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REVIEW

A review on the anti-inflammatory activities of Brazilian green, brown and red propolis

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Abstract

Humanity has used propolis since ancient times, and its use as a food supplement has significantly increased. Several reports on propolis´ biological activity and toxicity have highlighted its anti-inflammatory properties, unlike many natural food supplements. This review addresses the anti-inflammatory roles of Brazilian green, brown, and red propolis produced by *Apis mellifera*, their extracts, isolated compounds, and their mode of action. Despite advances in anti-inflammatory therapies, the development of inflammatory processes in several diseases has been a concern for centuries. Demands for new anti-inflammatory drugs have led to studies on propolis products as diet components to treat and prevent inflammatory disorders. Brazilian green, brown, and red propolis are alternatives for obtaining extracts and compounds of valuable anti-inflammatory properties.

Practical applications

Currently, propolis is a food supplement, and to the best of our knowledge, several studies have shown that despite advances in anti-inflammatory therapies, the inflammatory process continues to be a significant concern. However, due to the demand for new anti-inflammatory drugs, propolis products as dietary components can be used to treat and prevent inflammatory disorders.

KEYWORDS
anti-inflammatory, *Apis mellifera*, chemical composition, natural supplements, propolis

1 | INTRODUCTION

Propolis is a complex natural resin collected by bees and composed of plants' exudates, pollen, wax, and enzymes (Costa et al., 2020; de L. Paula et al., 2020; Pereira et al., 2002). It currently can be found in many pharmaceutical products from several countries. In addition, various herbal drugs products contain propolis in their composition (Dobrowolski et al., 1991; Kaminski & Absy, 2006; Sawaya et al., 2006). Since the XII century, it has occupied a central place among herbal drugs due to its antioxidant, antibiotic, and anti-inflammatory activities. Propolis extracts treat inflammatory conditions in both local and systemic applications. Several studies have reported its beneficial effects on cardiac protection, glucose regulation, lipoprotein metabolisms, regulation of gene expression, and decreased activity of inflammatory cytokines (Fernandes et al., 2015; Samadi et al., 2017; Silva et al., 2008). Its

biological activities depend on its chemical compositions, which vary in function of its botanical source and geographic region. In general, propolis is composed of wax, essential and aromatic oils, and compounds such as flavonoids, acid phenethyl ester cinnamic acid derivatives, and terpenoids (Castro, 2001; Gómez-Caravaca et al., 2006). Flavonoids and cinnamic acid derivatives are well known for their anti-inflammatory properties (Borrelli et al., 2002; de L. Paula et al., 2021; de Souza Silva et al., 2021), which are associated with the anti-inflammatory activity of propolis extracts and products. Based on data from the literature, this article reviews and discusses the uses of red, brown, and green Brazilian propolis as anti-inflammatory bee products and highlights pharmacological studies on reductions in the inflammatory process using this functional food supplement (Ccana-Ccapatinta et al., 2020; Rodrigues et al., 2020; Santos et al., 2021).

2 | METHODOLOGY

We conducted a qualitative literature search through available online databases. The keywords: "Brazilian red, green, and brown propolis and inflammation" focused on propolis's chemical composition and pharmacological activity to select articles. The sites consulted were Scopus, Web of Science, Capes Periodicals, Medline, SciFinder, Pub-Med, Science Direct.

3 | CHEMICAL COMPOSITION

The propolis depend on geographic region, which determines its biological activity and metabolite composition (Bankova et al., 2000; Sforcin et al., 2000) is associated with the flora at the collection site and changes with the region's seasonality. The species found in Brazil show differences in their chemical composition and pharmacological activities, justified by the biodiversity of Brazil (Bankova, 2005). The main types of propolis found in Brazil include green, red, and brown. Many compounds were isolated from propolis samples and analyzed by different methods (Rufatto et al., 2017).

Brazilian brown propolis characteristically contains diterpenes such as clerodane, 18,19-epoxy-2-oxocleroda-3,12(E),14-triene-6,18,19-triol 18,19-diacetate 6-benzoate (1), isocupressic acid (2), 15-acetoxy isocupressic acid (3), (E)-communication acid (4), (Z)-communication acid (5), and abietic acid (6). All such compounds are derived from araucaria from Parana in Brazil, their main botanical source (Tazawa et al., 2016). Mexican brown propolis contains pinocembrin (7), chrysin (8), galangin (9), alpinetine (10), 5-methyl-pinobanksin ether (11), dilenethine (12), isorhamnetin (13), 5-methylgalangin ether (14), 5-methylchrysine (15), ferulic acid (16), syringic acid (17), and caffeic acid (18), whose main botanical source is probably the typical Populus species North American countries (Figure 1). A brown propolis variation of similar chemical composition is found in Europe and is often used as a food supplement (Rivero-Cruz et al., 2020).

