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Yerba maté: Pharmacological Properties, Research and Biotechnology

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ABSTRACT

Maté (*Ilex paraguariensis* St. Hilaire) is a plant originary from the subtropical region of South America, and present in the South of Brazil, North of Argentina, Paraguay and Uruguay. *Maté* beverages have been widely consumed for hundreds of years as infusions popularly known as *chimarrão*, *tererê* (both from green dried mate leaves) and *maté* tea (roasted mate leaves). The popular medicine and the herbalists recommend it for arthritis, migraines, constipation, rheumatism, hemorrhoids, obesity, fatigue, retention of liquid, hypertension, and for stomach and liver diseases. Recently published research has proved scientifically the actions of *maté* which may explain many of the cited pharmacologic effects such as its chemopreventive activity, cholerectic effect and intestinal propulsion, vasodilatation effect, inhibition of the glication and as a free radical scavenger. *Maté* beverages are rich in many bioactive compounds such as caffeine, phenolic compounds (mainly phenolic acids) and saponins. This review discusses the latest scientific data on *maté* physiological properties and their correlation with the bioactive compounds present in the *maté* leaves and aqueous infusions.

Keywords: biological effects, caffeine, functional food, *Ilex paraguariensis*, minerals, phenolic compounds, saponins
Abbreviations: LDL, Low density lipoproteins; **CGA**, Chlorogenic acid; **5-CQA**, 5 caffeoylquinic acid; ***p*CoQA**, *p*-coumaroylquinic acid; **FQA**, feruoylquinic acid ; **diCQA**, di esters from caffeoyl quinic acids; **HPLC/MS**, High Pressure Liquid Cromatography/ Mass Spectrometry; **TBARs**, Thiobarbituric acid-reactive substances

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INTRODUCTION

Yerba maté (*Ilex paraguariensis*) is a plant originary from the subtropical region of the South America, present in the South of Brazil, North of Argentina, Paraguay and Uruguay. It was consumed by native South American Indians when the new world was discovered by the Europeans. Nowadays the aqueous extract of yerba maté (*product constituted exclusively from* dried and crumbled leaves and branches of *I. paraguariensis*, according to Brazilian and Argentinian legislation) is consumed at a rate of more than 1 liter per day by millions of people and constitutes the main alternative to coffee and tea (Mosimann *et al*. 2005). This product is prepared mainly as four different types of beverages: the *chimarrão* and *maté cocido*, consumed in the south of Brazil, Uruguay, Argentina and Paraguay; the *tererê*, consumed in the central west of Brazil and Paraguay, and the *maté* tea, consumed in the South-east of Brazil, Argentina and Uruguay. Both *chimarrão* and *tererê* are made with green dried and crumbled *maté* leaves. The first is prepared with hot water and the second with cold water. The beverages are prepared by compacting a certain amount of *maté*, previously moistened with water, against the wall of a vessel made from a gourd or "*cuia*". The beverage is drunk by sucking through a silver pipe called "*bomba*", which has a flattened perforated disc at the end immersed in the infusion to act as a filter (Mazzafera 1997). *Maté* tea is prepared with roasted leaves and brewed as any other herbal tea (Bastos *et al*. 2005). *Maté cocido* refers to green *maté* brewed as a herbal tea, usually commercialized in bags, as *maté*-tea.

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Invited Review

Table 1 International patents of products from *Ilex paraguariensis* (1963-2006).

Type of product	Number of International Patents
Weight loss/thermogenesis supplements	11
Cosmetic with slimming effects	5
Supplement to reduce glucose/cholesterol levels	2
Supplement against the oxidative stress and its consequences	1
Supplements to treat metabolic syndrome and obesity	1
Product for promotion of alcohol and acetaldehyde degradation	1
Energy drink/ powder	2
Sports drink	1
Aphrodisiac supplement	1
Hair cosmetic	2
Supplement against insomnia	2
Total	**29**

Source: www.isiknowledge.com - Derwent Innovations Index (2007)

The main *maté* producer is Argentina (270.000 tons in 2005), followed by Brazil (238.869 tons in 2005) (IBGE 2005; Parra 2007), and most part of the produced *yerba maté* is processed and sold as *chimarrão*.

The *maté* culture has great economic and social importance, once it is carried through by a great number of small producers and cooperatives. The genetic improvements of the culture are recent; having began in the 1970s in Argentina and in the 1990s in Brazil. They have been focused mostly the adaptation, production of green mass and resistance to plagues and diseases (Resende *et al*. 2000).

