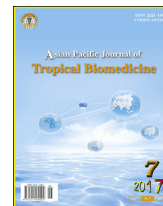


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Red propolis: Chemical composition and pharmacological activity

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ABSTRACT

Propolis has been used worldwide for years in folk medicine and currently marketed by the pharmaceutical industry. In Brazil, propolis was classified into 13 groups based on their organoleptics and physicochemical characteristics. The 13th type named red propolis has been an important source of investigation since late 90s. Their property comes from the countless compounds, including terpenes, pterocarpanes, prenylated benzophenones and especially the flavonoids. This last compound class has been indicated as the responsible for its potent pharmacological actions, highlighting the antimicrobial, anti-inflammatory, antioxidant, healing and antiproliferative activities. The red propolis can also be found in other countries, especially Cuba, which has similar features as the Brazilian. Therefore, with the compilation of 80 papers, this review aims to provide a key reference for researchers interested in natural products and discovery of new active compounds, such as from propolis.

1. Introduction

Natural products arising from the Brazilian flora have been attributed as valuable sources of substances used for the discovery and development of new therapeutic agents. Propolis is one of these products which have attracted the researchers' attention. Recently, the red propolis type, found in the Northeast of Brazil, has been highlight due to its features. This variety is found in the states of Alagoas, Sergipe, Paraíba, Pernambuco and Bahia, from mangroves regions. The main botanical origin was identified as *Dalbergia ecastophyllum* (*D. ecastophyllum*) (L) Taub. (Fabaceae), popularly known as 'rabo-de-bugio' [1–3].

Propolis is a complex natural resin collected by bees (*Apis mellifera*) from different parts of plants such as branches, buds, exudates, among others. Salivary secretions and enzymes are added, and this product is used mainly for protection against insects, invading microorganisms and in beehives repair [4,5]. In general, it is composed of 50–60% resins and balms, 30–40%

waxes, 5–10% essential oils, 5% pollen grain, microelements and vitamins [6–8].

The red propolis is classified as the 13th group and has shown several biological properties, e.g. antimicrobial, anticancer, antioxidant, which are related to its complex and variable chemical composition. Its main constituents are phenolic compounds, especially flavonoids, which have broad therapeutic range [9–12]. In this way, the presence of two flavanols pigments named Retusapurpurin B and Retusapurpurin A, give its red identity feature [13].

The chemical composition and pharmacological activities of this specific propolis class, have been intensely explored since the 90s, which is evidenced by the publication of over 100 papers between scientific articles and patents. Thus, this review aims to compile these information of the red propolis being a guide for future research related to this special type of propolis.

2. Chemical composition

The red propolis chemical composition is very complex and largely depends on the geographical origin and specific flora at the site of collection. Therefore, the compounds are directly related to the plant origin [14]. More than 300 components have been reported in red propolis samples, which have been analyzed by divers methods. Table 1 and Figure 1 show the compounds most frequently mentioned, which are representatives of terpenes, flavonoids, aromatic acids and fatty acids class. Furthermore,

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Table 1

The main compounds found in red propolis and some identification methods.

Compound	Identification method	Ref
Retusapurpurin A and B (1)	ESI/MS HPLC-PDA-ESI/MS	[15] [13]
Formononetin (2)	ESI/MS HPLC-PDA-ESI/MS	[15] [13]
Biochanin A (3)	ESI/MS HPLC-PDA-ESI/MS	[15] [13]
Medicarpin (4)	ESI/MS HPLC-PDA-ESI/MS GC/MS	[15] [13] [16]
Vestitol (5)	HPLC-PDA-ESI/MS GC/MS, NMR, HPLC	[13] [12]
Neovestitol (6)	HPLC-PDA-ESI/MS GC/MS; NMR; HPLC	[13] [12]
Daidzein (7)	RP-HPLC	[16]
Elemicin (8)	GC/MS	[17]
Guttiferone E (9)	HPLC-PDA-ESI/MS GC/MS, NMR	[13] [17]
Xanthochymol (10)	HPLC-PDA-ESI/MS GC/MS; NMR	[13] [17]
Isoliquiritigenin (11)	HPLC-PDA-ESI/MS GC/MS, NMR, HPLC	[13] [12]
Liquiritigenin (12)	ESI/MS HPLC-PDA-ESI/MS	[15] [13]
10-Octadecenoic acid, methyl ester (13)	GC/MS	[16]

there are inorganic elements such as copper, manganese, iron, calcium, aluminum, vanadium and silicon as well [4,5].

