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An exploratory review of the cultural, botanical, and phytochemical profiles of *Ilex paraguaiensis*, focusing on the biological activity of its secondary metabolites during different pathophysiological states

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Abstract

Ilex paraguaiensis popularly known as "yerba mate", is a tree native to South America, cultivated primarily in Paraguay, Brazil, Uruguay and, Argentina. In addition to its cultural value, and despite not being considered a medicinal plant, "yerba mate" has been the subject of scientific studies due to its supposed pharmacological and nutraceutical properties. This study aimed to conduct an updated review of the main therapeutic effects related to the consumption and/or treatment with *Ilex paraguaiensis* or its secondary metabolites in different organic systems. The search for articles was carried out in the databases PubMed (NCBI), Virtual Health Library (VHL), Scientific Online Electronic Library (SciELO), Medical Literature Analysis and Retrieval System Online - MedLine (PubMed), Scientific Electronic Library - SciELO and Latin American and Caribbean Literature in Health Sciences - LILACS. The consumption of Ilex paraguaiensis is a cultural tradition in some areas of South American countries and can represent a source of income when cultivated and commercialized. It is a plant with significant biological potential that is related to the antioxidant, anti-inflammatory, and stimulant properties of its secondary metabolites, which are mediated by different intracellular signaling mechanisms described in this review. The increase in clinical studies may corroborate the results of the preclinical studies presented in this review and, thus, contribute to the establishment of the pharmacological efficacy, safety, and risk of use of this plant. Thus, the continuity of scientific research on the biological activity of *Ilex paraguaiensis* and/or its secondary metabolites may lead to new perspectives related to the development of new drugs, pharmaceutical products, and nutraceuticals that are safe and may be useful in the treatment of different human pathophysiological conditions.

Key words: *Ilex paraguaiensis,* Botanical aspects, Folk medicine, Therapeutic uses, Secondary metabolites

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1. Introduction

Ilex paraguaiensis, commonly known as "yerba mate", "mate", or "congonha", is a plant belonging to the Aquifoliaceae family, native to the southern region of South America, including Paraguay, Brazil, Uruguay, and Argentina. This perennial plant is notable for its cultural and economic importance, especially in producing traditional beverages. In Brazil, "tereré" is a preparation made with cold water, and the yerba mate leaves are lightly crushed, while "chimarrão" is prepared with hot water, and the yerba mate used is extensively crushed so that it has a similar appearance to a coarse powder (Figure 1). *Ilex paraguaiensis* is a small to medium-sized tree that can reach heights of between 4 and 20 meters, depending on the growing conditions and the environment in which it is found or cultivated [1-2]. This plant has an erect trunk, with a diameter of approximately 20 to 50 cm, and rough, grayish-brown bark. Its leaves are simple, alternate, and leathery, with serrated margins, measuring between 6 and 20 cm in length. The color of the leaves is dark green on the upper side and lighter on the underside. The flowers are small, white, and arranged in corymboid inflorescences, occurring mainly in spring and early summer [1-2] (Figure 2). The fruits of *Ilex paraguaiensis* are globose drupes that turn red when ripe, containing 4 to 8 seeds. These fruits are important for

disseminating the plant, as they are eaten by birds that help disperse the seeds (Figure 2). The plant is dioecious, with male and female flowers on separate individuals, which can hinder natural pollination [1-2] (Figure 2). *Ilex paraguaiensis* is typically found in subforest environments, where it benefits from the shade provided by other trees and prefers fertile soils rich in organic matter and with a slightly acidic pH. Ideal growth occurs at temperatures between 20 °C and 25 °C. During commercial cultivation, it is recommended that plants be kept below 3 meters in height to facilitate leaf harvesting, however, for medicinal purposes, this recommendation is not necessarily a mandatory condition [2]. Medicinal plants have played a crucial role in folk or empirical medicine for centuries. These natural resources are valued for their therapeutic properties, accessibility, and low cost, and contemporary studies continue to validate many traditional uses of these plants, highlighting their potential in various areas of human and animal health. In addition, medicinal plants contain a wide variety of secondary metabolites, such as phenolics, terpenes, and alkaloids, which are endowed with a range of biological effects [3-6]. These compounds exhibit biological activity and can develop their effects through different molecular mechanisms, such as the regulation of intracellular signaling pathways that modulate oxidative stress and the inflammatory response. In this way, they may represent therapeutic options in the treatment of several diseases related to these conditions [3-7]. Currently, *Ilex paraguaiensis* is not yet scientifically considered a medicinal plant, but it is used for this purpose in the folk medicine of the peoples of South America. It is combined with various plants to treat conditions like digestive issues, diabetes, hypertension, and high cholesterol [8]. In addition to the cultural and botanical aspects described above, the present work aimed to conduct exploratory research in the literature on the major secondary metabolites of *Ilex paraguaiensis*, as well as the therapeutic effects of the administration or consumption of *Ilex paraguaiensis* against different diseases in distinct organic systems, the secondary metabolites of the plant that are responsible for these effects, and their respective mechanisms of action.

