Artigo

PHARMACOLOGICAL ACTIVITIES OF BRAZILIAN GREEN PROPOLIS: A NARRATIVE REVIEW

ATIVIDADES FARMACOLÓGICAS DA PRÓPOLIS VERDE BRASILEIRA: UMA REVISÃO NARRATIVA

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ABSTRACT: Introduction. Propolis is one of the products made by bees and its chemical composition depends on the region, available plant species and climatic conditions. Among the 13 types of propolis produced in Brazil, green, red and brown are the main ones. Objective. To present the pharmacological properties of Brazilian green propolis observed through experiments involving animals and humans. Methodology. Careful research of articles published from 2017 to 2022 was conducted at Pub-Med, Science direct, Embase and Scielo, focusing on the pharmacological effects of Brazilian green propolis or its constituents observed in clinical trials. Results and discussion. Published results suggest that short- or long-term administration of propolis does not cause toxic effects. Pharmacokinetic studies show that terpenes, such as artepillin C and drupanin, are the main active constituents. Conclusion. For decades the Brazilian green propolis pe used in the treatment and prevention of diseases. However more specific studies are suggested to clarify the pharmacokinetics of green propolis, to establish safe and more effective doses.
KEYWORDS: Propolis, Brazilian Green Propolis, In Vivo Testing, Clinical Trials.

RESUMO: Introdução. A própolis é um dos produtos elaborados pelas abelhas e sua composição química depende da região, espécies vegetais disponíveis e condições climáticas. Dentre os 13 tipos de própolis produzidos no Brasil, a verde, vermelho e marrom são as principais. Objetivo. Apresentar as propriedades farmacológicas da própolis verde brasileira observadas através de experimentos envolvendo animais e humanos. Metodologia. Uma cuidadosa pesquisa de artigos publicados de 2017 a 2022 foi realizada no Pub-Med, Science direct, Embase e Scielo, com foco nos efeitos farmacológicos da própolis verde brasileira ou de seus constituintes observados em ensaios clínicos. Resultados e discussão. Os resultados publicados sugerem que a administração de própolis a curto ou longo prazo não causam efeitos tóxicos. Estudos farmacocinéticos mostram que os terpenos, como a artepillina C e a drupanina, são os principais constituintes ativos. Conclusão. Há décadas a própolis verde brasileira é usada no tratamento e prevenção de doenças. No entanto estudos mais específicos são sugeridos para esclarecer a farmacocinética da própolis verde, para estabelecer doses seguras e mais eficazes.

PALAVRAS CHAVE: Propolis, Propolis Verde Brasileira, Testes In Vivo, Ensaios Clínicos.

1. Introduction

Contemporary life has become complex, changing life patterns, therefore, the choice for healthy food is very important for the prevention of diseases, especially non-communicable diseases (NCD) (Moraes; Colla; 2006; Dominguez et al., 2021). According to World Health Organization, NCD such as, cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes represent the leading causes of death worldwide (Budreviciute et al., 2020). The prevention of these diseases has been associated with the
regular and adequate consumption of fruit, vegetables and whole grains, which generate beneficial effects on health (Baena. 2015; Dominguez et al., 2021).

The medical benefits of foods can be attributed to phytochemicals, that play a role that goes beyond basic nutrition and include different classes of organic compounds, such as glucosinolates, terpenoids, flavonoids and other polyphenols (Gul; Singh; Jabeen; 2016; Gantenbein; Tsuda; Kumazawa; 2021). After the discovery of the existence of foods containing bioactive compounds capable of having beneficial effects on health and promoting a healthy way of living, the terms functional foods and nutraceuticals were created. Usually, in the literature the definitions of functional foods and nutraceuticals constantly refer to the same thing. However, functional foods are those that present beneficial properties beyond the basic nutritional ones, being presented in the form of common foods (Moraes; Colla; 2006; Tsuda; Kumazawa; 2021).

When talking about functional foods, it is important to highlight the role of bees, insects that have existed for over 125 million years, and are able to explore almost all terrestrial biomes (Kanaka-Gantenbein; 2021). In addition, bees are important in environmental preservation since they are the main pollinators (Winfree, 2010; Beche et al., 2022). About 90% of plant species are pollinated by animals, and bees are the main pollinators in most ecosystems (Winfree, 2010). Beyond their role in the preservation of wild species, bees play a crucial role in the pollination of agricultural crops (Winfree, 2010; Beche et al., 2022). Bees are also capable of producing a number of products such as honey, royal jelly, propolis and wax (Kanaka-Gantenbein; 2021). These products can be classified as functional foods because they have health benefits and are important for the food industry (Kanaka-Gantenbein; 2021). Although the medicinal properties of these products have been recognized for thousands of years by ancient
civilizations, in the modern era they have limited use as nutritional supplements, for the prevention of pathologies, or in combination with classical therapies (Giampieri et al., 2022).

An example of the importance of these insects is the honeybees, like Apis mellifera L and stingless bees species of the Hymenoptera family and Meliponinae subfamily, responsible to produce propolis, a natural resinous product, that presents potentially beneficial effects on human health. For its production, substances are collected from different parts of plants and resinous exudates, and then transported to the hive and modified by adding wax, pollen, and products of their metabolism (Pasupuleti et al., 2017; Giampieri et al., 2022). In general, propolis consists of resin, wax, essential oils, pollen, and other organic compounds. Phenolic compounds, esters, flavonoids, terpenes, beta-steroids, aromatic aldehydes and alcohols are the main constituents isolated from propolis. The chemical composition of propolis, as well as the concentration of its constituents, is variable and depends on the geographical origin and the flora in the vicinity of the hive (Pasupuleti et al., 2017). In function of the chemical constitution propolis presents biological properties such as antiviral (Kwon et al., 2019), anti-inflammatory (Franchin et al., 2018), antioxidant (Park et al., 2020), and antiparasitic (de Paula et al., 2022). Propolis also present immunomodulatory effect such as macrophage activation and increased humoral and cellular immune responses, with many of its mechanisms of action still unknown (Fischer et al., 2008).