2.1. Volatile compounds-Terpenes

Volatile compounds are among the most widely secondary metabolites found in plants, animals and insects. These can be dispersed in the air and related with pollinators attraction and seed dispersers, protect plants through repulsion or intoxication, among other functions. They are typically classified into four major categories: terpenes, fatty acid derivatives, amino acid derivatives and phenylpropanoid/benzenoid compounds. Several of these compounds have been identified in red propolis [18].

Terpenes, which are biosynthetically derived from units of isoprene, are a large and diversified class of volatile compounds present in propolis. Limonene, α -cubebene, β -caryophyllene, which were identified by GC/MS are some representatives [19].

The ester of oleic acid, 10-octadecenoic acid, methyl ester, was recently identified in red propolis by GC-MS [16]. Among all volatile compounds found by the author, this was one of the most prevalent. These esters are usually used by plants to attract insects during pollination, which should happen with bees. These volatile compounds are applied as flavors, fragrances, spices and used in perfumery, as well as food additives. Meanwhile, they have been reported also to have the broad range of the biological activity including analgesic,

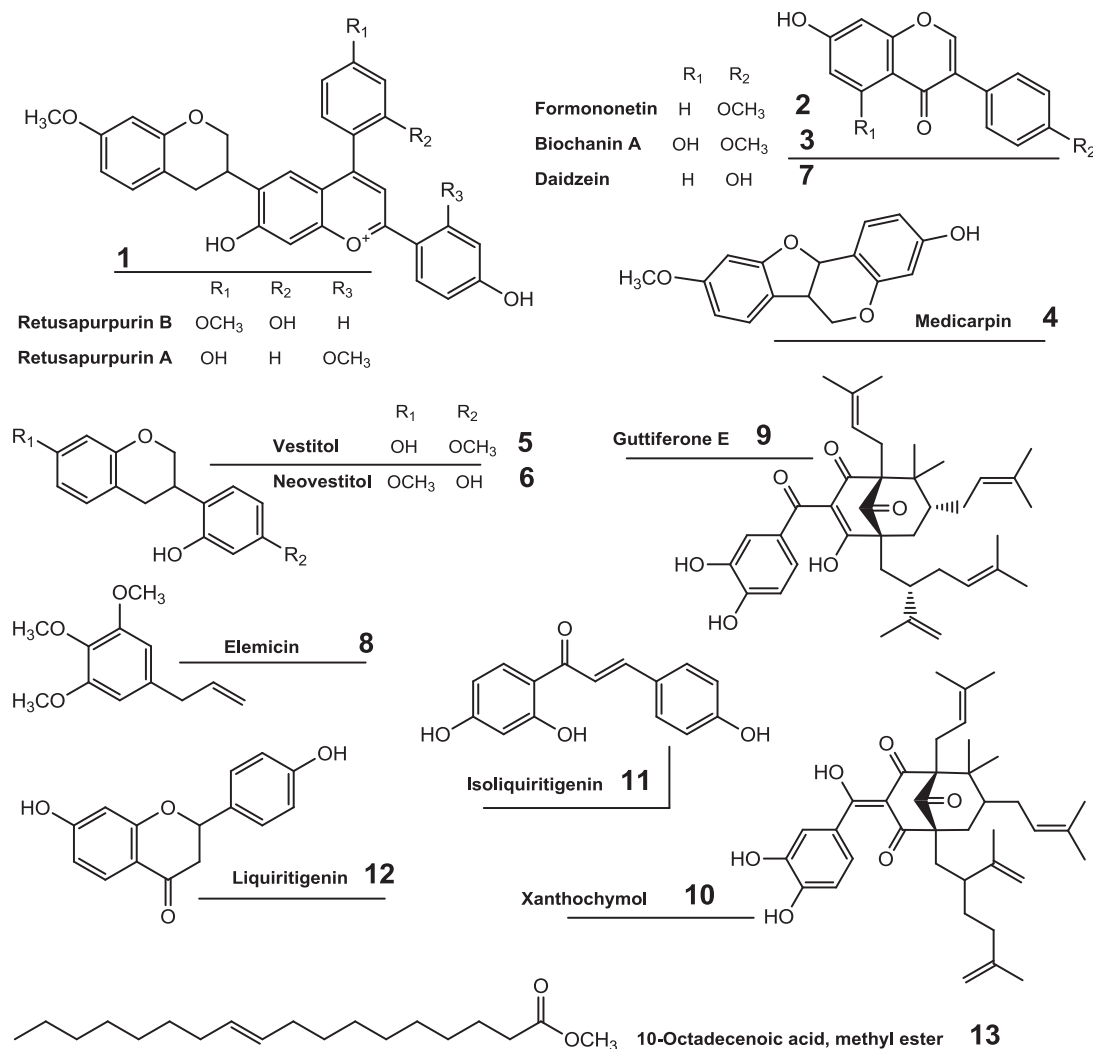


Figure 1. Chemical structures of main chemical markers of red propolis.

anti-inflammatory, cancer chemopreventive effects, antimicrobial, antifungal, antiviral and antiparasitic activities [20,21].