2. Methodology

The present work is a literature review where the identification of articles of interest was performed using the PubMed databases of the US National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/), database Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), and the search tool attached to the Virtual Health Library (VHL). The Institutional Repository of different Brazilian Universities for researching articles along with theses, dissertations, and monographs was also consulted. The predefined keywords "*Ilex paraguaiensis*", "Botanical aspects", "Folk medicine", "Therapeutic uses", "Secondary metabolites", were used in the searches. The search expression was the Boolean operator "AND", limiting the searches to the words of the title or abstract of articles, in English, Portuguese and Spanish, studies with human beings and/or experimental animals, as well as *in vivo* studies and/or *ex-vivo*. To ensure the quality of articles, only indexed publications were included in this database and articles that presented title and abstract according to the theme were included and those that did not fit were excluded.

3. Results and Discussion

3.1. Major secondary metabolites of *Ilex paraguaiensis*

Ilex paraguaiensis has, in its chemical composition, some bioactive compounds that have been studied due to their biological activities. Phenolic compounds are the most abundant secondary metabolites found in the plant and play a defensive role against ultraviolet radiation and pathogens [9]. Phenolic compounds are found in *Ilex paraguaiensis* mainly in the form of phenolic acids and, to a lesser extent, in the form of flavonoids [10]. The literature reports that, among phenolic acids, chlorogenic acids are present in more significant quantities in the plant and are mainly represented by 5-caffeoylquinic acid, 4-caffeoylquinic acid, 3-caffeoylquinic acid, 3,5-dicaffeoylquinic acid, 3,4-caffeoylquinic acid and 4,5-dicaffeoylquinic acid (Figure 3) and that the antioxidant property is the main biological activity related to the content of these secondary metabolites present in *Ilex paraguaiensis* [10]. Alkaloids are also secondary metabolites found in Ilex paraguaiensis. In this way, methylxanthines, such as caffeine and theobromine (Figure 4), are the main purine alkaloids found in the leaves of the plant [12]. These constituents, present in the plant, are mainly responsible for the biological activity in the central nervous system and for the increase in energy expenditure in athletes [13]. The literature also reports that the leaves of *Ilex paraguaiensis* present high amounts of triterpenoid saponins, containing mainly ursolic acid or oleanolic acid nuclei (Figure 4) [14] and that the saponins isolated from *Ilex paraguaiensis,* as well as the aqueous extract of the plant, can inhibit *in vitro* the passive diffusion of bile acids through cellulose membranes, which is a good experimental model that mimics the absorption of bile acids in the ileum and jejunum and thus it is possible to relate a hypocholesterolemic effect of the saponins present in *Ilex paraguaiensis* [14-15].

3.1. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the cardiovascular system

Cardiovascular diseases (CVD) are among the leading causes of death worldwide. Risk factors for CVD include increased blood pressure, dyslipidemia, overweight/obesity, and type 2 diabetes mellitus, among others [16]. In this context, the literature reports that regular consumption of yerba mate leads to a reduction in plasma levels of total cholesterol, LDL cholesterol, and triglycerides, in addition to reducing systolic and diastolic blood pressure in normocholesterolemic and hypercholesterolemic individuals, providing cardiovascular protection [17]. In this way, the literature also reports that the intake of yerba mate infusions for forty consecutive days improves lipid parameters in dyslipidemic individuals, leading to an additional reduction in LDL cholesterol in individuals undergoing statin treatment, which suggests a pharmacological synergism between this class of drugs and the constituents of yerba mate infusion [18]. In contrast, a randomized crossover clinical trial demonstrated no significant acute effects of yerba mate infusion intake on endothelial function, central hemodynamics, and/or autonomic parameters in healthy adults, regardless of infusion temperature [19].

