

## Recent advances in the bioactive properties of yerba mate

### Actualización en las propiedades bioactivas de la yerba mate

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#### ABSTRACT

Yerba mate (*Ilex paraguariensis* A. St. Hil.) is a perennial shrub of Aquifoliaceae family that grows naturally in South America and is cultivated in Argentina, Brazil, Chile, Paraguay and Uruguay. The aim of this review is to summarize concisely recent advances published in the last 4 years on the antioxidant, anti-diabetic, anti-obesity and antimutagenic activities of yerba mate. For this, a search was made in some of the databases on the web as PubMed, Google Scholar and Medline. There are several studies in the literature reporting the effects of yerba mate in the metabolic profile related to diabetes and obesity. Among the findings of the researches are the reduction of body weight, liver triglycerides and white adipose tissue. It also increases the levels of glucagon-like peptide 1 and leptin, reduces blood glucose and insulin resistance and contributes to a lower rate of growth of adipose tissue. Regarding the antioxidant properties, chlorogenic acid, caffeic acid and rutin are the compounds that contribute to the antioxidant activity. The aqueous extract also protects the red cells of hemolysis induced by hydrogen peroxide. In mutagenesis, researches suggest that dicaffeoylquinic acids in yerba mate could be potential anti-cancer agents. Saponins in leaves of yerba mate prevent the inflammation and colon cancer in vitro. Already in skin cancer, oral and topical treatment of rats exposed at ultraviolet radiation with mate tea prevented the lipid peroxidation and DNA damage.

**Keywords:** diabetes, *Ilex paraguariensis*, obesity, antioxidant, mutagenesis.

## RESUMEN

La yerba mate (*Ilex paraguariensis* A. St. Hil.) es un arbusto perenne de la familia Aquifoliaceae, que crece naturalmente en Sudamérica y es cultivada en Argentina, Brasil, Chile, Paraguay y Uruguay. Esta revisión se centró en las publicaciones de los últimos 4 años sobre las actividades antioxidante, antidiabética, antiobesidad y antimutagénicas de la yerba mate. Para esto, se efectuó una búsqueda en la que se utilizaron algunas de las bases de datos en la web como PubMed, Google Académico y Medline. Se investigaron los efectos de la yerba mate en el perfil metabólico relacionados con la diabetes y obesidad. Entre los hallazgos estuvieron la reducción del peso corporal, triglicéridos del hígado y tejido adiposo blanco. Con el consumo de la yerba mate se observó que los niveles del glucagon like peptide 1 y leptina aumentan, así como reducen la glucemia y resistencia a la insulina; contribuyendo a un menor crecimiento del tejido adiposo. El ácido clorogénico, ácido caféico y rutina contribuyen con la actividad antioxidante. El extracto acuoso protege a las células rojas de la hemólisis inducida por el peróxido de hidrógeno. En la mutagénesis, las investigaciones sugieren que los ácidos dicafeoilquinico en la yerba mate pueden ser agentes anticancerígenos potenciales. Las saponinas en las hojas previenen la inflamación y el cáncer de colon in vitro. En el cáncer de piel, el tratamiento oral y tópico de ratones expuestos a la radiación ultravioleta evitó la peroxidación lipídica y el daño del ADN.

**Palabras clave:** diabetes, *Ilex paraguariensis*, obesidad, antioxidante, mutagénesis.

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## INTRODUCTION

*Ilex paraguariensis* A. St. Hil., a native South American holly shrub from the Aquifoliaceae family, is mainly produced and consumed in the countries of Argentina, Brazil, Chile, Paraguay, and Uruguay.<sup>1</sup> Yerba mate, processed from the leaves and small stems of *I. paraguariensis*, is a nonalcoholic beverage consumed socially primarily in these countries, and like coffee, primarily for its caffeine content. Typical consumption of yerba mate is taken from a small cup or "mate". Small amounts of hot water are regularly poured over a serving, ca. 50 g of packed tea. The beverage is then drunk by using a metal straw or "bombilla", which has small holes that prevent the leaves from being consumed.<sup>2-4</sup>