2.2. Phenolic compounds

Phenolic compounds are a large class of plant secondary metabolites, showing a diversity of structures including phenolic acids, flavonoids, lignans, quinones, tannins, coumarins and others [22]. With ecological functions ranging from defense against microbial pathogens or herbivorous animals until sunlight protection, they can have simple or complex structures, as shown in fruits, vegetables, bark, roots and leaves.

In red propolis, several of these compounds have been found as Elemicin, *trans*-anethole, Methyl eugenol [13,17]. Also, these can play an important role in cancer prevention, anti-inflammatory and antioxidant activities [23,24]. The Isoliquiritigenin is considered a red propolis marker. In a comparative study between Brazilian and Cuban red propolis, this compound was among the major constituents in both samples [13]. The benzopyran known as Dalbergin is a *D. ecastophyllum* marker, and its presence in Brazilian red propolis confirms the botanical origin [3].

2.3. Flavonoids

Flavonoids represent the most common and widely distributed group of phenolics in red propolis. These are among the most active compounds in this resin, which act in different physiological processes, and perform various functions, including antimicrobial [25], such as Quercetin and Chrysin [2]. The Formononetin, an isoflavonoid with estrogenic, antiradical, cytotoxic and antifungal activities, was found in red propolis samples from Paraíba state [15]. In mammals it is metabolized to Daidzein, which has been reported efficient against breast and prostate cancer cells [26]. Another important flavonoid is the Biochanin A, which is a relevant chemical marker identified in red propolis [13,15] and has important activities such as inhibitory effects on cancer cells, anti-inflammatory action and others [27].

According to Hernandez *et al.* [28], studies dealing with chemical composition of propolis can help establishing criteria for the quality control of the samples. The quality of propolis is checked by the Ministry of Agriculture, in Brazil, using parameters standardized [29], since the biological properties of propolis are linked directly to its chemical composition.

2.4. Pterocarpanes

Pterocarpanes are isoflavonoids derivatives that can be described as benzo-pyrano-furano-benzenes. The Medicarpin is well-known in this resin, which was identified using techniques such as ESI/MS, HPLC-PDA-ESI/MS and GC/MS [13,15,16]. Another important compound of this class is the Homopterocarpin, also identified in red propolis by GC/MS and HPLC-PDA-ESI/MS [13,16].

The pterocarpanes have shown potent cytotoxic activity over a panel of tumor cell lines, highest antifungal activity and also play an important role as phytoalexins [30].

2.5. Benzophenones

Benzophenones are phenolic of natural origin and restricted distribution. They have important biological properties such as

antitumor, antibacterial, plasmodicidal, anti-HIV and others. They can be used in products such as perfumes, soaps, sunscreens, preventing against ultraviolet light [31]. Some benzophenones derivatives such as Guttiferone E, Xanthochymol and Oblongifolin A are present in red propolis [13,17].

2.6. Triterpenes

The triterpenes are one of the largest classes of plant natural products. Simple triterpenes are components of surface waxes, specialized membranes and may potentially act as signaling molecules. Complex glycosylated triterpenes provide protection against pests and pathogens, and also they have important activities such as antitumor, anti-inflammatory, antibacterial and others [32]. Some triterpenes derivatives such as lupeol and β -amyryn can be identified by GC-MS and found in red propolis [17].

3. Pharmacological activities

Propolis has been systematically used in folk medicine by different civilizations over centuries. Studies confirm that propolis has a good therapeutic potential, especially antimicrobial, anticancer and antioxidant activities. The biological features are directly linked with the chemical composition, which can be a problem because of the variety of conditions, including the flora and harvest time, the processing technique, as well as the bee species [33]. The aim here is to highlight the pharmacological experiments and studies reported with red propolis, mainly from Brazil.

