova V., Rodriguez J. G., Bankova V. New polyisoprenylated benzophenones from Venezuelan propolis. *Fitoterapia*. 2004;75:683-689.

[291] Cuesta-Rubio O., Frontana-Uribe B. A., Ramirez-Apan T., Cardenas J. Polyisoprenylated benzophenones in Cuban propolis. Biological activity of nemorosone. *Zeitschrift für Naturforschung*. 2002;57c:372-378.

[292] Hernandez I. M., Fernandez M. C., Cuesta-Rubio O., Piccinelli A. L., Rastrelli L. Polyprenylated benzophenone derivatives from Cuban propolis. *Journal of Natural Products*. 2005;68:931–934.

[293] Castro M. L., Nascimento A. M., Ikegaki M., Costa-Neto C. M., Alencar S. M., Rosalen P. L. Identification of a bioactive compound isolated from Brazilian propolis type 6. *Bioorganic and Medicinal Chemistry*. 2009;17:5332-5335.

[294] Ishida V. F. C., Negri G., Salatino A., Bandeira M. F. C. L. A new type of Brazilian propolis: Prenylated benzophenones in propolis from Amazon and effects against cariogenic bacteria. *Food Chemistry*. 2011;125:966–972.

[295] Duarte S., Koo H., Bowen W. H., Hayacibara M. F., Cury J. A., Ikegaki M., Rosalen P. L. Effect of a novel type of propolis and its chemical fractions on glucosyltransferases and on growth and adherence of mutans Streptococci. *Biological and Pharmaceutical Bulletin*. 2003;26:527-531.

[296] Duarte S., Rosalen P. L., Hayacibara M. F., Cury J. A., Bowen W. H., Marquis R. E., Rehder V. L., Sartoratto A., Ikegaki M., Koo H. The influence of a novel propolis on mutans streptococci biofilms and caries development in rats. *Archives of Oral Biology*. 2006;51:15-22.

[297] Castro M. L., Vilela W. R., Zauli R. C., Ikegaki M., Redher V. L., Foglio M. A., Alencar S. M., Rosalen P. L. Bioassay guided purification of the antimicrobial fraction of a Brazilian propolis from Bahia state. *BMC Complementary Alternative Medicine*. 2009;9:25.

[298] Diaz-Carballo D., Ueberla K., Kleff V., Ergun S., Malak S., Freistuehler M., Somogyi S., Kucherer C., Bardenheuer W., Strumberg D. Antiretroviral activity of two polyisoprenylated acylphloroglucinols, 7-epi-nemorosone and plukenetione A, isolated from Caribbean propolis. *International Journal of Clinical Pharmacology and Therapeutics*. 2010;48:670-677.

[299] Diaz-Carballo D., Malak S., Bardenheuer W., Freistuehler M., Reusch H. P. The contribution of plukenetione A to the anti-tumoral activity of Cuban propolis. *Bioorganic and Medicinal Chemistry*. 2008;16:9635-9643.

[300] Popolo A., Piccinelli L. A., Morello S., Cuesta-Rubio O., Sorrentino R., Rastrelli L., Pinto A. Antiproliferative activity of brown Cuban propolis extract on human breast cancer cells. *Natural Product Communications*. 2009;4:1711-1716.

[301] Popolo A., Piccinelli A. L., Morello S., Sorrentino R., Osmany C. R., Rastrelli L., Aldo P. Cytotoxic activity of nemorosone in human MCF-7 breast cancer cells. *Canadian Journal of Physiology and Pharmacology*. 2011;89:50-57.

[302] Melliou E., Stratis E., Chinou I. Volatile constituents of propolis from various regions of Greece– Antimicrobial activity. *Food Chemistry*. 2007;103:375-380.

[303] Kalogeropoulos N., Konteles S. J., Troullidou E., Mourtzinos I., Karathanos V.T. Chemical composition, antioxidant activity and antimicrobial properties of propolis extracts from Greece and Cyprus. *Food Chemistry*. 2009;116:452-461.

[304] Popova M. P., Chinou I. B., Marekov I. N., Bankova VS. Terpenes with antimicrobial activity from Cretan propolis. *Phytochemistry*. 2009;70:1262-1271.