Yerba mate has a very important social role and the act of offering it and sharing has connotations similar to those of the tea ceremony for some oriental cultures. Argentina is the first exporter of yerba mate while Uruguay has the highest per capita consumption: 6–8 kg/person/year. Argentina follows with 5 kg/person/year. Only 3 states in Brazil have mate drinkers in their population (lowering the per capita intake), but up to 70 % of the male population in the states of Rio Grande do Sul, Santa Catarina and Parana drinks "chimarrão" daily.<sup>5</sup>

Although with some exceptions, research on biomedical properties of this herb has had a late start and strongly lags behind the impressive amount of literature on green tea and coffee, also a reflection of the different economic development and sizes of the populations consuming the latter.<sup>3</sup>

However, in the past 19 years, there was a several-fold increase in the literature studying *I. paraguariensis* properties, that have been extensively reviewed earlier.<sup>3,6,7</sup>

The aim of this review is to summarize concisely recent advances published in the last 4 years on the antioxidant, antidiabetic, antiobesity and antimutagenic activities of yerba mate. For this, was performed a search in some of the databases on the web as PubMed, Google Scholar and Medline.

#### MAIN BIOACTIVE COMPONENTS OF ILEX PARAGUARIENSIS EXTRACTS

Yerba mate green (non-roasted) extracts contain purine alkaloids (methylxanthines), flavonoids, vitamin A, B complex, C and E, tannins, chlorogenic acid and its derivatives, and numerous triterpenic saponins derived from ursolic acid, known as matesaponins.<sup>3,6,8,9</sup> Though the presence of methyl xanthines account for many of the pharmacological activities of yerba mate, many other important properties have been found to be independent of the presence of these compounds.

Yerba mate extracts polyphenol levels are higher than those of green tea and parallel to those of red wines.<sup>10,11</sup> The extracts are especially rich in chlorogenic acids.<sup>3,6,7,8,12</sup> Chlorogenic acids are a family of esters formed between certain trans cinnamic acids and (–)-quinic acid and are also major phenolics compounds in coffee, strawberries, pineapples, apples, sunflower and blueberries. 5–caffeoylquinic acid (5–CQA) is the only chlorogenic acid commercially available and has been extensively studied due to its antioxidant activity. Chlorogenic acids are free radical and metal scavengers; may interfere with glucose absorption and has been shown to modulate gene expression of antioxidant enzymes, among other biological activities.<sup>13-16</sup>

Yerba mate also contains saponins that are known to bind bile salts<sup>6,17</sup> and have high foaming potential, non-ionic character and low skin toxicity being one promising alternative foaming agent of natural origin and renewable.<sup>18</sup>

Roasted extracts of *I. paraguariensis* (as consumed in Sao Paulo and Rio de Janeiro in Brazil) keep essentially the same components with the addition of melanoidins, which have some bioactive properties of their own.<sup>6</sup>

#### EFFECTS OF ILEX PARAGUARIENSIS EXTRACTS ON LIPID METABOLISM, DIABETES AND OBESITY

There are several studies in the literature reporting the effects of oral administration of yerba mate in the metabolic profile related to diabetes and obesity. The administration of the extract in ddY male mice resulted in a significant reduction in body weight and food intake after chronic ingestion of extract for three weeks (50, 100 mg/kg). The treatment improved plasma lipids (triglycerides–TG, fatty acids and cholesterol). It also reduced liver TG and the weights of the liver and white adipose tissue (WAT). The most significant finding in this study was that chronic administration of yerba mate induced significant increases in glucagon–like peptide 1 (GLP–1) levels and leptin levels in high–fat diet (HFD)–fed ddY mice compared with the controls.<sup>19</sup> GLP–1 is an incretin secreted by the intestinal enteroendocrine L–cells predominantly found in the ileum and colon. GLP–1 is a satiety signal released into the circulation after a meal or upon nutrient ingestion.<sup>20</sup>