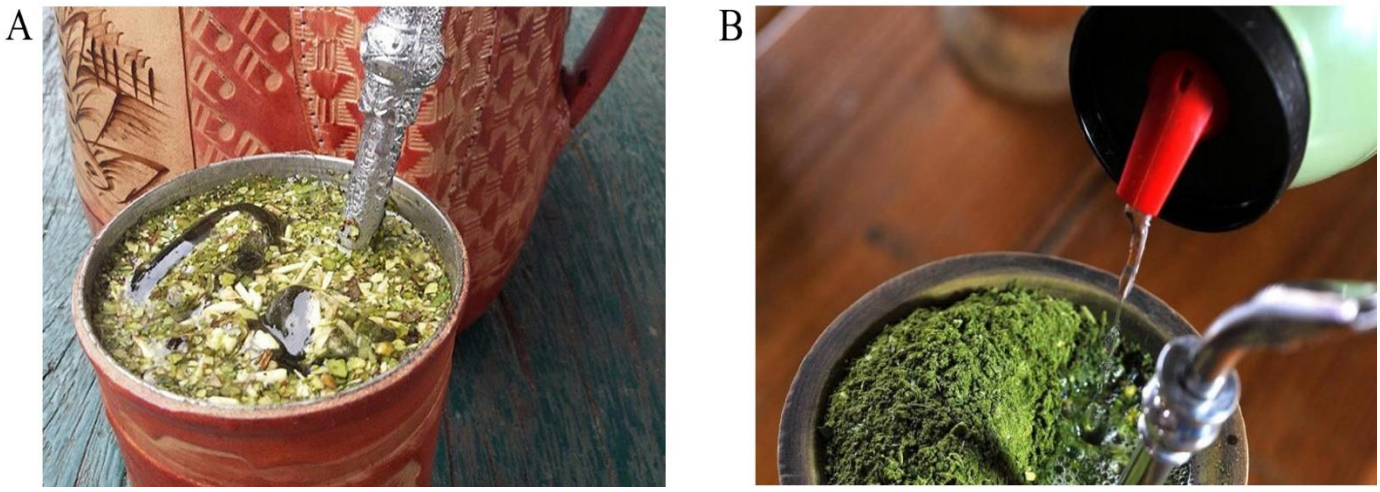

Figure 1. Yerba Mate preparations as a function of water temperature. (A) *Ilex paraguaiensis* prepared to be consumed with cold water (tereré). (B) *Ilex paraguaiensis* prepared to be consumed with hot water (chimarrão).