3.1. Antimicrobial activity

Red propolis demonstrated a notable antimicrobial activity against many microorganisms such as bacteria, fungi and protozoa. The antimicrobial activity was evaluated against *Streptococcus mutans* (*S. mutans*) and *Staphylococcus aureus* (*S. aureus*) where the chloroform fraction was the most active (minimum inhibitory concentration – MIC = 25–50 $\mu\text{g/mL}$) [16]. Cabral *et al.* [11] also verified antibacterial properties against *S. aureus*. The sub-fraction 4, obtained from an ethanolic extract of red propolis, presented the best activity (minimum bactericidal concentration – MBC = 31.7–62.5 $\mu\text{g/mL}$). Dausch *et al.* [3] described the antimicrobial activities of six samples of red propolis against *S. aureus*, four of them demonstrated higher inhibition of bacterial growth. The red propolis ethanol extract from Sergipe (Brazil) showed the highest antimicrobial activity for the three tested strains [*S. aureus* ATCC 33951, *S. aureus* ATCC 25923 and *Escherichia coli* (*E. coli*) ATCC 25922], and the MIC were (400–100) $\mu\text{g/mL}$, (50–25) $\mu\text{g/mL}$ and 400 $\mu\text{g/mL}$, respectively [34].

In a study developed by Oldoni *et al.* [12], chloroform fraction was active against *S. aureus* (MIC = 31.2–62.5 $\mu\text{g/mL}$), *S. mutans* and *Actinomyces naeslundii* (MIC = 62.5–125 $\mu\text{g/mL}$). The isoliquiritigenin was the most potent (MIC = 15.6–31.2 $\mu\text{g/mL}$).

Bispo Junior *et al.* [35] verified that the ethanol extract showed antimicrobial activity against Gram-positive (100%) and Gram-negative (62.5%) strains. All species analyzed [*Shigella flexneri*, *Proteus mirabilis*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *S.*

aureus, *Proteus vulgaris*, *Klebsiella pneumoniae*, *E. coli*] were susceptible to ethyl acetate fraction which demonstrated the best activity. Righi *et al.* [36] verified that methanol extract inhibited the growth of all tested microorganisms. The MIC (256 µg/mL) and MMC (512 µg/mL) were observed against *P. aeruginosa*, *Bacillus subtilis* and *Candida albicans* (*C. albicans*). This extract showed a higher MMC (1 024 µg/mL) against *Klebsiella pneumoniae*. Others MIC were: *E. coli* (512 µg/mL), *Salmonella typhimurium* (512 µg/mL), *Enterococcus faecalis* (*E. faecalis*) (512 µg/mL), *Proteus mirabilis* (512 µg/mL) and *Streptococcus pyogenes* (512 µg/mL). In addition, larger inhibition zones were obtained by the action of the ethanol extract (Brazilian red propolis) with (27.25 ± 0.25) mm (*S. mutans*) and (19.33 ± 0.94) mm (*Streptococcus sanguinis*) [37].

Lopez *et al.* [38] found that Brazilian red propolis (from Sergipe, Alagoas and Paraíba) presented a similar chemical profile to Cuban propolis and showed activity against Gram-positive and Gram-negative bacteria (MIC = 6.2–500 µg/mL). The antimicrobial tests presented a MIC below the cytotoxic concentration (50 µg/mL) for BALB/c 3T3 (murine fibroblast) and for HaCaT (human keratinocytes).

Virulent biofilms are responsible for a range of infections, including those occurring in the mouth. Dental caries is one of the most common and costly biofilm-dependent oral diseases, which afflicts children and adults worldwide [39]. Topical applications (800 µg/mL), containing neovestitol and vestitol, impaired the accumulation of biofilms of *S. mutans*. Also, the red propolis showed as effective as fluoride in reducing the development of carious lesions *in vivo* [40].

Regarding orthopedic implants, the four most prevalent bacterial species, accounting for over 75% of infections, are *S. aureus*, *Staphylococcus epidermidis*, *P. aeruginosa* and *E. faecalis*. Nanohydroxyapatite (nanoHA)-based surfaces containing Brazilian extracts of propolis (green and red) was investigated and showed a reduction of *S. aureus* activity at 6 µg/mL [41]. Also, Siqueira *et al.* [42] evaluated the activity of red propolis extract against strains of *E. faecalis* and it promoted inhibition zone of 12 and 16 mm with MIC of 18 000 mg/mL and MBC of 34 090 mg/mL.