Other study investigated the effects of yerba mate aqueous extract on metabolic syndrome in Tsumura Suzuki obese diabetic (TSOD) mouse model, particularly the effects of long-term oral administration on hyperglycemia, hyperinsulinemia, dyslipidemia, and metabolic syndrome histopathology. Yerba mate significantly lowered blood glucose (BG) level and showed significant ameliorative effects on obesity and adipose tissue, and improving effects on glucose and lipid metabolic indices. One of the most important findings in this study was that yerba mate significantly lowered BG level after insulin injection in insulin tolerance test (ITT), indicating a significant decrease in insulin resistance (InsR). It also lowered BG after glucose injection in intraperitoneal glucose tolerances test (ipGTT), indicating a significant increase of glucose uptake and tolerance.<sup>21</sup>

A similar study evaluated the effects of yerba mate extract on weight loss, obesity-related biochemical parameters, and diabetes in high-fat, diet-fed mice. Yerba mate has the ability to decrease the differentiation of pre-adipocytes and to reduce the accumulation of lipids in adipocytes, both of which contribute to a lower growth rate of adipose tissue, lower body weight gain, and obesity. The data revealed that yerba mate treatment affects food intake, resulting in higher energy expenditure, likely as a result of higher basal metabolism in yerba mate-treated mice. Furthermore, effects of yerba mate on lipid metabolism included reductions in serum cholesterol, serum triglycerides, and glucose concentrations in mice that were fed a high fat diet.<sup>22</sup>

The glucose homeostasis was also investigated by analyzing of the acute in vivo effect and short and long-term in vitro effect of native and commercial samples of *I. paraguariensis*. Also, the potential effect of *I. paraguariensis* on one of the best endogenous glucose regulators, insulin secretion, was investigated. The results for the serum glucose—lowering indicated that both fractions and both infusions were able to improve significantly the oral glucose tolerance curve. Additionally, both the ethyl acetate (EtOAc) and n-butanol (n-BuOH) fractions induced—insulin secretion, but EtOAc induced an early (at 15 min) and late (at 60 min) biphasic peak of insulin secretion similar to glipizide stimulatory effect. Both fractions increased liver glycogen content compared with fasted normal rats. Also, EtOAc and n-BuOH fractions inhibited in vitro disaccharidases activities after an acute treatment. The evident reduction of protein glycation by glucose or fructose with EtOAc and n-BuOH fractions increased from 7 to 28 days of in vitro incubation. Inhibition of bovine serum albumin glycation by glucose and fructose, by around 50 % and 90 %, respectively, was observed. Additionally, the green and roasted mate infusions reduced the formation of advanced glycation end-products (AGEs) in a characteristic long-term effect. In conclusion, this study showed that *I. paraguariensis* has an anti-hyperglycemic potential role able to improve the diabetic status and is probably a source of multiple hypoglycemic compounds.<sup>23</sup>

To clarify the effects of natural dietary components on the metabolic consequences of obesity, a study examined the effects of yerba mate extract on both central and peripheral inflammatory effects of diet-induced obesity and correlated the hypothalamic tumor necrosis factor (TNF)— $\alpha$  level with adipose depot weight. Yerba mate extract intake blunted the proinflammatory effects of diet-induced obesity in rats by reducing the phosphorylation of hypothalamic IKK and NF- $\kappa$ Bp65 expression and increasing the protein levels of I $\kappa$ B $\alpha$ , the expression of adiponectin receptor-1 and consequently the amount of IRS-2. Moreover, the increase in interleukin (IL)-6 levels in the liver and muscle and of the IL-10/TNF- $\alpha$  ratio in groups that received yerba mate extract showed the anti-inflammatory effects of this natural substance. Taken together, the data suggested that the use of yerba mate extract may be useful for reducing low-grade obesity-associated inflammation.<sup>24</sup>