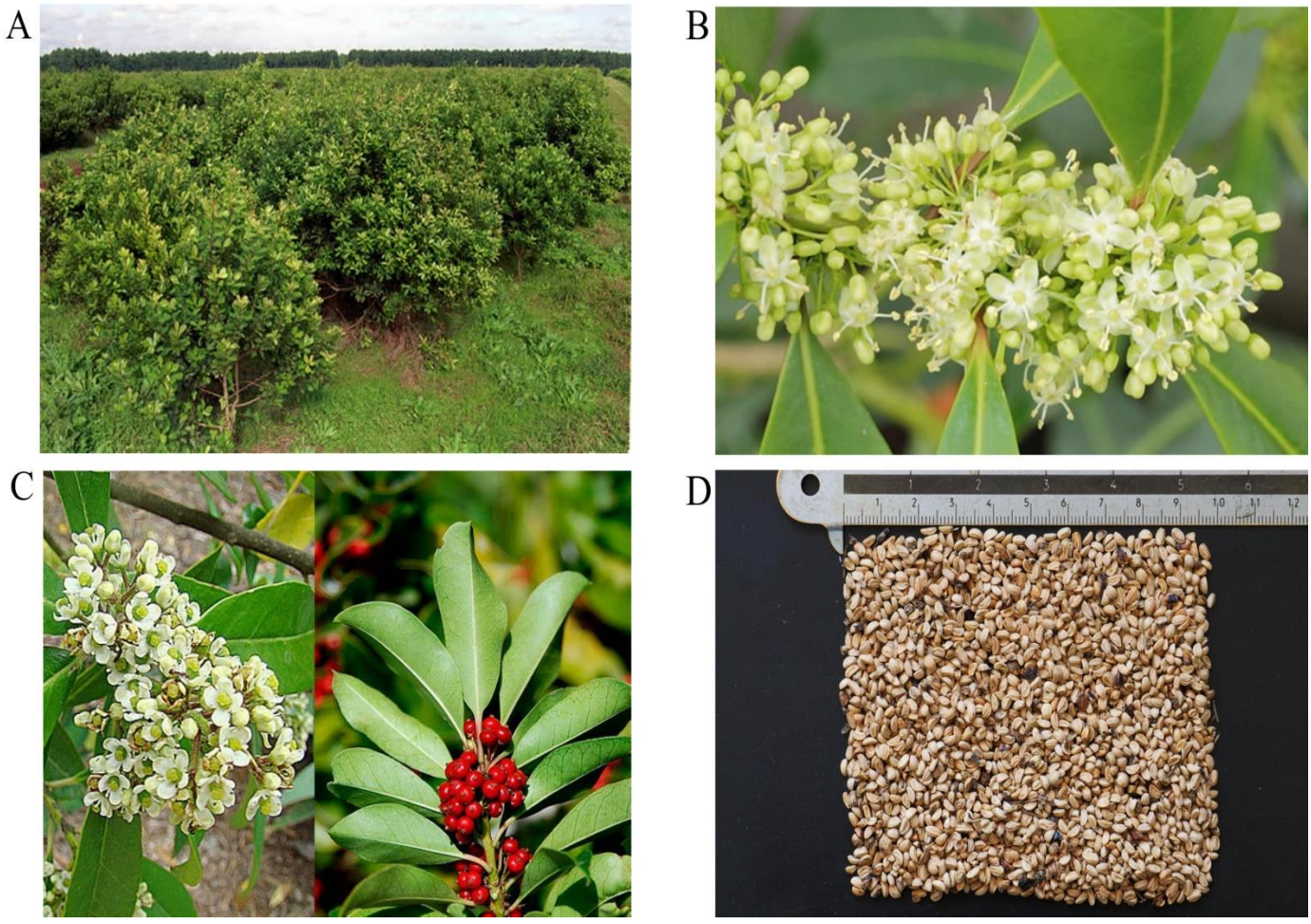

Figure 2. Some cultural and morphological aspects of yerba mate. (A) *Ilex paraguaiensis* cultivation for commercialization. (B) Male flowers. (C) Female flowers and globose drupe fruits. (D) Ripe and dry seeds.