Apart from vestitol and neovestitol aforementioned, other isolated molecules have also been tested for its antibacterial activity. In a recent study, the compound (6aS,11aS)-medicarpin exhibited the most potent antibacterial activity against *S. aureus*, *Bacillus subtilis* and *P. aeruginosa*, with MIC values of 16, 32 and 32 µg/mL, respectively [43]. Trusheva *et al.* [17] observed that isosativan and medicarpin are important antimicrobial compounds, especially concerning the activity against *C. albicans*, showing inhibitory zone of (15 ± 1) and (26 ± 0) mm, respectively. Also, the mixture of prenylated benzophenones demonstrated good activity against *S. aureus* (19 ± 1) mm.

Red propolis containing high concentration of prenylated and benzophenones compounds showed to be the most active extract against *Leishmania amazonensis*. Ethanolic extracts of propolis were capable to reduce parasite load as monitored by the percentage of infected macrophages and the number of intracellular parasites. The parasite load of macrophages was reduced by the extract (25 µg/mL), presenting no direct toxic effects on promastigotes and extracellular amastigotes [44].

The activity of red propolis against fungi has also been described in some studies. Oral candidiasis is an infection caused by *C. albicans*. It is known that saprobes microorganisms

depend on predisposing factors to become pathogenic. This type of infection is most common in immuno-compromised individuals and presented increasing incidence in recent years. Bezerra *et al.* [45] demonstrated in their study the antifungal action of the red propolis extract at 25% against *Candida*.

The dermatophytes are filamentous fungi belonging to three genera *Trichophyton*, *Microsporum* and *Epidermophyton* that are able to cause infection of the skin, hair and nails. The fungistatic activity of the red propolis alcoholic extract was determined for *T. rubrum* (8–128 µg/mL), *Trichophyton tonsurans* (32–128 µg/mL) and *Trichophyton mentagrophytes* (16–128 µg/mL). The fungicide activity of the same extract was observed in the concentrations of (128–256), (128–1024) and (256–512) µg/mL for the same species [46].

Recently, Neves *et al.* [47] analyzed the antimicrobial activity of Brazilian red propolis against the following bacteria and yeasts: *S. aureus* ATCC 13150, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *P. aeruginosa* ATCC 9027, *P. aeruginosa* ATCC P-12, *P. aeruginosa* ATCC P-03, *C. albicans* ATCC 76645, *C. albicans* LM P-20, *Candida tropicalis* ATCC 13803, *Candida tropicalis* LM 6, *Cryptococcus neoformans* ICB 59, *Cryptococcus neoformans* LM 2601. The hexane, acetate and methanol fractions of a variety of propolis inhibited all strains (MIC = 128–512 µg/mL for the bacteria and MIC = 32–1 024 µg/mL for the yeasts).

3.2. Antioxidant activity

The occurrence of many diseases is related to increases in the levels of free radicals, including cardiovascular, neurological diseases, cancer, osteoporosis, inflammation, diabetes and others [48]. In recent years, plants containing polyphenols showing antioxidant properties are target products used to control and prevent several diseases. In addition to the polyphenols, propolis contains an extensive range of other antioxidant compounds that interact with free radicals in body [49,50].

Many studies have reported antioxidant activity for flavonoids that is due to their ability to reduce free radical formation and to scavenge free radicals [51,52]. The hexane fraction of red propolis presented the highest concentration of total flavonoids and showed the best sequestering activity for the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) [16]. Cabral *et al.* [11] also found that the hexane fraction obtained from red propolis showed the highest antioxidant activity (74.4%), sequestering the free radical DPPH. In addition, Frozza *et al.* [15] demonstrated that the hydroalcoholic extract of red propolis has important DPPH scavenging ability (IC₅₀ 270.13 µg/mL). Also, Trusheva *et al.* [17] observed that the mixture of prenylated benzophenones showed significant radical scavenging activity against DPPH (49% inhibition). DPPH free radical scavenging activity has also been tested by Righi *et al.* [36] and the antioxidant activity of methanol extract of Brazilian red propolis (at maximum concentration 25 µg/mL) was 39.12%. In the β-carotene oxidation method, the methanol extracts (1.0, 1.5 and 2.0 mg/mL) gave 84.5%, 85.3% and 85.7% of antioxidant activity, in relation to rutin.

Oldoni *et al.* [12] observed an activity of 57% to chloroform fraction and 26% to ethanolic extract of propolis; the compound vestitol presented higher antioxidant activity (39.5%). More recently, the highest quantity of total phenols, flavonoids and the best antioxidant activity by ABTS were identified in the extract of red propolis (Sergipe), with values of

(300.36 ± 0.01) mg EAG/g, (57.60 ± 0.01) mg EQ/g and 98.50% ± 1.40%, respectively [34].