Baccharis dracunculifolia DC (Asteraceae), known as "broom," "rosemary of the field," or "rosemary of broom," is the botanical origin of Brazilian green propolis (Barroso, 1976; Menezes, 2005). It is widespread in South America, to Brazilian Cerrado, Atlantic Forest, and Pampas biomes, and in countries such as Argentina, Uruguay, Paraguay, and Bolivia (Moise & Bobiş, 2020). In addition, Araucaria angustifolia and Eucalyptus citriodora in Brazil also botanical sources of green propolis (Cazella et al., 2019). The metabolite composition of propolis counts on several elements (e.g., distinct varieties of plant sources collected by bees, geographical basis, and period of the year of their production) (Beserra et al., 2020). The main compounds isolated from Brazilian green propolis (Figure 2) are baccharin (19), artepillin C (20), kaempferide (21), and coumaric acid (22) (Moura et al., 2011; Oliveira et al., 2014; Przybyłek & Karpiński, 2019; Szliszka et al., 2013). The extract of Baccharis dracunculifolia leaves and Brazilian green propolis has anti-inflammatory, antibacterial, immunomodulatory, antigenotoxic, and antimutagenic effects (Wu et al., 2020). Among all the biological effects of green propolis and its botanical source, the anti-inflammatory effect stands out (Franchin et al., 2018; Hori et al., 2013; Paulino et al., 2008).

A novel type of propolis, named Brazilian red propolis, has drawn the of investigators and international companies and is the second most commercialized type in Brazil (Ccana-Ccapatinta et al., 2020). Its botanical sources are resin exudates from *Dalbergia ecastaphyllum* (L) Taub. (Leguminosae), a plant near mangroves that produces a red resin collected by bees (Ccana-Ccapatinta et al., 2020). Red Propolis contains isoflavones formononetin (23) and biochanin A (24) as the main components of the flavonoids class. Hesperetin-7-rhamnoglucoside (25), vestitol (26), neovestitol (27), and daidzein (28) are other isolated flavonoids (Bueno-Silva et al., 2013). The benzophenones guttiferone E (29), xanthochymol (30), and oblongifolin A (31) are isolated from the lipophilic extract from red Propolis (Rufatto et al., 2017). Such isolated compounds have important antitumor, antibacterial, and anti-inflammatory properties.

Phenolic compounds such as elemicin (32), trans-anethole (33), methyl eugenol (34), and isoliquiritigenin (35) are also isolated from red Propolis (Alencar et al., 2017), whose main class of compounds includes phenolic, benzophenones, and flavonoids compounds, of which many displays anti-inflammatory properties and are considered red propolis chemical markers (Figure 3).

4 | ANTI-INFLAMMATORY ACTIVITY OF GREEN PROPOLIS

In Brazil, green propolis is widely utilized as an herbal drug to treat inflammation, liver dysfunction, and stomach ulcers due to its biological activities (Menezes, 2005). The evaluation of green propolis ethanol extracts collected in various parts of Brazil conducted by Machado et al. (2016) revealed both metabolites and biological activities of Brazilian green propolis depend directly on the geographic region of collected resins by bee. Many scientific papers have concentrated on the anti-inflammatory potential of