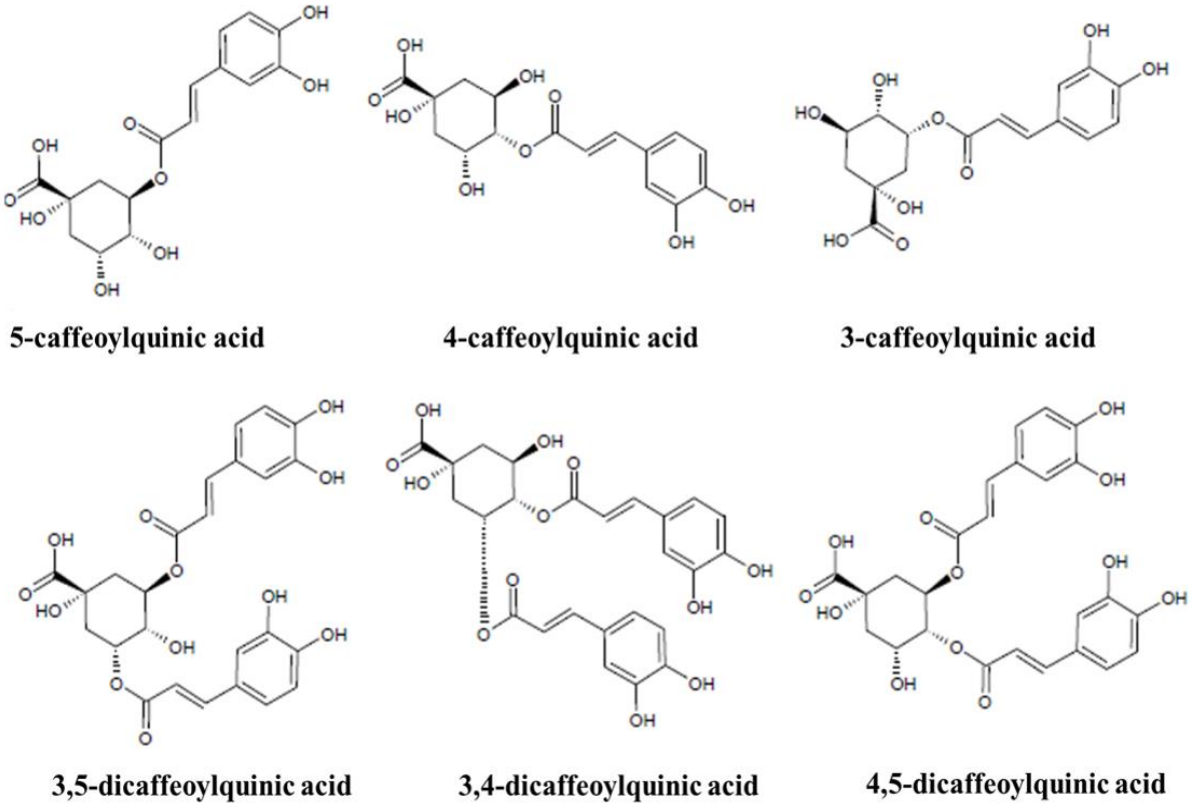

Figure 3. Phenolic acids and chlorogenic acids present in more significant quantities in *Ilex paraguaiensis*

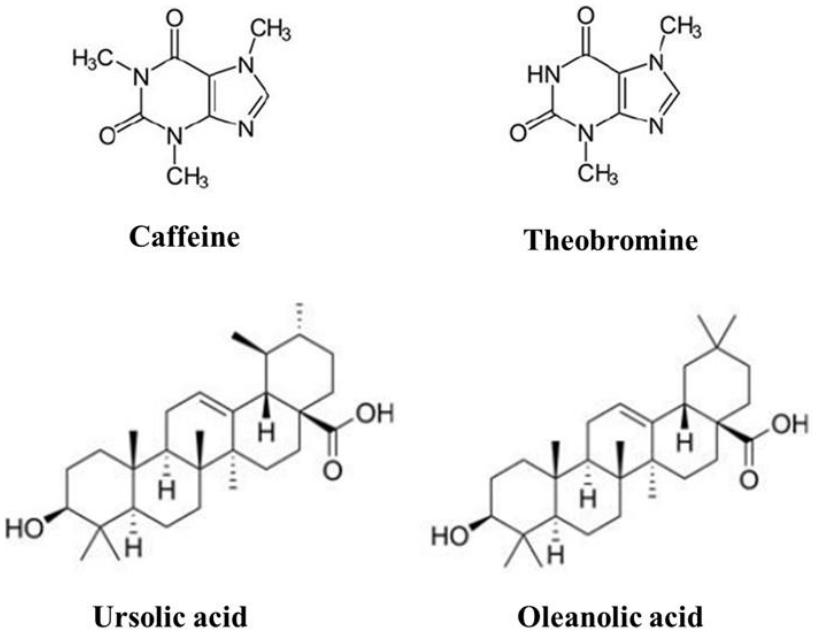

Figure 4. Main alkaloids and saponins that have biological activity and are found in the leaves of *Ilex paraguaiensis*

This suggests that the acute effects of *Ilex paraguaiensis* may be limited or require different doses or durations to manifest. In studies using experimental animal models, the literature reports that *Ilex paraguaiensis* has beneficial effects against cardiac ischemia/reperfusion injuries, and that this benefit is possibly related to mechanisms involving the reduction of oxidative stress and the positive modulation of eNOS/Akt-dependent pathways that determine an increase in the phosphorylation of serine and a subsequent increase in endothelial NO production, resulting in an increase in endothelium-dependent vasodilation [19]. Furthermore, *Ilex paraguaiensis* has been shown to reduce the magnitude of infarction in isolated rat hearts, suggesting a potential cardioprotective effect of this plant [20]. The literature also reports that *Ilex paraguaiensis* may have antiatherosclerotic effects, through its ability to reduce oxidative stress and the levels of inflammatory markers such as IL-1β and IL-6, in addition to increasing the levels of intracellular cGMP, which can reduce platelet aggregation [21]. In studies with high-fat diet models, treatment with *Ilex paraguaiensis* extracts reduces serum triglycerides and cholesterol in rodents, which may reduce the risk of cardiovascular diseases related to increased plasma lipid profile [21]. All of these findings indicate that although the acute effects of *Ilex paraguaiensis* in healthy humans may be limited, there is evidence from preclinical studies suggesting potential cardiovascular benefits, especially in conditions of oxidative stress, increased endothelial NO bioavailability and inflammation.