The processing of *yerba maté* consists of three different stages: a) a rapid drying process called "*sapeco*", made within 24 hours after the harvest, aiming to inhibit enzymatic activity and lower the moisture level; b) a partial drying stage called "*secado*" that reduces the moisture to a level between 3 and 6% that usually takes place in rotating drums heated by the burning of wood or gas ("*barbaqua*") or, depending on the technological level of the producer, takes place in more modern machines that reduces the processing time, and c) a further drying and subsequent grinding stage, after which the *yerba maté* is called "*cancheada*" (Esmelindro *et al*. 2002; Bastos *et al*. 2006). Processing conditions (time/temperature of the drying stages) and other parameters such as sex of the plant, genetic variability and type of ground may differ among diverse producers and have influence on the quality, sensorial characteristics and amount of bioactive substances of the final product (Resende *et al*. 2000; Esmerelindro *et al*. 2002). *Maté* processing remains practically unchanged from ancient times. Differences among the raw material as well as the design of the *maté* drying plants result in a product that does not reproduce chemical composition from one year to another.

The popular medicine and the herbalists recommend the use of *yerba maté* for arthritis, headache, constipation, rheumatisms, hemorrhoids, obesity, fatigue, fluid retention, hypertension, slow digestion and hepatic disorders (Bastos and Torres 2003). Recent published research have scientifically proven the actions of *I. paraguariensis* that explain many of the cited pharmacologic effects, such as: chemopreventive activities (preventing cellular damage that may cause chronic diseases) (Ramirez-Mares *et al*. 2004; Filip *et al*. 2007), choleretic effect and intestinal propulsion (Gorzalczany *et al*. 2001) vasodilatation effect (Baisch *et al*. 1998), inhibition of glication (non-enzymatic reaction between blood sugar, proteins and lipids, forming products that accumulate providing stables sites for catalyzing the formation of free radicals) (Lunceford and Gugliucci 2005) and inhibition of oxidative stress (Gugliucci 1996; Gugliucci and Menini 2002).

The increasing numbers of patents related to *yerba maté* products indicates the recent interest in the biological activities of this plant as well as its economical potential. There are 29 international patents of products made with *Ilex paraguariensis* registered since 1963, with several indications, as shown in **Table 1**. The majority of them were registered after 2000.

Maté contains many bioactive compounds. Native South Americans were aware of its stimulating properties due to caffeine, which was once incorrectly named *mateine*. Nowadays, *maté* beverages are also recognized as a rich source of phenolic acids, which are responsible for the *in vivo* and *in vitro* antioxidants activities demonstrated by many studies. The main phenolic acids presents in *maté* are the chlorogenic acids. In addition to substantial amounts of purine alkaloids and phenolic acids, the leaves of *maté* also contain triterpenoid saponins. These bitter and higher water-soluble compounds are likely to be responsible in part for the taste and foaming of the beverages and explain their choleretic effect.

Compared to other stimulant beverages, such as tea and coffee, there are few scientific reports relating to *yerba maté* and, unfortunately, the first papers published relating *yerba maté* and public health brings epidemiological data on the relationship of *chimarrão* intake and cancer of the esophagus. It seems, from these epidemiological studies, that the high incidence of esophageal cancer in the population that heavily consumes *chimarrão* is due to the water temperature, and not due to substances naturally present in the plant material. The same fact is observed in Asia, where populations drinking large volumes of tea at a high temperature present the same pathology. Only in the latter part of the 1990s was the first report on the antioxidant effect of *yerba maté* brought to the scientific media by Dr. Alessandro Gugliucci, and from that time on, the interest on this South American native plant is gradually increasing.

This review discusses some of the main bioactive compounds present in *maté* leaves and aqueous infusions and the latest scientific data on *maté* physiological properties.