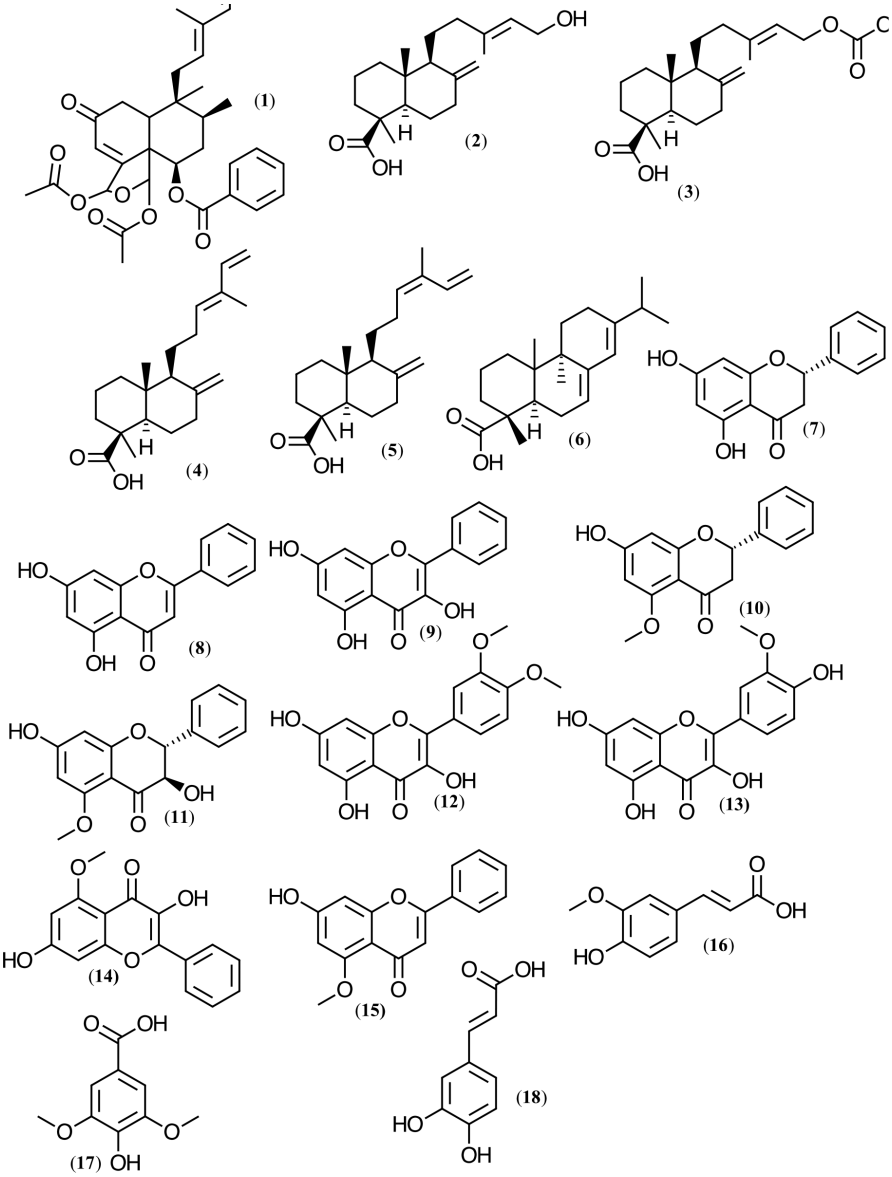

FIGURE 1 Compounds isolated and identification from brown propolis

green propolis. Menezes (2005) reported the anti-inflammatory action of *B. dracunculifolia* administered simultaneously with zymosan 500 μg inflammation inducer. The authors tested a crude aqueous extract prepared from *B. dracunculifolia* leaves (botanical source of green propolis) at 200 mg/kg in guinea pigs for 1 hr and 5 min before injecting the inducer. This study demonstrated the importance of the botanical source of propolis in biological activities. Therefore, it is necessary to characterize the propolis sample and its botanical source since they can secondary metabolites and biological effects.

Soleimani et al. (2021) reported a series of investigations on the action of green propolis in the treatment of Inflammatory bowel disease (IBD); due to its potent anti-inflammatory properties and capacity for modulating both immune response and the intestinal microbiome. According to the authors, the primary mechanism of action is probably mediated by preventing some transcription factors and associated proteins. IBD is a term for Crohn's disease and ulcerative colitis, which are two chronic disorders indicated by inflammation of the gastrointestinal tract. In addition, the utilization of green propolis extract can provide relief to those who suffer from such disorders.

Machado et al. (2012), Wang et al. (2018), Yuan et al. (2020), and Soleimani et al. (2021) demonstrated the action of green propolis extract and its isolated compounds such as baccharin (19), artepillin C (20) and kaempferide (21) on several fronts of anti-inflammatory action (e.g., reductions in the manifestation of inflammatory genes, production of nitric oxide, and blocking of the manifestation of proinflammatory cytokines). Moreover, the extract increased anti-inflammatory factors such as mucosal protective agents like luminal mucin production and expression of anti-inflammatory cytokines (Machado et al., 2012; Soleimani et al., 2021; Wang et al., 2018; Yuan et al., 2020).