Adipogenesis was evaluated by the effects of yerba mate extract and its principal bioactive compounds on adipogenesis. The anti-adipogenic effects of yerba mate, chlorogenic acid, quercetin and rutin were evaluated in 3T3—L1 cells using a PCR array. The results obtained in vitro were validated in vivo in a high-fat diet-induced model of obesity. The in vitro and in vivo results demonstrated that yerba mate extract down—regulated the expression of genes that regulate adipogenesis.<sup>25</sup>

More recent study showed the potential beneficial effects of *I. paraguariensis* aqueous solution upon body composition, glycemia, lipid and hormonal profiles, leptin signaling and neuropeptide—Y (NPY) content in early weaned rats developed obesity, hyperleptinemia, leptin and insulin resistance at adulthood. The therapy with yerba mate solution was capable to reverse abdominal obesity, leptin resistance and hypertriglyceridemia, suggesting an important role of this bioactive component in the management of obesity.<sup>26</sup>

#### EFFECTS OF ILEX PARAGUARIENSIS EXTRACTS WITH ANTIOXIDANT PROPERTIES

The infusion of aerial parts of *I. paraguariensis* is widely consumed. Its antioxidant activity suggests an important role of this plant in the treatment/prevention of oxidative stress related diseases. Plant extract active compounds are frequently found in esterified form that may be poorly absorbed. Hydrolysis of the extract is a possible approach to increase its bioavailability. The study was performed a phytochemical analysis and evaluated in rats the plasma concentration and tissue distribution of antioxidant compounds in the hydroethanolic extract of *I. paraguariensis*, before and after enzymatic hydrolysis. Both extracts presented high antioxidant activity and phenolic content. Rats given single or repeated doses of the hydrolyzed extract showed increased plasma antioxidant activity and higher plasma levels of caffeic acid. However, no changes of endogenous antioxidants were observed. In conclusion, hydrolysis of the extract of *I. paraguariensis* is a strategy to improve its bioavailability and in vivo antioxidant activity.<sup>27</sup>

The main bioactive compounds (caffeine, caffeic acid derivatives and rutin) extracts of *I. paraguariensis* with antioxidant activity (DPPH scavenging activity of free radicals and preventing lipid peroxidation) were investigated. Green (non—roasted) and commercial products were used to prepare aqueous extracts. The main bioactive compounds were identified and quantified by HPLC-DAD. The antioxidant activities of the pure compounds in the concentrations present in the extracts were also analyzed. Results demonstrated that chlorogenic acid, caffeic acid and rutin contribute to the antioxidant activity. However, caffeine induced lipid peroxidation of linoleic acid acting as a pro-oxidant compound. The caffeine content in the green extracts was lower when compared to the commercial extracts. The antioxidant and pro-oxidant antagonistic effects of the compounds in the amounts present in the extracts resulted in higher antioxidant potency of the green extracts when compared to the commercial ones.<sup>28</sup>

Another study evaluated the protective effect of yerba mate aqueous extract (green leaves) on the hemolysis of red blood cells induced by hydrogen peroxide and to correlate this activity with the enzymatic activity related to hydrogen peroxide metabolism. The antioxidant activity of chlorogenic acid and caffeine was also analyzed to evaluate their contribution to the activity of the crude extract. The extract as well as the isolated compounds protected red blood cells from hemolysis. This effect was related to a catalase-like activity.<sup>29</sup>