In this context, the objective of this review was to analyze results obtained through animal and human tests involving Brazilian green propolis, in order to understand the mechanisms involved in the pharmacological effects caused by this natural product and its derivatives.
2. Methodology

An extensive literature search was done on the biological effects of Brazilian green propolis in databases like Pub-Med, Science Direct, Embase and Scielo. In this study were considered articles published in the last six years (2017 a 2022). The key words used were: "propolis", "green propolis" and "Brazilian green propolis", focusing on review articles, clinical and experimental trials that evaluated the chemical composition and biological activity of propolis. In vitro experiments were not included in this work.

3. Chemical Composition of Brazilian Green Própolis

The term propolis is derived from the Greek words’ pro meaning "in front of or the entrance to", and polis meaning community or city, describing the substance to defend the hive (Bhargava et al., 2021; Forma; Brys, 2021). Propolis, also known as bee glue, is an essential antimicrobial factor for beehives survival (Pasupuleti et al., 2017). Bees carry botanical exudates derived from various parts of plants such as leaves, shoots, resins, balsams, waxes, oils, and pollen. The accumulated exudates are modified by enzymes released by the bees, and used as material for the construction and replenishment of the hives (Alvarenga et al., 2020). In general, crude propolis consists of resins and balsams including phenolic compounds (50-60%), waxes and fatty acids (30-40%), essential oils (5-10%), pollen (5%) and about 5% other substances including amino acids, micronutrients, and vitamins (Boisard et al., 2014).

The chemical composition of propolis depends on the ecological conditions of the region and the species of plants found in it, in addition to climatic factors, plant resources, place of origin and the time when it was collected by the bees from which the nectar is collected, and the genetic
variability of the queen bee (Kubina et al., 2015). Propolis has various colors including brown, yellow, green, and red, which depends on the source where it is collected and the storage time (dos Santos et al., 2022). According to the geographical region where it is produced, the most well-known types of propolis are Poplar (New Zealand, Europe and North America, Brazil), Birch (Russia), Mediterranean (Greece, Crete and Malta) and Pacific Propolis (Taiwan and Indonesia) (Bhargava et al., 2021).

Due to the great biodiversity existing in Brazil, about 13 types of propolis are produced, being the green, red and brown, the main types. The main plant sources used by bees to produce these types of propolis are Baccharis dracunculifolia DC. (Asteraceae), Dalbergia ecastaphyllum (L.) Taub. (Fabaceae) and Hyptis divaricata Pohl ex Benth. (Lamiaceae) (Kocot et al., 2018). Baccharis dracunculifolia is a native plant found in the southern of Brazil, popularly known as “alecrim do campo”. The resin of this plant furnishes the green color of Brazilian green propolis. This propolis is widely used for the treatment of inflammation and liver diseases (Simoes et al., 2004). In addition to resins, over 300 chemical constituents have been already isolated from propolis, being most, of which belong to the class of phenolic and terpenoids (Przybylek; Karpinski, 2019).

The main compounds isolated from Brazilian green propolis are baccharin, artempillin C, kaempferol, and p-coumaric acid (dos Santos et al., 2022). In addition, it is rich in flavonoids such as rhamnocitrin, eupalitin and acacetin and pentacyclic triterpenes such as α- and β-amyrin and lupeol (Kocot et al., 2018). Volatile sesquiterpenes such as (E)-nerolidol, spatulenol and selina-3,7(11)-diene, benzenopropanoic acid and longipinenene are responsible for the pleasant aroma in this bee product and also for important biological properties attributed to propolis (Berretta et al., 2012). The presence of metabolites such as amino acids, nucleic acids, sugars and enzymes such as succinic dehydrogenase, glucose-6-phosphatase,
adenosine triphosphatase, and acid phosphatase have also been reported (Berretta et al., 2012). Vitamins B1, B2, B6, E and C, body beneficial minerals such as magnesium, calcium, potassium, sodium, copper, zinc, manganese and iron have also been detected in a different propolis types (Przybylek; Karpinski, 2019; Bhargava et al., 2021). This wide diversity of chemical composition is beneficial, since it presents ingredients with specific biological properties that favors the use of propolis for the treatment and prevention of various diseases (Berretta et al., 2012).

4. Brazilian Green Propolis Metabolismo

Brazilian green propolis is a complex substance composed of several chemical compounds such as artemisinin C, baccharin and drupanin and other derivatives of cinnamic acid, and flavonoids (dos Santos et al., 2022). Although it is used in traditional medicine for the treatment of different conditions, few studies have evaluated how this substance is metabolized and which metabolites are generated by the metabolism of the main propolis compounds (Carrão et al., 2017; Yamaga et al., 2021; Yamaga; Tani; Murota; 2022).

Because it is a resinous substance with varied chemical composition, researchers have evaluated the activity of isolated components of propolis. Carrão et al. evaluated the metabolism of artemisinin C in a rat and human liver microsome model, which is used to study the metabolism of xenobiotics, mainly by the presence of cytochrome P450 enzymes (Carrão et al., 2017). It was suggested that cytochrome P450 isoforms, mainly CYP2E1 and CYP2C9, are involved in the metabolism of artemisinin C and the metabolism of this compound generates two metabolites in vitro model (Carrão et al., 2017). In vitro studies are relatively simpler models to perform and are suitable to assess how some reactions occur. On the other hand, preclinical
and clinical studies involve more complex beings and suffer interference from multiple factors.

Yamaga et al. evaluated the metabolic pathways of cinnamic acid derivatives in rats (Yamaga et al., 2021). After ingestion of artepillin A, capillartemisin A was identified in the plasma of the animals by action of cytochrome P450 enzymes, as suggested by (Carrão et al., 2017). Two peaks of this metabolite were observed in the human blood, suggesting that the clearance of artepillin C is slow, especially when compared to other derivatives of cinnamic acid (Yamaga; Tani; Murota; 2022).