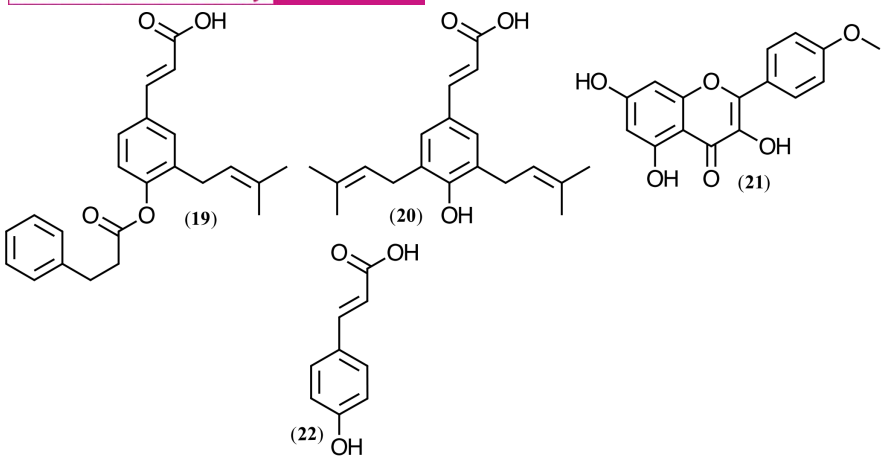

FIGURE 2 Main compounds isolated from green propolis

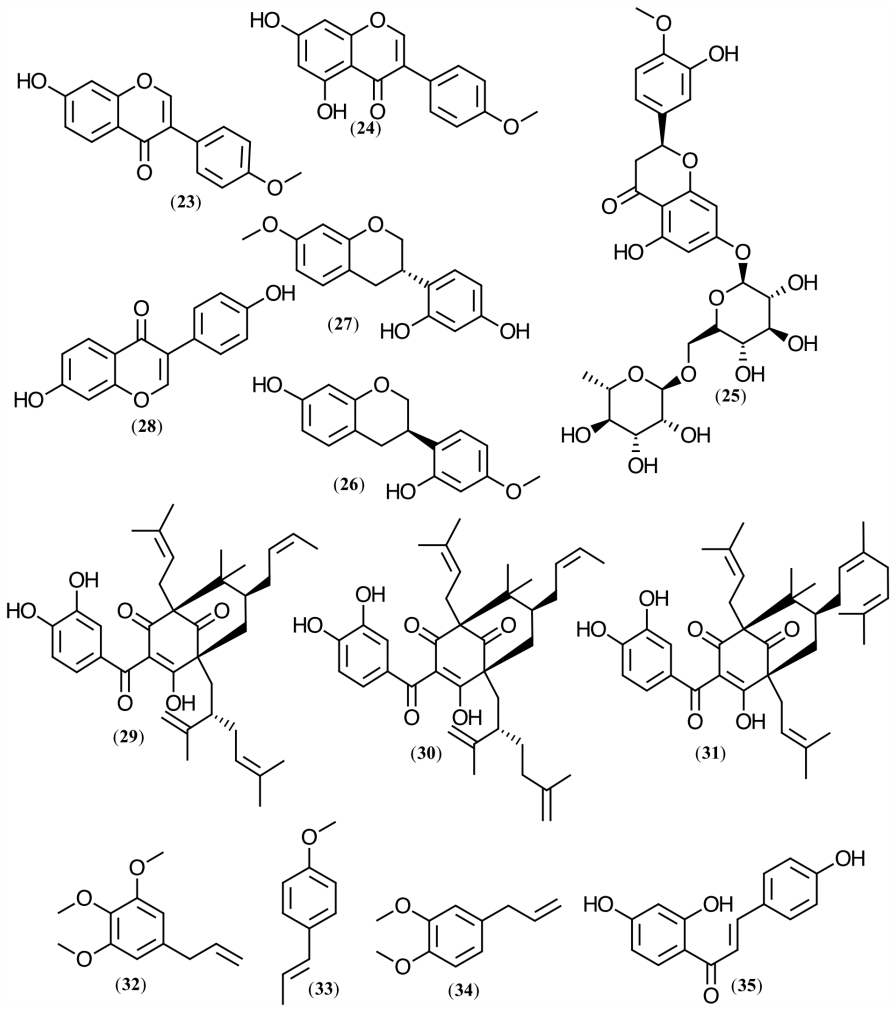

FIGURE 3 Compounds isolated and identification from red propolis

Cytokines are essential substances for the inflammatory response, which help wound healing. However, the exaggerated production of proinflammatory cytokines (IL-6, IL-1, and TNF-α) from a lesion can manifest itself in a structured way with the presence of metabolic disorders. Wang et al. (2018) and Mariano et al. (2018) observed the administration of a 300 mg/kg daily dose of propolis for 7 and 17 days, respectively, reduced not only the inflammatory genes (interleukin 1 beta [IL-1β], interleukin 6 [IL-6], monocyte chemoattractant protein 1 [MCP-1]) but also increased the expression of anti-inflammatory cytokines and luminal mucin levels in mice.

Machado et al. (2012) demonstrated the administration of propolis extracts (5 mg/kg) by oral route for 6 days improved the inhibition of proinflammatory cytokines and increased anti-inflammatory cytokines in treated mice, indicating an immunomodulatory action.

Wang et al. (2018), Yuan et al. (2020), and Soleimani et al. (2021) compared the anti-inflammatory effect of Brazilian green propolis with that of Chinese green propolis under the same conditions. Propolis ethanolic extract in 0.5% sodium carboxymethylcellulose (0.1 mL) was administered intragastrically rodents affected by an inflammatory reaction induced by lipopolysaccharide. A pretreatment with ethanol extract of Brazilian and Chinese propolis sample reversed serum levels of TNF-α, IL-6, and IL-1β after LPS injections (Yuan et al., 2020). The attenuating effects of both propolis sample were similar, with no significant difference between them. According to Yuan et al. (2020), the inhibitory effect of both propolis on the expression of LPS-dependent cytokines might be due to the existence of active flavonoids and the cinnamic acid derivatives caffeic acid (18) and artepillin C (20). Chromatographic analysis of Chinese and Brazilian propolis sample performed by HPLC-DAD/Q-TOF-MS revealed the presence of kaempferol in both samples, caffeic acid (18) in Chinese propolis, and artepillin C (20) in Brazilian propolis (Wang et al., 2018), thus evidencing the importance of bioactive metabolites present in the extract for the modulation of biological activity.