3.3. Anti-inflammatory activity

Inflammation is a natural response to a variety of hostile agents including parasites, pathogenic microorganism, toxic chemical substances, physical damage to tissue, among others [53]. The red propolis has also attracted interest for its anti-inflammatory properties, as observed by Cavendish *et al.* [54]. The pretreatment with the hydroalcoholic extract of red propolis (10 and 30 mg/kg) and formononetin (10 mg/kg) produced reduction in the number of abdominal writhes and the extract was more effective. All the extract doses (3, 10 and 30 mg/kg) inhibited the late phase (inflammatory pain) of formalin-induced licking. All doses of extract (3, 10 and 30 mg/kg) and formononetin inhibited the carrageenan-induced leukocyte migration. Also, Bueno-Silva *et al.* [40] verified an important inhibition activity against neutrophil migration caused by the ethanolic extract of red propolis, neovestitol and vestitol (10 mg/kg) in Male Balb/c mice.

In a recent study, Franchin *et al.* [55] investigated the mechanism of action of vestitol on the modulation of neutrophil migration in the inflammatory process. The LPS- or mBSA-induced neutrophil migration and the *in vivo* release of CXCL1/KC and CXCL2/MIP-2 were reduced by vestitol (1, 3 or 10 mg/kg). Likewise, the *in vitro* levels of CXCL1/KC and CXCL2/MIP-2 in macrophage supernatants were reduced by vestitol (1, 3, or 10 μM). Moreover, the administration of vestitol (10 mg/kg) reduced leukocyte rolling and adherence in the mesenteric microcirculation of mice. The pre-treatment with vestitol (10 mg/kg) in iNOS^{-/-} mice did not block its activity concerning neutrophil migration. With regard to the activity of vestitol (at 3 or 10 μM) on neutrophils isolated from the bone marrow of mice, there was a reduction on the chemotaxis of CXCL2/MIP-2 or LTB4-induced neutrophils and on calcium influx.

3.4. Healing activity

Propolis is an apitherapy product widely employed in natural medicine. Among the various therapeutic properties against a variety of conditions, its ability to heal tissues has been discussed in some studies. Albuquerque-Júnior *et al.* [56] observed that the collagen films with Brazilian red propolis were able to improve wound healing by modulating the collagen deposition process and the inflammatory evolution.

In another study, Almeida *et al.* [57] observed that the extract of red propolis provided decrease of the inflammatory severity of rodents, induced earlier replacement of type-III for type-I collagen, improved the epithelization rates and the myofibroblastic count was significantly increased in 14 and 21 days.

3.5. Cytotoxic activity

The search for new drugs against various types of cancer has led researchers to fractionate extracts and isolate compounds contained in propolis samples from different sources. Awale *et al.* [58] observed a cytotoxicity against human pancreatic cancer cells by the methanol extract of Brazilian red propolis (10 μg/mL). Brazilian red propolis ethanolic extract showed

cytotoxicity against human bladder cancer cells (IC₅₀ of 95 μg/mL) and induced apoptosis-like mechanisms [59]. Franchi Jr. *et al.* [60] demonstrated that red propolis was cytostatic in human cell lines of leukemia and induced apoptosis.

Ethanolic extract of red propolis showed cytotoxic activity for the human cervical adenocarcinoma (HeLa) cells with an IC₅₀ of 7.45 μg/mL [16]. Frozza *et al.* [15] analyzed the hydroalcoholic extract activity on human laryngeal epidermoid carcinoma cell (Hep-2), HeLa and human normal epithelial embryonic kidney (Hek-283) cell lines, with IC₅₀ 63.48 μg/mL, 81.40 μg/mL and > 150 μg/mL, respectively. A study conducted by Kamiya *et al.* [61] showed a reduction in the cellular viability of human breast cancer (MCF-7) by ethanol extract of Brazilian red propolis, through the induction of mitochondrial dysfunction, caspase-3 activity, DNA fragmentation and also induction of apoptosis through endoplasmic reticulum stress-related signaling.

The red propolis ethanol extracts (50 and 100 μg/mL) from Sergipe, Brazil, showed the lowest contents of viable cells in melanoma murine (B16F10) models [34]. Novak *et al.* [62] performed a study with the BRP-IV fraction that inhibited growth of tumor cell lines [IC₅₀ = (20.5 ± 2.4) to (32.6 ± 2.6) μg/mL] such as melanoma tumor xenografts in mice, acute promyelocytic leukemia (HL-60), human chronic myelogenous leukemia (K562), human multiple myeloma (RPMI 8226) and murine melanoma (B16F10). Already, the ethanolic extract induced cytotoxic effect with IC₅₀ of (29.7 ± 1.5) to (42.1 ± 8.7) μg/mL.