MAIN BIOACTIVE COMPOUNDS IN *MATÉ* LEAVES AND *MATÉ* BEVERAGES

Purine alkaloids

Caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine) and theophyline (1,3-dimetylxanthine) are the main purine alkaloids in plant foods (**Fig. 1**). Biological significance is attributed to the purine alkaloids, since the purine bases are the main component of nucleoproteins which

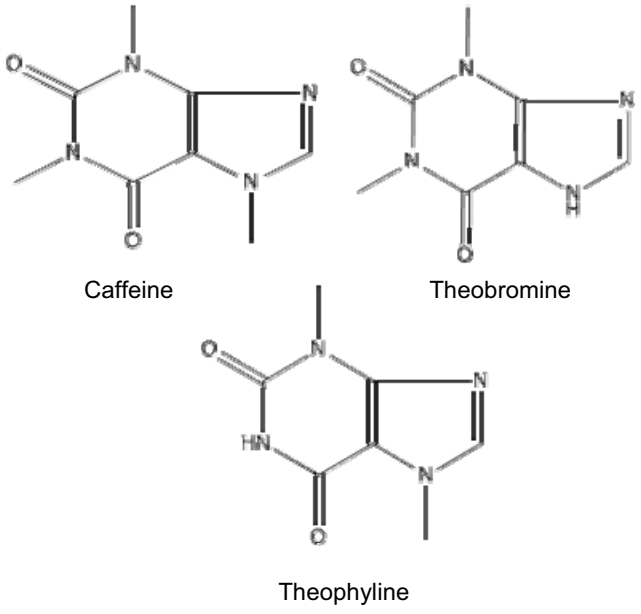


Fig. 1 Molecular structure of purine alkaloids.

make up the bulk of cellular nuclei, playing an important role in the living organism.

Amongst these three compounds, caffeine is the most abundant in coffee, tea and *yerba maté*, while theobromine is the most abundant in cocoa seeds. Theophyline is usually lower in coffee and tea, and its presence in *maté* is still a matter of controversy (Schubert *et al*. 2006).

The high concentration of caffeine that accumulates in some plants is related to its protection effect on the tissue from young leaves, fruits and flowers, from predators such as insect larvae and beetles, or by the inhibition effect that caffeine might have on the germination of other seeds, when it is released in the soil from the bean (Waller 1989; Chou and Benowitz 1994; Nurminen *et al*. 1999; Hewavitharanage *et al*. 2000; Ashihara and Crozier 2001).

Caffeine is one of the plant products with which the general public is familiar and its ingestion is commonly related with adverse effects on health. Short-term side effects from caffeine include palpitations, gastrointestinal disturbances, anxiety, tremor, increased blood pressure and insomnia (Chou and Benowitz 1994; Nurminen *et al*. 1999). On the other hand, caffeine influences central nervous, cardiac, muscular and renal activities. Its effect on the central nervous system (CNS) is confined to the cortical centers responsible for higher psychic functions, and results in a well coordinated enhancement of the cerebral functions and, consequently, in great vigilance and mental activity (Bokucaha and Skobeleva 1980). Stimulating properties long known by the native South America inhabitants are due to the presence of such compounds. Caffeine also accelerates metabolism and oxygen intake by body tissues and have the potential to produce significant effects on metabolic targets such as satiety, thermogenesis, and fat oxidation (Westerterp-Plantenga *et al*. 2006).

After its oral ingestion, caffeine is absorbed, distributed to various tissues and broken down to metabolites with variable pharmacological actions which are further excreted. Caffeine is believed to interact with receptors for which adenosine is the normal substrate.

Some authors indicate that coffee is the main source of caffeine in the adult population, although caffeine intake varies widely since half of the population does not drink coffee while some individuals consume substantial amounts (Barone and Roberts 1996; Mandel 2002). The consumption of *maté* or other typical beverages were not taken in account in any of the previous revisions on caffeine consumption, and it might not be wrong to state that the main source of caffeine in some South America regions is the *maté*, *chimarrão* or *tererê*.

It is very difficult to establish the amount of caffeine in one cup of coffee, tea or *maté*-tea and in one "*cuia*" of *chimarrão* or *tererê*. Mazzafera (1994) determined the contents of caffeine, theobromine and theophyline in developing and old leaves, fruits, bark and wood from *yerba maté* in southest Brazil. This study confirmed that the caffeine distribution pattern is the same described for coffee, and that the content of caffeine, theobromine and theophyline in young leaves and immature fruits were higher than the values found for old leaves and mature fruits.

Schubert *et al*. (2006) investigated variations of total methylxanthines in leaves from two *I. paraguariensis* populations collected at one-month intervals over the course of one year in the south region from Brazil (Rio Grande do Sul state). The levels varied from 1.92 to 10.37 mg/g (Ijuí city) and 1.77 to 9.17 mg/g (Santa Maria city). The presence of caffeine and theobromine were confirmed for all the analyzed samples, while theophyline was not detected. The authors found significant variation in the methylxanthine content of all samples analyzed, confirming seasonal fluctuation. Methylxanthine contents were higher during the summer in both localities. Lower contents were observed throughout the winter period and part of the fall period. Environmental and agronomical factors such as light intensity and temperature, stress conditions, presence of predators, kind and frequency of trimming, besides plant age, might contribute to the observed behavior.