## EFFECTS OF ILEX PARAGUARIENSIS EXTRACTS ON MUTAGENESIS

The biological functions of caffeoylquinic acid (CQA) derivatives from various plant sources have been partially elucidated. Dicafeoylquinic acid (diCQA) was isolated and purified from yerba mate tea leaves and assessed their anti-inflammatory and anti-cancer capabilities in vitro and explored their action mechanism. Methanol extracts of dried yerba mate leaves were resolved by flash chromatography and further purified resulting in two fractions one containing 3,4—and 3,5—diCQAs and the other 4,5—diCQA. Both fractions inhibited macrophage inflammation by suppressing nitric oxide/inducible nitric oxide and prostaglandin E2/cyclooxygenase-2. The diCQA fractions inhibited human colon cancer cells CRL-2577 (RKO) and HT-29 cell proliferation by inducing apoptosis in a time- and concentration-dependent manner. The diCQA fractions increased the activation of caspase-8 leading to cleavage of caspase-3 in both RKO and HT-29 colon cancer cells. The results suggest that diCQAs in yerba mate could be potential anti-cancer agents and could mitigate other diseases also associated with inflammation.<sup>30</sup>

In another study by the same authors was to quantified and purified saponins from yerba mate dry leaves, and assessed their anti-inflammatory and apoptotic mechanisms in human colon cancer cells in vitro. Matesaponins were extracted with methanol from dry leaves, partially purified and quantified. Leaves contained 10-15 mg/g dry weight total saponins, predominantly matesaponins 1 and 2. HPLC and LC/ESI-MS-MS identified saponins in six preparative chromatographic fractions (A, B, C, D, E, and F). Fraction F reduced nuclear translocation of nuclear factor- $\kappa$ B subunits p50 (49.8 %) and p65 (49.0 %) and induced apoptosis through suppression of Bcl-2 and increased Bax protein expressions and activated caspase-3 activity. Saponins in leaves of yerba mate prevented inflammation and colon cancer in vitro.<sup>31</sup>

Still addressing the cells of the colon, the study were evaluated potential toxic effects of water and ethanol (by Soxhlet extraction and shaking extraction methods) and free radical scavenging properties of yerba mate extracts on human normal colonic epithelial and human colon carcinoma cells. Depending on kind of extract, their concentration, kind of cells they influenced on and method of analysis, different toxic and stimulatory of cells viability effects were observed. Yerba mate extracts demonstrated strong free radical scavenging activity. The plant extracts also expressed immunomodulatory effects influencing on IL-6 production by normal and tumor cells. *I. paraguariensis* extracts stimulated normal colonic cells for the cytokine production while limited such production by human colon tumor ones. Yerba mate water and ethanolic extracts possess strong pharmacological activities against normal colonic epithelium and colon derived tumor cells. This activity may be used in health promoting endeavors and could be defined as chemopreventive factors.<sup>32</sup>

The skin cancer was also addressed in a study that evaluated the effects of green and mate teas on oxidative and DNA damages in rats exposed to ultraviolet radiation. Were utilized 70 adult male Wistar rats that received daily oral or topic green or mate tea treatment during exposed to radiation by seven days. After, animals were killed by decapitation. Thiobarbituric acid-reactive species levels, protein oxidative damage were evaluated in skin and DNA damage in blood. The results showed that the rats exposed to ultraviolet radiation presented DNA damage in blood and increased protein carbonylation and lipid peroxidation in skin. Oral and topic treatment with green tea and mate tea prevented lipid peroxidation, both treatments with mate tea also prevented DNA damage. However, only topic treatment with green tea and mate tea prevented increases in protein carbonylation. The findings contribute to elucidate the beneficial effects of green

tea and mate tea, here in demonstrated by the antioxidant and antigenotoxic properties presented by these teas.<sup>33</sup>

## CONCLUSION

Research on the effects of *I. paraguariensis* in health and disease has confirmed its antioxidant, anti-inflammatory, antimutagenic, anti-diabetic and lipid-lowering activities. The evidence seems to provide support for beneficial effects of yerba mate drinking on chronic diseases with inflammatory components and lipid metabolism disorders, diabetes and uncoupling of electron transport.

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