After consumption of drupanin or baccharin, 12 different metabolites were detected in human plasma. These metabolites were produced by action of enzymes such as catechol-O-methyltransferase, sulfotransferase, cytochrome P450 and UDP-glucuronosyltransferase (Yamaga; Tani; Murota; 2022). However, 3-(4-hydroxyphenyl)-propionic acid is produced only by the metabolization of baccharin, and it is suggested that this metabolite has anti-inflammatory and anti-tumorigenic effects (Sova; Saso, 2020).

Yamaga, Tani and Murota (2022) reported that metabolites derived from cinnamic acid, such as glucuronides from artepillin C and capillartemisin A were detected in rat plasma, but not in sulfate form. These authors also described that drupanin was metabolized to glucuronide and sulfate, but p-coumaric acid underwent sulfation without glucuronidation. And that, methylated derivatives of cinnamic acid were also detected (Yamaga; Tani; Murota; 2022).

Glucuronides of artepillin C, capillartemisin A and drupanin, drupanin sulfates and p-coumaric acid, and some methylated derivatives of cinnamic acid were detected in human plasma after ingestion of Brazilian green propolis (Yamaga et al., 2021). The findings of this study indicated that the cinnamic acid derivatives may have a different rate of absorption in the human organism. These authors also reported that artepillin C and drupanin
were detected in higher concentration in human plasma after ingestion of Brazilian green propolis. In a similar way, metabolites of propolis compounds such as capillartemisin A, drupaninglucoronins, dupanin and p-coumaric acid were detected in plasma rat (Yamaga; Tani; Murota; 2022). It has also been observed that components of green propolis other than the main cinnamic acid derivatives can be converted to artepillin C or drupanin and affect the absorption efficiency (Yamaga et al., 2021). Baccharin can be hydrolyzed to drupanin and 3-phenylpropionic acid, metabolites that contribute to the pharmacological activity of Brazilian green propolis (Yamaga et al., 2021).

Experimental and clinical studies are important to identify compounds with biological activity and elucidate the mechanisms involved in the pharmacological effects of green propolis. However, more accurate studies are needed to understand the metabolism of each constituent of propolis.

5. Biological Activities of Green Própolis

5.1 Evidences from in Vivo Studies

Several researchers have studied the biological activity of Brazilian green propolis. The main results are shown in Table 1. Experiments using different animal models have demonstrated beneficial effects of green propolis in the treatment and prevention of diseases such as gastric ulcer (Costa et al., 2018; Costa et al., 2019; Costa et al., 2020), colitis (Mariano et al., 2018; Shimizu; Suzuki, 2019), drug intoxication (36) (Tsuchiya et al., 2018), cancer (Doi et al., 2017; Gastaldello et al., 2021), sepsis (Silveira et al., 2021), acute inflammation (Ferreira et al., 2021), infection (de L Paula et al., 2022), oral mucosal irritation (Furukawa et al., 2021), obesity (Sakai et al., 2017; Chen et al., 2022), diabetes (Watanabe et al., 2021), retinal
injury (Park et al., 2020), asthma (Piñeros et al., 2020; Martins et al., 2021) and allergic rhinitis (Shaha et al., 2018).

Table 1. Experimental models used to evaluate the effect of extracts and isolated compounds of Brazilian green propolis