[305] Popova M., Trusheva B., Antonova D., Cutajar S., Mifsud D., Farrugia C., Tsvetkova I., Najdenski H., Bankova V., The specific chemical profile of Mediterranean propolis from Malta. *Food Chemistry*. 2011;126:1431-1435.

[306] Pratsinis H., Kletsas D., Melliou E., Chinou I. Antiproliferative activity of Greek propolis. *Journal of Medicinal Food*. 2010;13:286-290.

[307] Lu L. C., Chen Y. W., Chou C. C. Antibacterial activity of propolis against *Staphylococcus aureus*. *International Journal of Food Microbiology*. 2005;102:213-220.

[308] Yang H. Y., Ho W. L., Chang C. M., Chou C. C. Antibacterial activity of propolis ethanol extract against *Streptococcus mutans* as influenced by concentration, temperature, pH and cell age. *Journal of Food and Drug Analysis*. 2007;15:75-81.

[309] Chen Y. W., Wu S. W., Ho K. K., Lin S. B., Huang C. Y., Chen C. N. Characterisation of Taiwanese propolis collected from different locations and seasons. *Journal of the Science of Food and Agriculture*. 2008;88:412-419.

[310] El-Bassuony A., AbouZid S. A new prenylated flavanoid with antibacterial activity from propolis collected in Egypt. *Natural Product Communications*. 2010;5:43-45.

[311] Raghukumar R., Vali L., Watson D., Fearnley J., Seidel V. Antimethicillin-resistant *Staphylococcus aureus* (MRSA) activity of 'pacific propolis' and isolated prenylflavanones. *Phytotherapy Research*. 2010;24:1181-1187.

[312] Chen C. N., Wu C. L., Shy H. S., Lin J. K. Cytotoxic prenylflavanones from Taiwanese propolis. *Journal of Natural Products*. 2003;66:503–506.

[313] Kumazawa S., Ueda R., Hamasaka T., Fukumoto S., Fujimoto T., Nakayama T. Antioxidant prenylated flavonoids from propolis collected in Okinawa, Japan. *Journal of Agricultural and Food Chemistry*. 2007;55:7722–7725.

[314] Huang W. J., Huang C. H., Wu C. L., Lin J. K., Chen Y. W., Lin C. L., Chuang S. E., Huang C. Y., Chen C. N. Propolin G, a prenylflavanone, isolated from Taiwanese propolis, induces caspase-dependent apoptosis in brain cancer cells. *Journal of Agricultural and Food Chemistry*. 2007;55:7366-7376.

[315] Weng M. S., Liao C. H., Chen C. N., Wu C. L., Lin J. K. Propolin H from Taiwanese propolis induces G1 arrest in human lung carcinoma cells. *Journal of Agricultural and Food Chemistry*. 2007;55:5289-5298.

[316] Aguero M. B., Svetaz L., Sanchez M., Luna L., Lima B., Lopez M. L., Zacchino S., Palermo J., Wunderlin D., Feresin G. E., Tapia A. Argentinean Andean propolis associated with the medicinal plant *Larrea nitida* Cav. (Zygophyllaceae). HPLC–MS and GC–MS characterization and antifungal activity. *Food and Chemical Toxicology*. 2011;49:1970-1978.

[317] Nieva Moreno M. I., Zampini I. C., Ordonez R. M., Jaime G. S., Vattuone M. A., Isla M.I. Evaluation of the cytotoxicity, genotoxicity, mutagenicity, and antimutagenicity of propolis from Tucuman. Argentina. *Journal of Agricultural and Food Chemistry*. 2005;53:8957-8962.

[318] Aguero M. B., Gonzalez M., Lima B., Svetaz L., Sanchez M., Zacchino S., Feresin G. E., Schmeda-Hirschmann G., Palermo J., Wunderlin D., Tapia A. Argentinean propolis from *Zuccagnia punctata* Cav. (Caesalpinieae) exudates: phytochemical characterization and antifungal activity. *Journal of Agricultural and Food Chemistry*. 2010;58:194-201.

[319] Vera N., Solorzano E., Ordonez R., Maldonado L., Bedascarrasbure E., Isla M. I. Chemical composition of Argentinean propolis collected in extreme regions and its relation with antimicrobial and antioxidant activities. *Natural Product Communications*. 2011;6:823-827.