Li *et al.* [63] tested isolated compounds of red propolis against a variety of cell lines, among them 7-hydroxy-6-methoxyflavone exhibited the most potent activity against Lewis lung carcinoma - LLC (IC₅₀ 9.29 μM), murine B16-BL6 melanoma (IC₅₀ 6.66 μM), human lung A549 adenocarcinoma (IC₅₀ 8.63 μM) and human HT-1080 fibrosarcoma (IC₅₀ 7.94 μM) cancer cell lines. Other compound, the mucronulatol, was potent against LLC (IC₅₀ 8.38 μM) and A549 (IC₅₀ 9.9 μM) cell lines.

Oral carcinogenesis is a highly complex multi-focal process that occurs when squamous epithelium is affected by several genetic alterations. DMBA-induced oral squamous cell carcinomas growth was inhibited (40%) by hydroalcoholic extract (50 and 100 mg/kg) of Brazilian red propolis. Also, it promoted a 3-week delay in development of clinically detectable tumors in murine models (adult Swiss male mice, *Mus musculus*) [64].

4. Other pharmacological potential uses

Table 2 describes other pharmacological applications reported in literature of Brazilian red propolis.

5. Red propolis worldwide

Propolis is a natural product widely used by the world population due to its interesting properties and this has generated distinct research lines in several countries. The red type is found in Brazil, as previously described, but also in countries such as Cuba, Mexico, China and Nigeria.

Some studies are being developed in Cuba with respect to chemical composition and biological activity of this propolis. Fernández *et al.* [70], through GC-MS, analyzed seven samples of Cuban red propolis and some compounds were identified:

Table 2

Potential uses of red propolis.

Sample	Activity	Ref
Methanolic extract	Brine shrimp DL ₅₀ of 18.9 µg/mL, suggesting an antitumor activity.	[19]
Ethanollic extracts	Induced the differentiation of 3T3-L1 preadipocytes into adipocytes and enhanced the PPAR γ transcriptional activity, suggesting its usefulness in obesity prevention and treatment.	[65]
Ethanollic extracts	The ApoA-I-mediated cholesterol efflux in THP-1 macrophages was enhanced, beyond the induction of ABCA1 gene, indicating a potential use for prevention/treatment of cardiovascular disease.	[66]
Ethanollic extracts	The potential anticancer was evaluated on Hep-2 and Hek-293 cells. The mechanism was assessed by proteomics, which was associated to cell metabolism and the predominant molecular function was catalytic activity.	[67]
Hydroalcoholic extract	The anticancer mechanism was evaluated on Hep-2. 177 proteins were identified and most were down-regulated (IC ₅₀ 120 µg/mL): GRP78, PRDX2, LDHB, VIM, TUBA1A. Late apoptosis in a dose-dependent manner was induced also.	[68]
Hydroalcoholic extract	The extract was tested in rats with renal ablation (150 mg/kg/day in drinking water) for 60 days reducing hypertension, proteinuria, oxidative stress, renal macrophage infiltration, serum creatinine retention and glomerulosclerosis. The renoprotective effects might be related to the reduction of oxidative stress and renal inflammation.	[69]

Formononetin; Medicarpin; Vestitol; Neovestitol; Isoiquiritigenin; Liquiritigenin; Homopterocarpin; 3-Hydroxy-8,9-dimethoxypterocarpin; 7-O-Methylvestitol; 3,10-Dihydroxy-9-methoxypterocarpin; 3,4-Dihydroxy-9-methoxypterocarpin and 3,8-Dihydroxy-9-methoxypterocarpin.

Piccinelli *et al.* [13] verified that some isoflavones, isoflavans, pterocarpan and compounds such as isoliquiritigenin, liquiritigenin and naringenin are present in both Brazilian and Cuban propolis, as well as in *D. ecastophyllum* exudates. On the other hand, there are compounds present only in Brazilian propolis: Xanthochymol, Oblongifolin A and Guttiferone E.

In another study, Cuesta-Rubio *et al.* [71] analyzed methanolic extracts of Cuban propolis and observed that the red propolis presented a more complex composition and the isoflavonoids are the main constituents, highlighting Formononetin and Medicarpin as markers.