3.2. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the central nervous system

Folk medicine reports the effects of *Ilex paraguaiensis* on the central nervous system and some of these effects are corroborated by the scientific literature, however, currently, reports in the scientific literature are restricted to preclinical experiments. In this way, the literature reports that this plant has stimulant, anxiolytic, neuroprotective, and antidepressant properties. Santos *et al.* evaluated the behavioral response of mice treated with hydroethanolic (HE) and aqueous (AE) extracts of *Ilex paraguaiensis* leaves, administered acutely and/or chronically [22]. The animals were subjected to tests in an elevated plus maze (anxiety-like paradigm), open field (locomotor activity), or step avoidance task (memory assessment). After the behavioral studies, Santos *et al.* also performed tests on brain acetylcholinesterase (AChE) activity *ex vivo*. The authors describe that chronic treatment with HE produces an anxiolytic effect and increases locomotor activity, in addition to enhancing AChE activity [22]. According to the authors, acute treatment with AE prevents scopolamine-induced memory deficits in the step avoidance task. These results indicate the significance of the CNS effects induced by *Ilex paraguaiensis*, as it is a widely used nutraceutical, and these effects are potentially positively modulated by the cholinergic system and caffeine, a secondary metabolite of the plant [22]. Other studies have shown that different types of *Ilex paraguaiensis* extracts are rich in phenolic compounds in their composition, these phenolic compounds being mainly represented by chlorogenic acid and quercetin, which can cross the blood-brain barrier and reduce neuroinflammation in mice. Furthermore, in models of exposure to chronic stress, treatment with *Ilex paraguaiensis* extract can prevent morphological damage to the brain induced by stress, this prevention being directly related to the antioxidant and anti-inflammatory properties of the extracts [23-25]. The literature also reports that *Ilex paraguaiensis* also has antidepressant and anticonvulsant effects. In this way, in experimental and behavioral models with rodents, the effects on the CNS of the hydroalcoholic extract of *Ilex paraguaiensis* are observed and are related to the negative modulation of NMDA receptors and the decrease in the activity of the L-arginine-nitric oxide pathway, implying a reduction in the immobility time of rodents in forced swimming tests, suggesting an antidepressant effect [26-28]. In pentylenetetrazol-induced seizure models in rats, infusions of *Ilex paraguaiensis* reduced the frequency of seizures and associated neuronal damage, which may be attributed to the polyphenol content found in the infusions [26-28]. These studies suggest that *Ilex paraguaiensis* may have a positive impact on the treatment of pathophysiological conditions of the CNS, and this is due to the antioxidant and anti-inflammatory properties of the secondary metabolites produced by this plant. However, it is important to note that most of the evidence comes from preclinical studies, and more research is needed to confirm these effects in humans.

3.3. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the gastrointestinal system

The consumption of *Ilex paraguaiensis* is closely related to reports in folk medicine about several beneficial effects on the activity of the gastrointestinal system, some of which have already been corroborated by the literature. And one of the main effects is the positive modulation of intestinal microbiota. In this context, the phenolic compounds contained in *Ilex paraguaiensis* can increase the presence of beneficial genera such as *Lactobacillus* sp and *Prevotella* sp., thus contributing to the homeostasis of intestinal microbiota [29]. The literature also reports that *Ilex paraguaiensis* has anti-inflammatory properties on gastrointestinal system that may be beneficial in inflammatory conditions of the intestine, such as colitis. In this way, studies with animal models indicate that chronic treatment with *Ilex paraguaiensis* reduced symptoms of colitis and promoted the differentiation of macrophages towards an anti-inflammatory-M2 phenotype, suggesting therapeutic potential for conditions such as ulcerative colitis [29]. Another notable effect determined by the oral administration of *Ilex paraguaiensis* is gastric protection. Thus, polysaccharides isolated from *Ilex paraguaiensis* can prevent the progression of ethanol-induced gastric lesions in animal models, indicating a possible gastroprotective role for these secondary metabolites [30]. Furthermore, yerba mate has a choleretic effect that is inherent in the increase in bile flow, which can aid in the digestion of fats and improve intestinal propulsion [31-32]. All these effects suggest that *Ilex paraguaiensis* may be a promising option as a nutraceutical for the modulation of the intestinal microbiota and the management of inflammatory gastrointestinal disorders.