[320] Awale S., Shrestha S. P., Tezuka Y., Ueda J., Matsushige K., Kadota S. Neoflavonoids and related constituents from Nepalese propolis and their nitric oxide production inhibitory activity. *Journal of Natural Products*. 2005;68:858–864.

[321] Li F., Awale S., Tezuka Y., Kadota S. Cytotoxicity of constituents from Mexican propolis against a panel of six different cancer cell lines. *Natural Product Communications*. 2010;5:1601-1606.

[322] Murase M., Kato M., Sun A., Ono T., Nakamura J., Sato T., Kumazawa S. *Rhus javanica* var. *chinensis* as a new plant origin of propolis from Okayama, Japan. *Bioscience Biotechnology and Biochemistry*. 2008;72:2782-2784.

[323] Silva M. S. S., de Lima S. G., Oliveira E. H., Lopes J. A. D., Chaves M. H., Reis F. A. M., Citó A. M. G. L. Anacardic acid derivatives from Brazilian propolis and their antibacterial activity. *Ecletica Quimica*. 2008;33:53-58.

[324] Ito J., Chang F. R., Wang H. K., Park Y. K., Ikegaki M., Kilgore N., Lee K. H. Anti-AIDS agents. 48.1 anti-HIV activity of moronic acid derivatives and the new melliferone-related triterpenoid isolated from Brazilian propolis. *Journal of Natural Products*. 2001;64:1278–1281.

[325] Li F., Awale S., Tezuka Y., Kadota S. Cytotoxic constituents of propolis from Myanmar and their structure-activity relationship. *Biological and Pharmaceutical Bulletin*. 2009;32:2075-2078.

[326] Li F., Awale S., Zhang H., Tezuka Y., Esumi H., Kadota S. Chemical constituents of propolis from Myanmar and their preferential cytotoxicity against a human pancreatic cancer cell line. *Journal of Natural Products*. 2009;72:1283-1287.

[327] Segueni N., Magid A. A., Decarme M., Rhouati S., Lahouel M., Antonicelli F., Lavaud C., Hornebeck W. Inhibition of stromelysin-1 by caffeic acid derivatives from a propolis sample from Algeria. *Planta Medica*. 2011;77:999-1004.

[328] Sha N., Guan S. H., Lu Z. Q., Chen G. T., Huang H. L., Xie F. B., Yue Q. X., Liu X., Guo D. A. Cytotoxic constituents of Chinese propolis. *Journal of Natural Products*. 2009;72:799-801.

[329] Kumazawa S., Suzuki S., Ahn M. R., Kamihira M., Udagawa Y., Bang K. S., Nakayama T. A new chalcone from propolis collected on Jeju Island, Korea. *Food Science and Technology Research*. 2006;12:67-69.

[330] Ophori E. A., Eriagbonye B. N., Ugbodaga P. Antimicrobial activity of propolis against *Streptococcus mutans*. *African Journal of Biotechnology*. 2010;9:4966-4969.

[331] Petrova A., Popova M., Kuzmanova C., Tsvetkova I., Naydenski H., Muli E, Bankova V. New biologically active compounds from Kenyan propolis. *Fitoterapia*. 2010;81:509-514.

[332] Trusheva B., Popova M., Koendhori E. B., Tsvetkova I., Naydenski H., Bankova V. Indonesian propolis: chemical composition, biological activity and botanical origin. *Natural Product Research*. 2011;25:606-613.

[333] Trusheva B., Popova M., Kortenska V., Totseva I., Rodriguez J.G., Bankova V. Chemical composition and antioxidant activity of propolis from Venezuela. *Oxidation Communications*. 2005;28:490-496.

[334] Kumazawa S., Goto H., Hamasaka T., Fukumoto S., Fujimoto T., Nakayama T. A new prenylated flavonoid from propolis collected in Okinawa, Japan. *Bioscience Biotechnology and Biochemistry*. 2004;68:260-262.

[335] Huang W. J., Lin C. W., Lee C. Y., Chi L. L., Chao Y. C., Wang H. N., Chiou B. L., Chen T.J., Huang C.Y., Chen C.N. NBM-HD-3, a novel histone deacetylase inhibitor with anticancer activity through modulation of PTEN and AKT in brain cancer cells. *Journal of Ethnopharmacology*. 2011;136:156-167.