Szliszka et al. (2013) investigated the metabolic composition and the anti-inflammatory action of the ethanol extract of Brazilian green propolis on a J774A.1 macrophages culture stimulated by LPS. The objective was to extend the knowledge of the anti-inflammatory action mechanism of such extract and help its application in alternative treatments. The authors identified artepillin C (20), kaempferide (21), and their derivatives as the major phenolic components of green propolis. Green propolis inhibited the synthesis of cytokines and the production of nitric oxide, TNF-α in J774A.1 macrophages culture. The authors argued that propolis affected nonspecific immunity via modulation of macrophage activity. Macrophages are cells of the immune system that protect it against microbial disorders and damaged tissue. Their essential functions involve antigen presentation, phagocytosis, and various mediating inflammatory processes.

The hydroalcoholic extract of green propolis inhibited inflammation in animals provided with a low-protein diet. Miranda et al. (2019) administered 500 mg/kg daily doses of green propolis extract associated with a low-protein diet in mice for 1–2 weeks, which led to weight reduction and keeping of total serum protein levels after 15 day-treatment. In addition, the green propolis extract in vivo studies of showed anti-inflammatory action in the liver. Rimbach et al. (2017) encapsulated it in γ-cyclodextrin (γCD) and fed mice for nearly 3 months. Such a differentiated diet did not influence the food input or body composition of the mice and significantly induced the expression of the hepatic ferritin gene. The authors concluded that green propolis extract acts as hepatoprotection against chronic inflammation.

The anti-inflammatory action of green propolis extract was observed by Xu et al. (2020) at 5, 10, and 20 μg/mL by reducing the levels of inflammatory cytokine. Further analysis of the extract revealed a new compound, namely p-coumaric acid ester of 5-isoprenyl caffeic acid (18), and, including artepillin C (20) and kaempferide (21). The metabolic composition of ethanolic extracts of Brazilian green propolis was analyzed by UPLC/Q-TOF-MS/MS.

Zaccaria et al. (2017) were the first to show green propolis' hydroglyceric extract exerted an anti-inflammatory action under physiological circumstances and decreased the manifestation of pro-inflammatory cytokine via an epigenetic action. This effect indicates that green propolis has a protective influence on healthy individuals, preventing the evolution of chronic inflammation, which is a typical pathological cause numerous inflammatory disorder. Gastroprotective and anti-inflammatory properties were also promoted by the hydroalcoholic extract and artepillin C (20) (Costa et al., 2020).

Artepillin C (20) is the main compound of Brazilian green propolis. Paulino et al. (2008) estimated the absorption and bioavailability of artepillin C (20) in mouse plasma through chromatographic analysis and GC–MS technique after a single 10 mg/kg oral dose. Artepillin C (20) had 38% of inhibition after 360 min in vivo paw edema, reduced the number of neutrophils during peritonitis with IC50 of 0.9 (0.5–1.4) mg/kg, and reduced prostaglandin E2. In in vitro models, artepillin C (20) (3, 10, and 100 μM) the nitric oxide production, whereas, in HEK 293 cells, it reduced NF-κB activity, suggesting an anti-inflammatory action, especially in the critical phase of inflammation. Artepillin C (20) produces anti-inflammatory action mediated by inhibiting prostaglandin E2 and NO via NF-κB modulation. Moreover, it is bioavailable by oral administration and regulates inflammasomes, responses to stress signals, toxins, and microbial infections. Hori et al. (2013) observed that green propolis extract did not show toxicity to cells in tests with 30 μg/mL doses after 18 hr-treatment.

Thereby it was evident that different extracts of green propolis and its main compounds showed anti-inflammatory activities, which confirms the immense potential of these extracts and isolated metabolites. However, it is necessary to observe possible additive and synergistic effects that may be present. Therefore, the best alternative at the moment would be to use green propolis as an extract (Table 1).