Processing widely influences the bioactive compound content of the aqueous extract. According to Bastos *et al*. (2006) and López *et al*. (2006) the content of methylxanthines as well as phenolic acids increased after the drying stages of *maté* leaves, which is in disagreement with Esmerelindo *et al*. (2002). This incongruence might be due to the great differences in the processing technology used among producers, specially the time and temperature of leaves exposure and to the extraction methodology.

Few published research studies have reported on the caffeine content of *maté* beverages. And among those published, comparison is rather difficult due to the differences in the brewing process and analytical procedure (**Table 2**).

Heavier *chimarrão* and *tererê* drinkers may intake from 1 to 6 L of these beverages per day, indicating that *maté* is an important source of caffeine in the diet (Barros *et al*. 2000). Curiously, unlike coffee drinkers, *chimarrão* and *tererê* drinkers do not complain about caffeine side effects.

Table 2 The content of caffeine in a cup or *cuia* of maté beverages (*chimarrão*, *tererê* or *maté*-tea).

Beverage	Caffeine (ug/mL)		
	Clifford and Ramirez 1990	Mazzafera 1997	Bastos *et al.* 2005
Chimarrão	90-180	290-790	202-330
Tererê	na	na	112-204
Maté tea	na	na	44-110

na = not analyzed

Phenolic compounds

The presence of phenolic acids in *yerba maté* leaves is known since 1935, when Woodard and Cowland (apud Alikaridis 1987) reported the presence of a substance that they called "coffetannin" which, when hydrolyzed, resulted in caffeic acid.

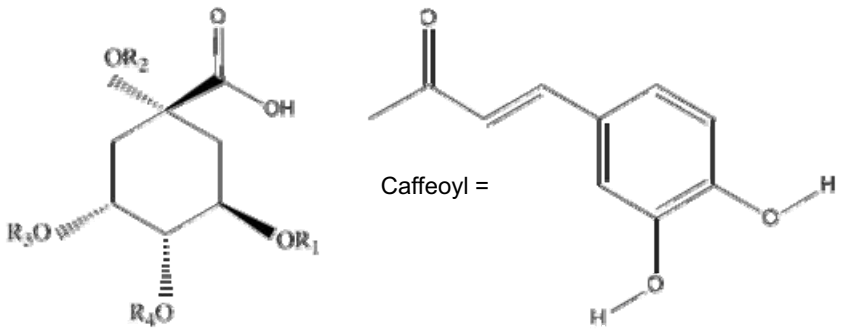


Fig. 2 ***Yerba maté*** **main phenolic compounds molecular structure.**

Caffeoylquinic acid derivatives
$R^1 = R^2 = R^3 = H$; R^1 = caffeoyl (chlorogenic acid)
$R^1 = R^3 = R^4 = H$; R^2 = caffeoyl (neo-chlorogenic acid)
$R^1 = R^2 = R^4 = H$; R^3 = caffeoyl (crypto-chlorogenic acid)

Dicaffeoylquinic acid drivatives
$R^1 = R^4 = H$; $R^2 = R^3$ = caffeoyl
$R^1 = R^2 = H$; $R^3 = R^4$ = caffeoyl
$R^1 = R^3 = H$; $R^2 = R^4$ = caffeoyl
$R^2 = R^3 = H$; $R^1 = R^4$ = caffeoyl

Chlorogenic acids (CGAs) belong to the cinnamic acids family, which comprehend a series of *trans*-phenyl-3-propenoic acids differing in their ring substitution. These compounds are widely distributed as conjugates in plant material. The most common are caffeic (3,4-dihydroxicinnamic), ferulic (3-methoxy,4-hydroxy), sinapic (3,5-dimethoxy,4-hydroxy) and *p*-coumaric (4-hydroxy) acids.

CGAs are a family of esters formed between certain of these *trans*-cinammate acids and quinic acid (1l-1(OH),3,4/5-tetrahydrocyclo-hexane carboxylic acid) and the most common individual chlorogenic acid is 5-*O*-caffeoylquinic acid (5-CQA). According to Clifford (2000) the CGAs may be subdivided by the identity, number and position of the acyl residues. Mono-esters of caffeic acid (caffeoylquinic acids – CQA), *p*-coumaric acid, *p*-coumaroylquinic acids (*p*CoQA) and ferulic acid (feruloylquinic acids – FQA) and di-esters (diCQA) are the main phenolic acids in *yerba maté* (**Fig. 2**).