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Conditions</th>
<th>Studied samples</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fat diet (mice)</td>
<td>Addition of 2% Brazilian propolis powder in the feed for 14 weeks</td>
<td>Adipose tissue</td>
<td>↓ weight gain and adipose tissue accumulation, suppresses macrophage infiltration of adipose tissue</td>
<td>Sakai et al., 2017</td>
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<tr>
<td>Colon Carcinogenesis (rats)</td>
<td>Addition of 1% ethanol-extracted propolis to the feed for 29 weeks</td>
<td>Liver, kidney, colon</td>
<td>↓ expression of iNOS, TNFα, NF-κB and GPX2 in animals treated with propolis extract in water</td>
<td>Doi et al., 2017</td>
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<tr>
<td>Acetaminophen intoxication (rats)</td>
<td>Oral administration of 291 mg/kg of ethanol extract Brazilian green propolis of for 7 consecutive days</td>
<td>Liver</td>
<td>Reduction of hepatocellular necrosis</td>
<td>Tsuchiya et al., 2018</td>
</tr>
<tr>
<td>Dextran sulfate sodium-induced colitis (mice)</td>
<td>3, 30 or 300 mg/kg of Brazilian green propolis hydroalcoholic extract for 7 consecutive days in drinking water</td>
<td>Colon</td>
<td>Maintained mucin levels similar to the control group, ↑ GSH levels and SOD activity</td>
<td>Mariano et al., 2018</td>
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<td>Allergic rhinitis (mice)</td>
<td>Oral administration of 40 and 80 mg/kg of ethanol extract propolis powder for 3 weeks</td>
<td>Nasal mucosa</td>
<td>Suppressed sneezing and nasal symptoms, ↓ IL-4, IL-5 and IL-9</td>
<td>Shaha et al., 2018</td>
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<tr>
<td>Hydrochloric acid-induced gastric ulcer (mice)</td>
<td>Oral administration of 30 mg/kg of artempillin C, baccharin, drupanin, aromadendrin-4′-O-methyl-ether or kaempferide from green propolis</td>
<td>Stomach</td>
<td>The compounds attenuated histological damage by decreasing lesion areas, ↓ SOD, CAT, and MPO activity</td>
<td>Costa et al., 2018</td>
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<tr>
<td>Acetic acid-induced ulcer (mice)</td>
<td>Oral administration of 30, 100 and 300 mg/kg hydroethanolic propolis extract for 7 consecutive days</td>
<td>Stomach</td>
<td>↓ ulcer area; mucin production and antioxidant enzyme activity</td>
<td>Costa et al., 2019</td>
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<tr>
<td>Study Type</td>
<td>Model</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Reference</td>
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<tr>
<td>Low-protein diet (mice)</td>
<td>Oral administration of 500 mg/kg of hydroalcoholic green propolis extract for 7 or 15 days</td>
<td>Blood</td>
<td>Propolis extract promoted weight recovery and maintenance and maintenance of serum protein levels</td>
<td>Miranda et al., 2019</td>
</tr>
<tr>
<td>Ischemia and reperfusion retinal injury (mice)</td>
<td>Intraperitoneal administration of 200 mg/kg Brazilian green propolis ethanol extract</td>
<td>Retina</td>
<td>Propolis treatment prevented the increase of Bax and p53, blocked NF-κB translocation, ↑ Nrf2 HO-1 expression</td>
<td>Park et al., 2019</td>
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<tr>
<td>Colitis (mouse)</td>
<td>Addition of 0.3% ethanol extract of Brazilian propolis in the feed for 9 days</td>
<td>Colon</td>
<td>Propolis administration restored weight loss, ↓ tissue injury, ↓ TNF-α, IL-1β and IL-17 expression</td>
<td>Shimizu et al., 2019</td>
</tr>
<tr>
<td>Alcohol and acetic acid induced ulcer (rats)</td>
<td>30, 100, or 300 mg/kg of hydroalcoholic extract from green propolis, 1 hour before induction of injury or for 7 consecutive days 2 times daily after induction of injury</td>
<td>Stomach</td>
<td>In both models, propolis administration promoted reduction of ulcer area, ↑ mucin production, ↑ SOD, CAT and glutathione S-transferase activity, ↓ MPO activity</td>
<td>Costa et al., 2020</td>
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<td>OVA-induced asthma (mice)</td>
<td>150 mg/kg of Brazilian green propolis dry extract by gavage for 17 or 22 days</td>
<td>Bronchoalveolar lavage and lung</td>
<td>↓ influx of inflammatory cells, especially eosinophils, ↓ mucus production, ↓ expression of IL-13 and IL-5</td>
<td>Piñeros et al., 2020</td>
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<td>Pain model (rats)</td>
<td>50 and 100 mg/kg of propolis alcohol extract intraperitoneally</td>
<td>-</td>
<td>Propolis showed an inhibitory effect on pain threshold.</td>
<td>Al-Hariri; Abualait, 2020</td>
</tr>
<tr>
<td>Sepsis induced by caecal ligation and puncture (rats)</td>
<td>500 mg/kg of ethanol extract of propolis, 6 hours after induction of sepsis intraperitoneally</td>
<td>Kidney and lung</td>
<td>↑ survival, restored renal tubular function, ↑ glutathione levels ↓ TLR-4, NF-κB expression and levels of IL-17, IL-12, IL1β, TNF-α</td>
<td>Silveira et al., 2021</td>
</tr>
<tr>
<td>OVA-induced asthma (mice)</td>
<td>80 µg intranasal Artepillin C from crude extract of green propolis, 7 doses</td>
<td>Lung</td>
<td>↓ influx of eosinophils, lung inflammation, and mucus secretion</td>
<td>Martins et al., 2021</td>
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<tr>
<td>Model</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Diabetes - ob/ob (mice)</td>
<td>10 or 50 mg/kg Baccharin from crude ethanolic extract of green propolis intraperitoneally for 5 weeks</td>
<td>↓ blood glucose</td>
<td>Watanabe et al., 2021</td>
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<tr>
<td>Air pouch model - acute inflammation (mouse)</td>
<td>500 or 1000 μg/kg Baccharin and p-coumaric acid into the air pouches</td>
<td>↓ influx of inflammatory cells, Baccharin promoted ↓ of IL-6, TNFα and IL-1β levels; p-coumaric acid reduced TNFα and IL-1β levels</td>
<td>Ferreira et al., 2021</td>
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<tr>
<td>Melanoma model (mouse)</td>
<td>500 mg/kg Baccharin and p-coumaric acid from green propolis extracted with hydroalcoholic solution, orally for 26 days</td>
<td>↓ Mitosis cells in the tumor and angiogenesis in the tumor, ↓ neutrophil recruitment</td>
<td>Gastaldello et al., 2021</td>
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<tr>
<td>Gingivitis (mouse)</td>
<td>2.5% propolis ointment topical</td>
<td>↓ Cell infiltration, suppression of IL-1β and TNF-α expression, ↑ expression of keratin 1 and 5. Promoted mucosal repair</td>
<td>Furukawa et al., 2021</td>
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<tr>
<td>Schistosoma mansoni infection (mouse)</td>
<td>300 mg/kg propolis extract, using dichloromethane/hexanes solution, orally for 21 days</td>
<td>↓ worm burden and number of eggs, degree of inflammation</td>
<td>Paula et al., 2022</td>
<td></td>
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<tr>
<td>Obesity model (mouse)</td>
<td>Oral administration of 250 mg/kg propolis or 20 mg/kg Artepillin C synthesized</td>
<td>↓ fasting glucose in obese mice by disrupting CREB/CRTC2 complex formation. ↑ insulin sensitivity, ↓ lipid levels in serum and liver</td>
<td>Chen et al., 2022</td>
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</table>

CAT: catalase; CREB: cAMP response element-binding protein; CRTC2: CREB regulated transcriptional coactivator 2; GSH: glutathione; GPX2: glutathione peroxidase 2; HO-1:heme-oxygenase 1; IL-1β: interleukin 1β; IL-4: interleukin 4; IL-5: interleukin 5, IL-6: interleukin 6; IL-9: interleukin 9; IL-12: interleukin 12; IL-13: interleukin 13; IL-17: interleukin 17; iNOS: Inducible nitric oxide synthase; MPO: myeloperoxidase; Nf-κB: Nuclear factor-κB; Nrf2: nuclear erythroid-related factor 2; OVA: ovalbumin; SOD: superoxide dismutase; TNFα: tumor necrosis factor α; TLR-4: Toll-like receptor 4.