5 | ANTI-INFLAMMATORY ACTIVITY OF RED PROPOLIS

Several studies have shown red propolis extracts act anti-inflammatory medications utilized as positive controls in investigations (Bankova, 2005), and flavonoids, flavones, phenolic acids, and esters are their main compounds with anti-inflammatory activity (Bankova, 2005). Cytokine TNF-α is related to an inflammatory process that stimulates neutrophil migration and increases adhesion molecule expression by endothelial cells, which is directly associated with inflammatory processes (White, 1999). In addition, the TNF-α modulation slows the progression of inflammatory diseases (Bradding & Holgate, 1996). moreover, TNF-α and IL-1β are involved

TABLE 1 Anti-inflammatory activity of extracts and compounds from Brazilian green propolis

Type/compounds	Model	Dose	Discovery	References
Polyphenol-rich of Brazilian propolis	Male Sprague Dawley rats with dextran sulfate sodium-induced colitis	300 mg/kg	Decreased expression of inflammatory genes; increased anti-inflammatory cytokines	Wang et al. (2018)
Green propolis hydroalcoholic extract	Mice with dextran sodium sulfate -induced colitis	3 mg/kg 30 mg/kg 300 mg/kg	Decreased of colon length shortening. Increased of mucin levels	Mariano et al. (2018)
Artepillin C (**20**)	Male Swiss mice carrageenan-induced paw edema model	0.1 mg/kg 1 mg/kg 10 mg/kg	Decrease of edema. Reduction of neutrophils number; decrease in prostaglandin E2 level	Paulino et al. (2008)
Green propolis ethanolic extract	RAW 264.7 cells	25 μM 50 μM 100 μM	Inhibition of IL-1β, IL-3, IL-4, IL-5, IL-9, IL-12p40, IL-13, IL-17, TNF-α, G-CSF, GM-CSF, MCP-1, MIP-1α, MIP-1β, RANTES, KC and NF-κB	Szliszka et al. (2013)
Kaempferide (**21**)	Male rats carrageenan-induced paw edema model	10 mg/kg	Reduction of the volume of the paw edema. Reduction of infiltrates, cellularity and area of the injured tissue	Almeida-Junior et al. (2019)
Aqueous green Propolis extract	Swiss mice LPS-Induced	5 mg/kg	Inhibition of proinflammatory cytokines; Increased of anti-inflammatory cytokines	Machado et al. (2012)
Ethanol extracts of Brazilian green propolis	Cells culture	5 μg/mL 10 μg/mL 20 μg/mL	Decreased the levels of inflammatory cytokine protein tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)	Xu et al. (2020)

in inflammatory events and several inflammatory diseases. Other essential factors in an inflammatory process are the chemokine receptor CXCR2, which activates CXCL2/MIP-2 and CXCL1/KC chemokines (Bradding et al., 1995; Roche et al., 2007).

Red propolis extract is a promising anti-inflammatory leukocytes along with KC, MIP-2, IL-1β, and TNF-α (Bueno-Silva et al., 2016). A treatment by subcutaneous injection of the extract at 10 mg/kg in mice prevented the migration of neutrophils and inhibited the release of inflammatory mediators (Bueno-Silva et al., 2016). The extract at 0.01, 0.1, and 1 μg/mL stimulated the inhibition of pro-inflammatory neutrophils without affecting cell viability. The extract at 1 μg/mL also decreased MIP-2-induced calcium influx (Bueno-Silva et al., 2016), pro-inflammatory cytokines, and inhibited several genes that control the inflammatory response (Bueno-Silva et al., 2016; Liu et al., 2009; Liu et al., 2014).

Crude hydroalcoholic extract of Brazilian red propolis (80:20, v/v) was administered to male mice at a daily dose of 10 and 100 mg/kg, after which both the biological activity and the safe dose were determined (Corrêa, Schanuel, Moura-Nunes, Monte-Alto-Costa, & Daleprane, 2017). The extract reduced NF-kB phosphorylation and, consequently, reduced the expression of TNF-α in the group treated with red propolis extract (Corrêa, Schanuel, Moura-Nunes, Monte-Alto-Costa, & Daleprane, 2017). The extract protected the group from the effect of acetic acid-induced ulcerative colitis (Bezerra et al., 2017). Ulcerative colitis is a common inflammatory bowel disease. Male rats treated for 7 days had colitis induced at day seven. Animals were randomly grouped into vehicle-treated and treated with 10 and 100 mg/kg of the extract (Bezerra et al., 2017). The study suggested that such an extract was non-toxic. Histopathological analysis of the colons of vehicle-treated animals showed tissue damage (Bezerra et al., 2017). Oral administration of the extract reduced tissue damage, indicating its chemopreventive role in the progression of colitis in rodents (Bezerra et al., 2017). In addition, the extract showed a modulating effect on the intensity of the inflammatory response because the content of MPO found in the tissues was reduced, which suggests an anti-inflammatory effect. Moreover, inhibition of expression of inducible nitric oxide synthase also attenuated ulcerative colitis due to the anti-inflammatory effect (Bezerra et al., 2017).

Cavendish et al. (2015) demonstrated red propolis extract's antinociceptive and anti-inflammatory action in an experimental model of abdominal writhes induced by acetic acid in rodents. Intraperitoneal (i.p.) acetic acid injection-induced abdominal writhes were treated orally with the extract (Cavendish et al., 2015). The extract showed antinociceptive and anti-inflammatory activities (Cavendish et al., 2015), which reduced abdominal constrictions, suggesting that it can decrease the inflammatory response at doses of (3, 10 and 30 mg/kg of extract). The extract also inhibited neurogenic pain at more elevated doses (10 and 30 mg/kg) (Cavendish et al., 2015).