3.3. Effects of *Ilex paraguaiensis* on inflammatory processes in the respiratory system

The effects of *Ilex paraguaiensis* on pathophysiological conditions related to inflammatory

processes in the respiratory system have also been studied. Thus, studies in animal models, such as murine pleurisy, have demonstrated that treatment with hydroethanolic extract of *Ilex paraguaiensis* can reduce leukocyte migration, the amount of exudate, and the activities of myeloperoxidase (MPO) and adenosine deaminase (ADA), in addition to decreasing the levels of nitrogen oxides (NOx) during induced pleurisy [33]. These effects are accompanied by the inhibition of the release of pro-inflammatory Th1/Th17 cytokines and by increased production of IL-10, an anti-inflammatory cytokine [33]. Furthermore, the literature reports that the consumption of *Ilex paraguaiensis* can protect against lung inflammation induced by cigarette smoking, reducing macrophage migration and inactivating matrix metalloproteinases [34]. All these findings suggest that *Ilex paraguaiensis* is capable of modulating immune system responses and that this modulation may be beneficial against respiratory inflammatory diseases in experimental animals. In this way, while preclinical data are promising, the translation of these effects to clinical practice requires further investigation, especially through randomized controlled clinical trials that can validate the efficacy and safety of *Ilex paraguaiensis* use in human respiratory conditions.

3.4 Antimicrobial effects of *Ilex paraguaiensis*

Studies have also demonstrated the antibacterial effect of *Ilex paraguaiensis* against different highly pathogenic Gram-positive and Gram-negative bacterial strains capable of determining severe infectious conditions in humans, suggesting that the plant may have a broad spectrum of antibacterial action [35–37]. In this way, the literature reports that *Ilex paraguaiensis* shows promising antibacterial activity against pathogenic bacteria such as *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii* and *Salmonella* spp., and this activity is obtained with variable minimum inhibitory concentrations (MICs) for each pathogenic strain [36–39]. The antibacterial effects of the plant can be attributed to the high concentration of phenolic compounds in its constitution, which are extremely effective against *Escherichia coli* and *Staphylococcus aureus* [39–40]. El-Sawalhi *et al.* identified Libanstin, a new pyrazinone compound present in *Ilex paraguaiensis*, which exhibits antibacterial activity against *Staphylococcus aureus*, with MIC values ranging from 0.19 to 1.56 µg/ml [41]. The literature also reports that aqueous extracts of *Ilex paraguaiensis* exhibit biological activity against non-typhoidal *Salmonella* strains, with MIC values ranging from 0.78 mg/ml to 6.25 mg/ml, which suggests great antibacterial efficacy [42]. Furthermore, Onetto *et al.* reported that ethanolic extracts of *Ilex paraguaiensis* demonstrated activity against carbapenemase-producing and carbapenem-resistant bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with MIC and minimum bactericidal concentration values ranging from 0.125 to 32 mg/ml [43]. Regarding the combination of *Ilex paraguaiensis* extracts with conventional antibiotics drugs, the literature reports that *Ilex paraguaiensis* can determine a synergistic effect of the additive type when combined with macrolide antibacterials such as clarithromycin. In contrast, the association of *Ilex paraguaiensis* with aminoglycosides drugs such as gentamicin can result in antagonism and impairment of the efficacy of gentamicin [37]. These findings suggest that the antibacterial effect of *Ilex paraguaiensis* extracts probably occurs at the level of inhibition of bacterial protein synthesis. However, other antibacterial mechanisms proposed for *Ilex paraguaiensis* are iron chelation that results in alteration of bacterial metabolism and reduction of catalase activity [44]. Although these studies do not reveal the exact mechanism of action of these substances, it is possible to assume that *Ilex paraguaiensis* has secondary metabolites that present significant antibacterial potential and that can be explored for the development of new antimicrobial agents, especially in the context of increasing bacterial resistance.

3.5. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the renal system

In folk medicine, infusions of *Ilex paraguaiensis* are well-known for their supposed diuretic properties, however, the effects of this plant on the renal system are not widely documented in the literature from studies conducted on human beings. In a case-control study, Veiga *et al.* showed that the consumption of *Ilex paraguaiensis* infusions may be associated with a lower prevalence of arterial hypertension in postmenopausal women due to the diuretic effect induced by the consumption of the infusion [45]. Although Veiga *et al.,* suggests a direct relationship between the consumption of *Ilex paraguaiensis* and the reduction in diagnoses of arterial hypertension, the results obtained are not inherent to a study specifically designed to evaluate the antihypertensive effects of *Ilex paraguaiensis*. In addition, the results of Veiga *et al.* are based on self-reports, which may introduce bias. Despite these limitations, studies with experimental animals indicate a possible beneficial effect of *Ilex* sp on renal function [46]. In this way, treatment with *Ilex paraguaiensis* infusion results in a reduction in renal oxidative stress and improves the glomerular filtration rate (GFR) in rats subjected to oxidative stress induced by $K_2Cr_2O_7$ (potassium dichromate), suggesting that the infusion has an important nephroprotective effect on GFR [47]. The results obtained in the study by Kuropka *et al.* corroborate these findings and attribute the nephroprotective effects to the saponins present in the infusion of *Ilex paraguaiensis* [48]. Kuropka *et al.* also suggest that the saponins present in the extracts are not nephrotoxic and offer a protective role for the kidneys, both in normal diets and in diets rich in cholesterol [48]. Although all these findings suggest potential indirect benefits, more specific studies are needed to elucidate the direct effects of *Ilex paraguaiensis* on the renal system.