Source: Authors.
Gastric ulcers are caused mainly by modern life habits such as diet, alcohol, use of nonsteroidal anti-inflammatory drugs, and *Helicobacter pylori* infection (Sverden et al., 2018; Costa et al., 2020). These factors lead to a reduction of the protective mucus layer, leading to injury of the gastric mucosa. Previously, Chung et al. (2015) reported an inflammatory process with neutrophil migration associated to an increased production of reactive oxygen species. The treatment of peptic ulcer disease was based on the reduction of gastric juice secretion, which happens through the administration of proton pump inhibitors or H2 receptor antagonists (Kamada et al., 2021). In this context Costa et al. (2018; 2019; 2020) evaluated the effects of administering propolis or isolated propolis components in gastric disorders. In these studies, it was observed that the administration of green propolis and its components favored the defense of the gastric mucosa by promoting an increase in the mucus layer. Furthermore, were also observed an increase in lipid peroxidation products and depletion of antioxidant defenses, such as glutathione (GSH) (Costa et al., 2020). The protective mechanism of propolis in the gastric ulcer involves an increase in antioxidant defenses and a decrease in the activity of the oxidant enzyme myeloperoxidase (Costa et al., 2018; Costa et al., 2019).

In addition to the effects observed using gastric ulcer models, the effects of Brazilian propolis extract reduces intestinal barrier defects and inflammation in a colitic mouse model (Shimizu et al., 2019). Injury to the intestinal mucosa is related to decreased mucus levels which leads to an alteration in the barrier function, leading to increased permeability and making the organ more susceptible to bacterial translocation (Suzuki, 2013; Neurath, 2014). As observed using gastric ulcer models, propolis can maintain mucin levels, thus playing a protective role of the intestinal mucosa (Mariano et al., 2018; Shimizu et al., 2019). In addition to the antioxidant activity of green propolis extract, it can also act by modulating the activity...
of the enzyme superoxide dismutase (Mariano et al., 2018). By means of an experimental model of ulcerative colitis, evidence suggests that green propolis increased the production of cytokines by Th-17 lymphocytes, such as interleukin 17 (IL-17). This inflammatory mediator plays a role in tissue destruction and in the maintenance of inflammation (53) (Ueno et al., 2018). Shimizu et al. demonstrated that supplementation with green propolis extract can minimize IL-17 expression in mice with colitis induced by dextran sodium sulfate (35). Besides modulating the Th-17 lymphocyte-mediated response, these authors observed a lower mRNA expression of tumor necrosis factor α (TNF), interleukin 6 (IL-6) and interleukin 1β (IL-1β) (35).

Lifestyle habits, besides being associated with the development of gastrointestinal tract diseases, are determining factors in metabolic diseases such as obesity and diabetes. Sakai et al. (2017) observed through a high-fat diet model, that supplementation with green propolis rich in phenolic compounds and flavonoids, inhibit the fat absorption in adipocytes (Sakai et al., 2017). The mechanisms by which green propolis supplementation may induce decreased fat uptake by adipocytes is not yet fully understood. However, some researchers suggest mechanisms that may be involved in lipid metabolism in obese animals treated with propolis. Xie et al (2014) suggested that upregulation of carnitine and palmitoyl transferase 1 may improve lipid metabolism. Other possible mechanisms are improved insulin sensitivity and increased glucose uptake (Sakai et al., 2017). Watanabe et al, (2021) reported that there was an increase in GLUT4 expression and decrease in glucose levels, and associated with this, an increase in adiponectin levels was observed, directly related to a decrease in adipose tissue accumulation (Watanabe et al, 2021).

The hyperglycemic state caused by obesity is one of the most important factors in the development of type 2 diabetes. In addition to the increased glucose uptake previously observed by Watanabe et al, (2021)
Chen et al., (2022), using a high fat diet model, evaluated the mechanisms involved in this hyperglycemic state. These authors reported that the CREB/CRTC2 (cAMP response element-binding protein/regulated transcriptional coactivator 2) complex is a key transcription factor of hepatic gluconeogenesis, Chen et al. observed that green propolis, especially artemillin C, acts as an inhibitory molecule of the CREB/CRTC2 transcriptional complex, improving insulin sensitivity both in mice with high fat diet induced obesity and in animals with genetic mutation.

The use of natural compounds represents an advance for the treatment and prevention of different conditions. Propolis has been studied in different experimental models and studies show that it may represent an advance in cancer treatment (Doi et al., 2017; Gastaldello et al., 2021). Propolis seems to be able to disrupt oncogenic signaling pathways, inhibit cell proliferation and angiogenesis. Gastaldello et al., (2021) evaluated the effects of baccharin and $p$-coumaric acid, isolated from green propolis, on an experimental model of melanoma. These compounds inhibit mitosis, as well as reduce the amount of blood vessels in the neoplastic areas (Gastaldello et al., 2021). Doi et al (2018) evaluated the effect of the administration of alcohol extract of propolis on colon cancer. It was observed that propolis promoted reduction in tumor load. The antitumor effects observed by Doi et al (2018) seem to be related to the suppression of inflammation, which was observed by the lower expression of nuclear factor kappa B (Nf-$\kappa$B). This transcription factor is involved in the regulation of inflammatory response inducing the higher expression of pro inflammatory genes, associated with the lower expression of the transcription factor the administration of propolis extract led to the decrease of TNF-$\alpha$ (Doi et al, 2018). Furthermore, propolis in the colon cancer model acted modulating oxidative stress by undermining the expression of inducible nitric oxide synthase (iNOS) (Doi et al, 2018). The iNOS is an enzyme involved in the synthesis of nitric oxide (NO) and the
increased expression of this enzyme may be associated with tumor progression playing pro-tumorigenic effects (Lechner et al., 2005), meaning that propolis can prevent disease progression.