Approaches for photoprotection include natural anti-inflammatory substances and crude extracts into sunblock. The oral administration of antioxidant and anti-inflammatory extract is

also used (Das et al., 2013). Batista et al. (2018) demonstrated the photoprotective action of Brazilian red propolis hydroalcoholic extract in a rodent model through antioxidant and anti-inflammatory mechanisms. The effect observed was attributed to isoflavonoids in red propolis, which present antioxidant and anti-inflammatory action.

When administered topically, forms containing red propolis extract had a protective action against UVB radiation and reduced tissue MPO levels suggesting anti-inflammatory activity. On the other hand, oral administration did not increase protection during treatment. Nevertheless, it had a chemoprotective effect, probably due to the presence of biochanin A (24), daidzein (28), and formononetin (23) present in the extract. Because of such findings, Brazilian red propolis hydroalcoholic extract can be considered promising for incorporation into cosmetic formulations for photoprotection (Batista et al., 2018). For example, red propolis extract from Cuba applied at 50 mg/kg exerted an anti-inflammatory effect on cotton-pellet granuloma assay and, at 2.5 μL, on an edema oil-induction assay in rats (Ledón et al., 1997).

Among the metabolites from Brazilian red propolis, Formononetin (23), vestitol (26), and neovestitol (27) had their anti-inflammatory activity evaluated. Vestitol (26), an isoflavonoid, stood out for its anti-inflammatory activity (Franchin et al., 2016), modulating the neutrophil migration in the inflammatory process. Bueno-Silva et al. (2013) administered it at doses of 1, 3, or 10 mg/kg subcutaneously in mice. Bueno-Silva et al. (2013) reported a reduction in the release of chemokines by vestitol (10 mg/kg) (26), demonstrating its modulatory capacity for the release of KC and MIP-2 chemokines. It also reduced the levels of chemokines in vitro at doses 1, 3, and 10 μM. Its direct action on neutrophils showed that in blood and bone marrow neutrophils, the reduction in the LTB4 mediator was significant. Therefore, vestitol (26) (10 μM) reduced calcium influx in neutrophils stimulated by MIP-2 and LTB4. When evaluating the NO increase in the reduction of neutrophil migration, it suggested that the anti-inflammatory activity of vestiol (26) is independent of NO production. This study showed that vestitol (26) has good anti-inflammatory properties (Bueno-Silva et al., 2013).

Franchin et al. (2016) evaluated Neovestitol (27), an isoflavonoid obtained from the hydroalcoholic extract of red propolis. In the in vivo model of acute and chronic inflammation induced intraperitoneally by LPS, mice pretreated with neovestitol (27) at 1, 3, and 10 mg/kg sc showed a reduction in neutrophil migration. LPS-induced inflammation is related to the effect of reduced expression of ICAM1. Neovestitol (27) also increased nitric oxide levels, corroborating the ICAM-1 expression data. However, in vitro results showed that cellular exposure to neovestitol (27) has a nitric oxide-dependent activity that does not directly inhibit ICAM-1. The activity evaluated in collagen-induced arthritis showed a reduction in the clinical scores of animals with arthritis by decreasing the IL-6 cytokines involved in the inflammatory action. Such a reduction is related to the previously reported increase in nitric oxide levels. Results showed anti-inflammatory activity involving the nitric oxide pathway and ICAM-1 suppression (Franchin et al., 2016).

Formononetin (**23**), the main compound of polar extract of red propolis, also showed anti-inflammatory and antinociceptive activities in mice after oral administration (Cavendish et al., 2015). The compound inhibited the formalin induced inflammatory edema. At 10 mg/kg, it had an antinociceptive action on the generated paw licking reaction (Cavendish et al., 2015).

The results show the potential of red propolis extracts and compounds for use in the composition of several propolis-based products, thus helping treatments of inflammation (Boschelli et al., 1995) (Table 2).

6 | ANTI-INFLAMMATORY ACTIVITY OF BROWN PROPOLIS

Sartori et al. (2012) described the protective effect of the hydroalcoholic extract of brown propolis from Santa Flora city in southern Brazil; in acute vaginal lesions induced by the herpes simplex virus in female mice. It was observed to have a protective effect since brown propolis extract reduced lesions and tissue damage. It effectively attenuated extravaginal lesions, avoiding the progression of the lesion, and prolonging the animals' life. It also reduced inflammation in both epidermis and dermis and maintained normal epithelialization with no morphological changes in the dermis, indicating a decrease in viral infection. The lack of studies on the anti-inflammatory activity of brown propolis is justified because such propolis is not yet widely known.