3.6. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the bone system

Popularly, the consumption of Ilex paraguaiensis has been associated with beneficial effects on bone health and the literature has reported that the consumption of yerba mate infusions can positively influence bone mineral density (BMD) and osteoblastic differentiation. In this way, the soluble extract of *Ilex paraguaiensis* can stimulate osteoblast differentiation of mesenchymal stromal cells derived from bone marrow, resulting in increased alkaline phosphatase activity and bone mineralization, in addition to upregulating the expression of genes associated with bone formation, such as Runx2, osterix and osteocalcin [49]. These effects are mediated by changes in MAPK signaling pathways, suggesting a potential promoting effect on bone formation at

adequate concentrations [49]. Furthermore, an observational study in postmenopausal women associated regular consumption of *Ilex paraguaiensis* with higher BMD in the lumbar spine and femoral neck, suggesting a protective effect against bone loss [50]. In animal models, treatment with *Ilex paraguaiensis* extracts appears to partially mitigate the adverse effects of a low-calcium diet on trabecular bone volume, although it does not completely reverse the negative impacts on biomechanical properties and trabecular connectivity [51]. All these studies indicate that chronic *Ilex paraguaiensis* consumption may be beneficial for bone health, possibly due to its antioxidant and anti-inflammatory effects, which contribute to the maintenance of bone integrity. However, it is important to consider that most of the available evidence comes from in vitro studies and animal models, with some observational evidence in humans. Therefore, further clinical research is needed to confirm these effects and determine the optimal doses to maximize the bone benefits of *Ilex paraguaiensis* consumption.

3.6. Effects of *Ilex paraguaiensis* on pathophysiological conditions of the pancreatic system and diabetes

In folk medicine, the consumption of *Ilex paraguaiensis* is associated with the treatment of diabetes [52]. However, scientific studies corroborate the reports in folk medicine and have shown beneficial biological effects of consuming yerba mate on the pancreatic system and the management of diabetes in humans [53-55]. *Ilex paraguaiensis* has antioxidant and antihyperglycemic properties that can positively influence glucose homeostasis, insulin resistance, and pancreatic function during diabetes and metabolic syndrome [53-55]. Studies conducted with animal models also reveal that dietary supplementation with *Ilex paraguaiensis* can improve insulin sensitivity and insulin secretion in pancreatic islets by inducing increased mRNA levels of IRS-1 and PI3K, resulting in improved glucose tolerance and glucose-stimulated insulin secretion in rats. These effects are attributed to *Ilex paraguaiensis* ability to reduce oxidative stress and enhance insulin sensitivity [56]. Furthermore, the literature also reports that *Ilex paraguaiensis* improves energy metabolism in rodents [57] and glucose homeostasis *in vitro* and *in vivo* studies, noting that this ability is related to both a reduction in the oral glucose tolerance curve and the induction of insulin secretion, which occurs similarly to the effect of glipizide, a conventional oral hypoglycemic drug belonging to the sulfonylurea class [58]. Oliveira *et al.* showed that Ilex paraguaiensis consumption can induce a decrease in gene expression for SGLT1 in the intestines of rodents, implying a reduction in glucose absorption and glycemia [59]. These findings suggest that *Ilex paraguaiensis* may serve as an ally in the management of diabetes and the protection of pancreatic function, although further clinical studies are needed to confirm these effects in humans and determine the ideal doses for therapeutic use.

4. Final considerations

The secondary metabolites of *Ilex paraguaiensis* described in this study reinforce the idea that this plant has biological potential to be considered an adjuvant in the treatment of different pathophysiological conditions, especially those related to inflammatory conditions. Future research with *Ilex paraguaiensis* should prioritize randomized clinical trials to establish dose-response relationships, long-term safety profiles and molecular mechanisms inherent to the beneficial effects determined by this plant and/or its secondary metabolites in different organ systems, which may contribute to *Ilex paraguaiensis* being considered a promising candidate for the development of new and safer drugs in the therapy of different diseases.

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