Carini *et al*. (1998) using HPLC/MS and HPLC/Tandem MS were able to identify 10 different phenolic constituents from *yerba maté* aqueous infusion, including the 3 naturally isomers 5-CQA (which were named neo-chlorogenic acid, chlorogenic acid and crypto-chlorogenic acid), as well as 3 isomeric dicaffeoylquinic acids, rutin (quercitin-3 rutinoside), a diglycosyl derivative of luteolin and 2 isomeric caffeoyl-glucosides. Bastos *et al*. (2007) using direct infusion electrospray insertion mass spectrometry (ESI-MS) identified the main phenolic compounds from aqueous, ethanolic and ether extracts from green and roasted *yerba maté*. Compounds identified in water and ethanolic extracts from green *maté* were: caffeic acid, quinic acid, caffeoyl glucose, caffeoylquinic acid, feruloylquinic acid, dicaffeoylquinic acid and rutin. The roasted *yerba maté* polar extracts exhibited also caffeoylshikimic acid and dicaffeoylshikimic acid.

CGAs are potent antioxidant compounds and may act as hydrogen or electron donors and also as transition metal ion chelators (Carini *et al*. 1998). Previous studies have demonstrated the antioxidant activities of the polyphenols as hydrogen-donating free radical scavengers and their structural dependence (Jovanovic *et al*. 1994; Rice-Evans *et al*. 1996). Its ability to inhibit the oxidation of low-density lipoproteins (LDLs) demonstrates their potential as chain-breaking antioxidants (Mangiapane *et al*. 1992; Miura *et al*. 1995; Salah *et al*. 1995; Vinson *et al*. 1995). Other studies suggest that polyphenols might inhibit free radical formation and propagation of free radical reactions though the chelating of transition-metal ions (Morel *et al*. 1993; Paganga *et al*. 1996; van Acker *et al*. 1996).

CGA is absorbed by humans in the intestine after bacterial metabolism (Oltoff *et al*. 2000, 2003).

Ingestion of CGAs improved glucose tolerance and mineral pool distribution in obese Zucker rats and resulted in the decrease in postprandial blood glucose concentrations, important parameters related to diabetes mellitus type 2 (Herlinget *et al*. 1999; Sotillo and Hadley 2002a, 2002b). A similar effect was observed in studies with humans (Johnston *et al*. 2003, 2004). Some of the proposed mechanisms are (a) the ability of CGAs to inhibit enzymes responsible for the glucose intake at the intestine lumen (Hara and Honda 1990; McCarty 2005) and (b) the dissipation of an Na^+ gradient in the cells' apical region, which, according to Welsch (1989) reduced in 89% the glucose absorption by the intestine membrane in the presence of CGA.

Another source of CGAs, *Cecropia obtusifolia*, was able to reduce rats blood glucose concentration to levels similar to those obtained with the reference drug glibenclamide (Andrade-Cetto *et al*. 2001).

Six from nine cohort studies in Europe and the United States related coffee consumption to a lower risk in the development of type 2 diabetes. The CGAs present in coffee seems to respond for this property (Johnston *et al*. 2003, 2004; van Dam 2006).

Most of the biological activities of *yerba maté* are attri-

Table 3 Yerba maté phenolic content determined in several researches (1990-2005).