Inflammation, oxidative stress and tissue damage, mitochondrial dysfunction and apoptosis are mechanisms involved in organ damage. The study of sepsis in the experimental model of cecal puncture and ligation is considered the most reliable model to mimic human sepsis, since it causes a polymicrobial infection, systemic inflammation and multiple organ damage (Doi et al., 2009). Through the experimental model of cecal puncture, Silveira et al. (2021) observed that the inflammatory response in sepsis, induced by green propolis extract, involves the activation of Toll-like 4 (TLR4) /NF-κB signaling that the activation of this pathway can trigger the expression of inflammatory cascade factors. Green propolis in the sepsis model promoted a lower infiltration of macrophages in the lung and kidney of the animals, a lower expression of TLR4 and the phosphorylated subunit of NF-κB was observed, which was related to decreased levels of IL-17, IL-12, IL-1β and TNFα. In addition to leading to a decrease in apoptosis in renal tissue (Silveira et al., 2021).

The inflammatory response was evaluated through different experimental models. In allergic responses, especially in asthma, the influx of eosinophils, lung inflammation, and increased mucus secretion are characteristic (Martins et al., 2021). The administration of green propolis or artemisinin C alone modulated the inflammatory response by reducing the influx of eosinophils (Piñeros et al, 2020; Martins et al., 2021). Piñeros et al. (2020) suggested that the modulatory role of propolis is dependent on polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) and regulatory T lymphocytes (Treg). The effect of propolis observed using this model is dependent on the secretion of IL-10 by PMN-MDSC, and the results suggested that MDSC promotes the differentiation of Treg lymphocytes,
which regulate the responses of different subpopulations of T lymphocytes (Piñeros et al., 2020; Martins et al., 2021). Propolis administration promoted lower expression of IL-5 and IL-13 in the lungs of the animals, which demonstrates an attenuation of the inflammation mediated by T helper 2 (Th2) lymphocytes (Piñeros et al., 2020). In addition to being involved in the immune response in asthma, Th2 cells are an important element of the allergic response and are involved with the production of IL-4, IL-5, IL-9 and IL-13 (Wills-Karp et al., 1998; Bischoff et al., 1999). Anti-histaminic medications suppress the Th2 response and are used in the management of symptoms caused by allergic rhinitis (Shaha et al., 2018). These authors demonstrated that administration of green propolis extract promoted a lower expression of IL-4, IL-5 and IL-9 which suggests that it can be used in the treatment of allergic conditions.

It was observed that propolis administration is able to modulate the Nf-κB signaling pathway, minimizing the expression of inflammatory mediators and the influx of cells to the site of inflammation (Silveira et al., 2021). Furthermore, previous studies suggest that propolis exerts antioxidant effects by altering the activity of antioxidant enzymes, such as superoxide dismutase and by promoting increased glutathione levels (Costa et al., 2018; Costa et al., 2019; Costa et al., 2020). Modulation of oxidative stress involves activation of the Nuclear erythroid-related factor 2 (Nrf-2) pathway (de Figueiredo et al., 2014). Park et al. (2020) evaluating a model of retinal injury observed that Nrf2 expression was increased in animals receiving green propolis. The Nrf-2 pathway is essential in regulating antioxidant defense, its activation promotes the expression of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and heme-oxygenase 1 (HO-1) (Wardyn et al, 2015). Subsequently, this result was confirmed by Park et al. (2020), which also observed an increase of HO-1. The heme-oxygenase 1 (HO-1) catabolizes heme protein into carbon
monoxide, biliverdin and free iron, molecules that play antioxidant roles in other metabolic pathways (Wagener et al., 2003). In the context of retinal injury, the increased expression of HO-1 is important, since it is one of the main protectors under stress conditions in neuronal tissue (Wardyn et al., 2015).

The administration of propolis seems to also exert an effect on the control of verminosis, however, studies are scarce and there is still no description of the mechanisms involved. Through a model of animals infected with *Schistosoma mansoni* it was observed that the administration of propolis for 5 to 6 weeks acted to control the infection by reducing the load of worms and the number of eggs found in liver tissue (de L Paula et al., 2022). The studies reviewed here suggest that propolis has a broad spectrum of effects in experimental models.

In this context, Al-Hariri and Abualait (2020) described another beneficial effect of propolis. These authors demonstrated that the administration of propolis caused a significant antinociceptive effect in rats submitted to a pain model induced with acetic acid, infrared and formalin.

### 5.2 Evidences From Clinical Trials

Before testing a drug in people, researchers must find out whether the sample has potential to cause serious damages, also called toxic effects. The two types of preclinical research are *in vitro* and *in vivo* assays. Food and Drug Administration (FDA) requires researchers to use good laboratory practices, defined in medical product development regulations, for preclinical laboratory studies (Collins et al., 1986). However, while preclinical research answers basic questions about a drug’s safety, it is not a substitute for studies of ways the drug will interact with the human body. Clinical research refers to studies, or trials, that are done in people (Collins et al., 1986). As
the researchers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and then, begin the Investigational New Drug Process, a process they must go through before clinical research begins (Collins et al., 1986). Although there are several preclinical trials in the literature that have demonstrated beneficial effects of green propolis administration, when it comes to studies conducted in humans the results are still scarce. Extrapolation of the results obtained in preclinical trials to humans is difficult, so initially it is necessary to understand the pharmacokinetics of propolis in humans and whether it exerts toxic effects.

Initially the studies using propolis have focused on the analysis of topical effects, mainly on oral diseases such as stomatitis (Marucci et al., 2017), dental caries (Santiago et al., 2018), and periodontitis (Giammarinaro et al., 2018). The use of propolis has been shown to be effective in relation to antimicrobial and anti-inflammatory properties. (Marucci et al., 2017; Santiago et al., 2018; Giammarinaro et al., 2018; dos Santos et al., 2022).