7 | OVERVIEW OF PROPOLIS AND ANTI-INFLAMMATORY EXPERIMENTS

This review cited articles that investigated brown, green, and red propolis extracts and their compounds e.g., flavonoids, terpenoids, and phenolic compounds with supposed anti-inflammatory activity, with an effect superior to the drugs used (Alencar et al., 2007; Berretta et al., 2012; Moura et al., 2011; Pereira et al., 2021; Reis et al., 2000). Some researchers use protocoled animal models to prove those activities with respected ethical principles.

Several models have been described and adapted for studies of the inflammatory response and the mechanisms involved. Experimental models of inflammatory bowel diseases are widely used and generally divided into four categories: spontaneous colitis, chemical agent-induced colitis (e.g., acetic acid), dextran sulfate sodium and formalin, adoptive transfer, and genetic modification (Hibi et al., 2002). The chemical agent-induced colitis model is the most used for studies of the anti-inflammatory activity of Brazilian propolis. Some of mimic individuals with acute or chronic inflammation (Clapper et al., 2007), which is essential since the consumption of propolis as a food supplement occurs in many countries. The injection model of an irritant such as acetic acid and formalin into the peritoneal cavity can obtain important information about the anti-inflammatory capacity of propolis. However, different

TABLE 2 Anti-inflammatory activity of extracts and compounds from Brazilian red propolis

Type/compounds	Model	Dose	Discovery	References
Extract ethanolic	Neutrophil migration into the peritoneal cavity	10 mg/kg	Inhibiting the release TNF-α, IL-1β, CXCL1/KC and CXCL2/MIP-2	Bueno-Silva et al. (2016)
Crude extract ethanol: water (80:20, v/v)	Inflammation in mice, using a tissue repair model.	100 mg/kg	Low TNF-α expression	Corrêa, Schanuel, Moura-Nunes, Monte-Alto-Costa, & Daleprane (2017)
Hydroalcoholic extract	Acetic acid-induced ulcerative colitis using a rodent model	10 mg/kg	Reduced gross tissue damage suggesting reduced gross tissue damage suggesting	Bezerra et al. (2017)
Hydroalcoholic extract	Experimental models in rodents with acetic acid-induced abdominal writhes	3, 10, or 30 mg/kg	Reduced the acetic acid-induced abdominal constrictions	Cavendish et al. (2015)
Crude extract	Orally-or-topically-administered in formulations	–	Decreased tissue MPO levels in the UVB-irradiated	Batista et al. (2018)
Neovestitol (27)	Acute and chronic inflammation in vivo	1, 3 and 10 mg/kg	LPS-induced neutrophil migration	Franchin et al. (2016)
Vestitol (26)	Acute and chronic inflammation in vivo	1, 3 and 10 mg/kg	Neutrophil migration was LPS-induced	Franchin et al. (2016)
Formononetin (23)	Formalin-induced inflammatory phase in mice	10 mg/kg	Decreased the inflammatory oedema response	Cavendish et al. (2015)

methodologies to investigate the anti-inflammatory activity of propolis are needed, especially in brown and red propolis.

Ex-vivo Anti-inflammatory effect measuring PGE2 plasmatic concentration values by UPLC-MS/MS (Rosa et al., 2021; Santos et al., 2019) has been absent in anti-inflammatory tests of the researched propolis. Ex-vivo assays can be an alternative to animal sacrifice and before study with a rodent model. In addition, there is a need for clinical studies to assess the contribution of Brazilian propolis to the well-being of people who consume products based on propolis.

The results of the anti-inflammatory assay with hydroalcoholic extracts of studied propolis are considered promising for further investigation, as the consumption of the hydroalcoholic extract of propolis is quite widespread in many parts of the world. In the tests carried out, they presented results that confirmed its ethnopharmacology.

8 | CONCLUSIONS

Extracts and isolated compounds of green, brown, and red Brazilian propolis displayed in vitro and in vivo anti-inflammatory activities, confirming propolis shows good therapeutic potential for treating inflammatory processes (Ramos & Miranda, 2007). As propolis is already commercialized, in different countries, it can be an ally in food supplementation once several studies considered in this review showed that the use of different types of Brazilian propolis (green, red and brown) could be helpful to alleviate the chronic and acute inflammatory processes, in internal and external regions, observed in vivo and in vitro assays. Its effectiveness in those assays is related to several fronts of attenuation of inflammation, reducing the expression of inflammatory genes and inhibiting the synthesis of pro-inflammatory cytokines and the modulation of the immune response. However, advanced studies are necessary for investigations on the clinical usefulness of Brazilian propolis extracts, mainly regarding synergistic and additive effects of its main constituents, since propolis extract has strong characteristics of an excellent anti-inflammatory candidate, according to tests performed in the studies cited in this review.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

No data sharing.

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