Ledón *et al.* [72] observed the antipsoriatic, anti-inflammatory and analgesic effects of Cuban red propolis ethanollic extract through several tests. In the model of acetic acid-induced writhings the extract presented significant analgesic effect. The anti-inflammatory activity was observed in tests such as peritoneal capillary permeability, cotton-pellet granuloma assay and croton oil-induced edema in mice. Also, it induced the formation of granular layer demonstrating the antipsoriatic action.

Also, Rodríguez *et al.* [73] verified the action of an ethanollic extract of Cuban red propolis against hepatitis induced by galactosamine, which was able to prevent hepatocytes alterations and it induced reversion of the increased activity of alanine aminotransferase and malondialdehyde concentration.

In another study with Cuban red propolis, the antibacterial, antiprotozoal and antifungal properties were evaluated and can be associated with the chemical composition. The samples showed the following IC₅₀: 4.4–25.9 µg/mL (*S. aureus*), > 64 µg/mL (*E. coli*), > 64 µg/mL (*C. albicans*), 1.2–8.3 µg/mL (*Trypanosoma brucei*), 1.2–6.4 µg/mL (*Plasmodium falciparum*), 2.5–9 µg/mL (*Trypanosoma cruzi*), 14.9–39.4 µg/mL (*Trichophyton rubrum*) and 3.3–16.1 µg/mL (*Leishmania infantum*) [74].

The red Mexican propolis was studied by Lotti *et al.* [75]. They verified the chemical composition and isolated three new compounds: (Z)-1-(2'-methoxy-4',5'-dihydroxyphenyl)-2-(3-phenyl)propene, 3-hydroxy-5,6-dimethoxyflavan and 1-(3',4'-dihydroxy-2'-methoxyphenyl)-3-(phenyl)-propane, together with Arizonicanol A; Vestitol; Pinocembrin; Mucronulatol; Melilotocarpin A; Melilotocarpin D and 7-Hydroxyflavanone.

Hatano *et al.* [76] studied the red propolis from Shandong, China. Ethanol extracts (EE) showed strong antioxidant activity. The total polyphenol content, the flavonoid content, DPPH and ABTS radical scavenging activity, ferric reducing activity power (FRAP assay) and the oxygen radical absorbance capacity (ORAC) values were (433.8 ± 1.7) mg/g of EE, (129.6 ± 1.1) mg/g of EE, 98.8% ± 1.0%, 90.9% ± 0.6%, (89.2 ± 3.8) µg/mL and (14900 ± 443) µmol Trolox equivalents/g of EE, respectively. It was also possible to identify the major components in the EE sample, by HPLC: Apigenin (15.4 ± 0.8) mg/g of EE; Benzyl caffeate (21.1 ± 2.1) mg/g of EE; Caffeic acid (3.8 ± 0.4) mg/g of EE; Chrysin (47.2 ± 3.7) mg/g of EE; Cinnamic acid (4.2 ± 0.6) mg/g of EE; Cinnamyl caffeate (7.6 ± 0.6) mg/g of EE; *p*-Coumaric acid (6.8 ± 0.7) mg/g of EE; 3,4-Dimethoxycinnamic acid (18.8 ± 1.2) mg/g of EE; Ferulic acid (9.8 ± 0.5) mg/g of EE; Galangin (101.6 ± 4.5) mg/g of EE; Phenethyl caffeate (32.7 ± 2.3) mg/g of EEP; Pinobanksin (3.0 ± 0.3) mg/g of EEP; Pinobanksin 3-acetate (85.7 ± 3.4) mg/g of EEP; Pinobanksin 5-methyl ether (17.2 ± 1.1) mg/g of EEP; Pinocembrin (38.2 ± 2.8) mg/g of EEP; Pinostrobin (4.0 ± 0.5) mg/g of EEP; and Tectochrysin (10.6 ± 1.1) mg/g of EEP.

The Nigerian red propolis was evaluated with respect to the activity against *Trypanosoma brucei* and its chemical composition. Some compounds were identified: Vestitol; Calycosin; Pinocembrin; Macarandin; Medicarpin; Liquiritigenin; 8-Prenylnaringenin; 6-Prenylnaringenin; Propolin D and Riverinol. The compounds showed anti-trypanosomal activity with EC₅₀ values from 4.2 µg/mL for the crude extract to 16.6 µg/mL for Riverinol [77].

6. Conclusion

This review highlighted the chemical composition and the biological features of red propolis. The potential of this special bee resin has been demonstrated by its broad spectrum of therapeutic properties. However, due to its distinct and complex chemical constitution, the development of further research is important, ensuring its safe use.

Conflict of interest statement

We declare that there is no conflict of interest.

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