Pharmacological effects of orally administered Brazilian green propolis observed by clinical trials are showed in Table 2.

<table>
<thead>
<tr>
<th>Disease surveyed</th>
<th>Experimental conditions</th>
<th>Design of study</th>
<th>Main results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>300 mg three times a day for 12 weeks (900 mg/day)</td>
<td>Double-blind, placebo-controlled clinical trial</td>
<td>↓Fasting blood glucose and HbA1c levels</td>
<td>Samadi et al., 2017</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>500 mg three times a day for 2 months (1500 mg/day)</td>
<td>Double-blind, placebo-controlled clinical trial</td>
<td>↓Fasting blood glucose and HbA1c levels, ↑Total antioxidant capacity, SOD and GPx</td>
<td>Afsharpoor et al., 2019</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>500 mg per day for a year</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>Patients who received propolis for one year had ↓ proteinuria, ↓ urinary MCP1 and</td>
<td>Silveira et al., 2019</td>
</tr>
</tbody>
</table>
### Table 1: Effects of Oral Administration of Brazilian Green Propolis on Various Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Details</th>
<th>Study Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy patients</td>
<td>4 propolis tablets contained 406.8 mg of propolis powder for 1 week (1627.2 mg/day)</td>
<td>Randomized, single-blinded control study</td>
<td>After administration of the tablets, artepillin C was observed in the blood of almost all volunteers. Women showed higher levels of artepillin C than men. Ding <em>et al.</em>, 2021</td>
</tr>
<tr>
<td>COVID-19</td>
<td>400mg or 800mg per day for 7 days</td>
<td>Single-center, open-label, randomized, controlled trial</td>
<td>Propolis was associated with lower hospitalization time, ↓ risk of mortality, and better prognosis. Silveira <em>et al.</em>, 2021</td>
</tr>
<tr>
<td>Healthy patients</td>
<td>3 capsules containing 360 mg propolis (1080 mg/day)</td>
<td>Clinical trial</td>
<td>The results show the pharmacokinetics of green propolis, it was observed that the main metabolites in blood were artepillin C-4-O-β-D-glucuronide and drupanin-4-O-β-D-glucuronide. Yamaga <em>et al.</em>, 2021</td>
</tr>
<tr>
<td>HIV</td>
<td>500 mg per day for 3 months (1500 mg/day)</td>
<td>Randomized, double blind, parallel-group, placebo-controlled trial</td>
<td>↓ INF-γ levels, ↑ Foxp3 expression. A positive correlation was observed between CD4+ cells and IL-10 production. Conte <em>et al.</em>, 2021</td>
</tr>
</tbody>
</table>

Foxp3: forkhead box P3; GPX: glutathione peroxidase; HbA1C: glycosylated hemoglobin; HIV: Human immunodeficiency; INF-γ: Interferon-gama; IL-10: interleukin 10; MCP1: monocyte chemoattractant protein 1; SOD: superoxide dismutase.

Source: Authors.

The evaluation of the effects of oral administration on metabolic disorders has been little studied to understand the metabolism and pharmacokinetics of propolis. Ding, *et al.* (2021) and Yamaga *et al.* (2021) evaluated oral administration of Brazilian green propolis in humans. This natural substance comprises a complex mixture of compounds and verifying the contribution of these components is important to understand the efficacy of propolis. Ding, *et al.* (2021) evaluated the effect of the concentration of artepillin C after oral administration of 400 mg of propolis per day in 134
participants. After daily ingestion for one week blood concentrations of artemelin C between 0 and 357.6 ng mL\(^{-1}\) were observed. Furthermore, artemelin C levels were higher in the serum of women, which was not influenced by menopause. Ingesting propolis for one week elevates the levels of artemelin C, which may be related to its biochemical activity (Ding, et al., 2021). The kinetics and metabolism of propolis were studied after administration of 360 mg sample and the products of metabolism in blood were determined at different times (Yamaga et al. 2021). After enzymatic hydrolysis, a significant increase in the levels of propolis components was observed, indicating that these components were absorbed into the body and metabolized into their conjugates. And, among the propolis components the conjugates of artemelin C and drupanin were the major metabolites found (Yamaga et al. 2021). The results of both studies are important in elucidating the efficacy of propolis and may help elucidate the pharmacological effects of propolis in other clinical trials, such as in Diabetes.

Diabetes is an endocrine disorder with high prevalence worldwide and high risk of complications (Garber et al., 2020). Non-drug tools that assist in the treatment of the disease are of great importance. Experimental studies using mice model have shown that propolis can control hyperglycemia in animals (Watanabe et al., 2021). In humans, Afsharpoor et al. (2019) indicated that supplementation with 1500 mg/day of green propolis in humans, for 8 weeks, leads to significant differences in blood glucose level, insulin resistance and hemoglobin A1c (HbA1c) in patients with type 2 diabetes (DM2). Samadi et al. (2017) working with DM2 patients showed that daily intake of 900 mg of green propolis for 12 weeks results in improved blood glucose in patients. In the study developed by Afsharpoor et al. (2019), green propolis supplementation reduced HbA1C by 1.19% compared to the baseline level. In contrast, there is evidence that green propolis may not affect patients with diabetes, such in the study by Samadi et al. (2017), that
demonstrate no significant difference in serum insulin level and insulin resistance between propolis and placebo after 12 weeks. In addition, previous studies have also shown that the administration of green propolis did not promote changes in the levels of serum glucose, insulin, and HOMA index (Fukuda et al., 2015; Zhao et al., 2016). A possible explanation for the results found in these studies would be the low dose of propolis, which would be at sub-therapeutic levels. Although studies show that propolis has no effects on markers of diabetes mellitus, studies suggest that green propolis acts by regulating blood glucose by mechanisms involving a decrease in glucose-6 phosphate expression and activity (Kang et al., 2010). Or by an increase in the glucose transporter (GLUT4), promoting an increase in glucose uptake, thus reducing insulin resistance (Ueda; Hayashibara; Ashida, 2023). In addition, the regulation of blood glucose level by propolis occurs through suppression in the production of reactive oxygen species and modulation of antioxidant activity (Ueda; Hayashibara; Ashida, 2023). Hyperglycemia leads to an imbalance between oxidants and antioxidants, promoting oxidative stress (Tangvarasittichai et al., 2015). Glucose oxidation is one of the sources of reactive oxygen species which worsens insulin resistance (Asmat; Abad; Ismail, 2016). Propolis supplementation promoted an increase in total antioxidant capacity and the activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, and propolis has beneficial effects in DM2 by regulating blood glucose and minimizing oxidative stress (Afsharpour et al. 2019).

In addition to playing a role in diabetes control, propolis can be used as an adjuvant in the treatment of chronic kidney disease (CKD). In CKD high levels of proteinuria and albuminuria are associated with a rapid decline in glomerular filtration rate (Iseki et al., 2003; Iimori et al., 2018). Silveira et al. (2019) evaluated the administration of 500mg per day, for one year, and the administration of propolis promoted lower proteinuria. These authors
suggested that propolis appears to decrease oxidative stress and reduce macrophage infiltration (Silveira et al. (2019). Besides decreasing proteinuria, Silveira et al. (2019) observed lower levels of monocyte chemoattractant protein 1 (MCP1), this cytokine is related to the recruitment of transformation and monocytes to the kidneys. In CKD, MCP-1 elimination in urine indicates inflammatory aggression to renal tissue, besides being related to CKD progression (Nadkarni et al., 2016). The findings found in this study suggest that propolis administration may act to control renal inflammation in CKD and may be used in the treatment of kidney disease. As propolis exerts this anti-inflammatory effect, its applicability in SARS-CoV2 was also studied (Fiorini et al., 2021).

Recently, the severe acute respiratory syndrome caused by SARS-CoV-2 has become a major object of study by the scientific community, with the aim of understanding the mechanisms involved in this disease, as well as ways to treat it. SARS-CoV-2 is highly contagious; the number of global infections has increased steadily since the first confirmed case of infection (Fiorini et al., 2021). In the context of the pandemic, numerous therapies, such as supportive intervention and the use of immunomodulating agents, antiviral therapy, antibiotics, antimalarial agents, convalescent plasma transfusion, and blood transfusion-related technologies, have been adopted in clinical practice (Fiorini et al., 2021). From this clinical point of view, propolis can be used as a possible complementary treatment for patients with SARS-CoV-2. Still in the context of the pandemic, before the start of vaccination Silveira et al. developed a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of standardized Brazilian green propolis as adjuvant treatment in hospitalized adults with acute moderate to severe SARS-CoV-19 (Silveira et al., 2021). In this trial, two doses of propolis (400 mg/day and 800 mg/day) were tested for 7 days. The administration of propolis was associated with a reduction in hospital length of stay, being
between 6 and 7 days for patients receiving propolis when compared to the average of 12 days for patients receiving standard care alone (Silveira et al., 2021). In addition, the higher dose of propolis was associated with a lower incidence of acute kidney disease. These findings have great clinical relevance, as it is associated with a better prognosis and lower risk of mortality (Silveira et al., 2021). The mechanisms involved in the response elicited by propolis were not explained in this study, however, the data are promising and suggest that propolis can be used as an adjuvant in the treatment of Covid-19 (Silveira et al., 2021) and other infectious diseases like HIV.

In the context of viral diseases Conte et al. (2021) evaluated the administration of propolis in people infected with the HIV virus. HIV infection represents an important public health problem, with many new infections every year (Girum; Wasie; Worku, 2018). Although antiretroviral therapy represents an advance in the management of the disease, it only allows partial control of immune activation and inflammation in people living with HIV/AIDS (Conte et al., 2021). In these patients, persistent immune activation and chronic inflammation are related to several factors such as pathogenic effects of the virus, residual virus replication, translocation of bacteria, stimulation by other pathogens, and dysregulated production of cytokines and chemokines. In this study, Conte et al. evaluated 40 people living with HIV/AIDS and administered 500 mg propolis for 3 months. The viral load in these patients remained undetectable, showing that propolis has no influence on antiretroviral therapy (Conte et al., 2021). In the propolis group, CD4+ T cells showed a positive correlation with IL-10 production, and high levels of IL-10 are associated with lower production of the inflammatory cytokine interferon gamma (INF-γ) (Conte et al., 2021). In addition, these authors observed increased expression of Foxp3, a marker of Treg lymphocytes (Conte et al., 2021). Previously, these cells are related to the
regulation of the immune response, secreting anti-inflammatory cytokines and controlling the inflammatory response (Raphael et al., 2015. de Miranda et al., 2019). These results are important, as they demonstrate the ability of propolis to enhance the immune response in people living with HIV/AIDS by regulating mainly the activation of regulatory T lymphocytes (Conte et al., 2021).

In summary, the few clinical studies already published suggest that short or long-term administration of propolis has no toxic effects. Pharmacokinetic studies show that propolis promotes an increase, mainly associated to artemisinin C and drupanin, in the blood, which suggests that possibly the biological activities triggered by propolis both in metabolic disorders and in different viral infections pass through the action of these compounds.

6. Final Considerations

The study of substances of natural origin has been growing in recent years since they are associated with a reduction in the risk of developing diseases. This review evaluated animal and human studies that analyzed the properties of Brazilian green propolis, emphasizing its variety of pharmacological properties. Despite its use in several diseases, there is still no standardization of the dose of propolis that should be used to observe its beneficial effects. Therefore, more studies are needed to understand the digestion and absorption of green propolis, as well as its pharmacokinetics, to establish safe doses which induces greater and more effective effect.
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