Sample/extraction procedure	Analytical methodology	Results	Reference
Methanolic extract from five samples of green *yerba maté* and *maté* tea commercialized in Argentina and United Kingdon were analysed.	Reverse Phase HPLC Detection at 313 nm.	Chlorogenic acids content varies from 16 to 41 mg fro the brownish samples and from 107 to 133 mg for the greenish samples (in 200 mL volume).	Clifford and Ramirez-Martinez 1990
Aqueous or methanolic extracts from leaves from *I. argentina* Lillo, *I. chamaedrifolia* Reisseck, *I. integerrima* (Veel. Conc.) Reisseck, *I. microdonta* Loes, *I. paraguariensis* A. St. Hill and *I. taubertiana* Loes.	Paper chromatography; UV detection for flavonoids; Detection of flavonols and flavones with $AlCl_3$; Detection of protoantocyanidines with HCl	Free and glycoside kaempferol were detected in *I. chamaedrifolia*; free quercitin was detected in all samples; rutin was detected in all species but *I. chamaedrifolia*; and proantocianidines were detected in *I. integerrima.*	Ricco *et al*. 1991
Water infusion from 18 *chimarrão maté* samples from south Brazil (3 g/60 mL)	5-CQA and caffeic acid were determined by RP- HPLC. Detection at 313 nm. Total phenolics were measured by the Folin-Ciocalteau method with phenol as standard.	Total phenolics varied from 0.78-1.6 mg/mL.	Mazzafera 1997
Water infusion from dried and minced leaves at 30% (p/v) and 5% (p/v).	Caffeoyl derivatives were determined by spectrophotometry with 5-CQA as standard.	Phenolic content was 10.71% (w/w) for *Ilex paraguariensis* and varied from 0.96-6.83% (p/p) for the other *Ilex* species.	Filip *et al*. 2000
Aqueous extract from *I. paraguariensis* 5% (w/v). Aqueous extracts from other *Ilex* spp. 30% (w/v).	EP-HPLC detection at 325 nm for caffeic acid derivatives; Rutin detection at 255 nm; Quercitin detection at 254 nm; Kaempferol detection at 263 nm.	*I. paraguariensis* showed the highest phenolic content among the species. Total phenolic content for *I. paraguariensis* was 9.608% (w/w) and varied from 0.118-1.900 (w/w) for the other species. Rutin, quercitin and kaempferol contents were 0.0060; 0.0031 and 0.0012% (w/w), respectively for *I. paraguariensis* and lower for the other species.	Filip *et al*. 2001
Water infusions from maté-tea (1 bag/cup) and chimarrão-maté (3 g/60 mL) prepared as *chimarrão* (hot water) or *tererê* (cold water).	RP-HPLC. Detection at 323 nm.	5-CQA content varied from 427.0 to 464.6 μg/mL for the chimarrão beverage; from 264.9 to 370.7 μg/mL for the *tererê* beverage and from 59.7 to 126.9 μg/mL for the *maté*-tea.	Bastos *et al*. 2005

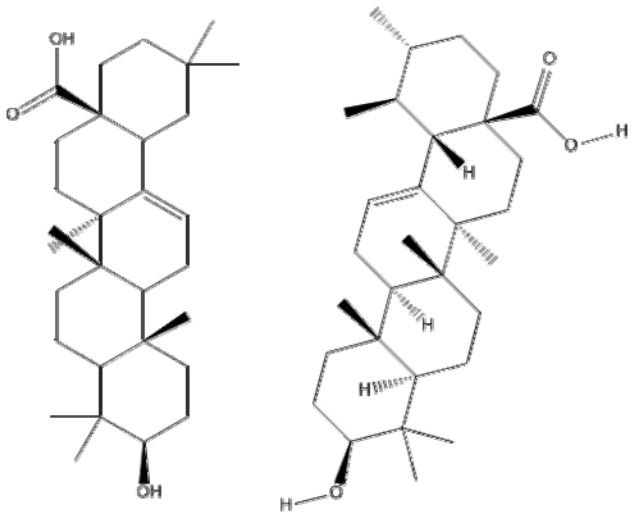
buted to the presence of phenolic compounds, and the amount of these substances present in the leaves or in the beverages may vary considerably due to innumerous factors, such as agronomic procedures, processing technology and brewing methodology. Some of the different results for phenolic composition of *yerba maté* leaves and beverages are shown in **Table 3**.

Saponins

Saponins are a vast group of glycosides widely distributed in higher plants which are distinguishable from other glycosides by their surface active properties. They dissolve in water to form colloidal solutions that foam upon shaking. The biological applications of saponins are usually based on their membrane-disrupting properties, and formation of large mixed micelles with steroids and bile acids. They are believed to form the mains constituents of many plants drugs and folk medicines, and are considered responsible for numerous pharmacological properties. For example, the ginseng (*Panax ginseng*) root, one of the most important medicinal oriental products used worldwide, has saponins as the major bioactive constituents.

Saponins can be classified into two major groups based on the nature of their aglycone skeleton: the steroidal saponins, mostly present in the angiosperms and the triterpenoids saponins, most common in the dicotyledonous angiosperms. Biological and pharmacological activities of saponins have been related in several reviews, the most recent being by Sparg *et al*. (2004). Haemolytic activity, molluscicidal activity, anti-inflamatory activity, antifungal/antiyeast activity, antibacterial/antimicrobial activity, antiparasitic activity, cytotoxicity and antitumoral activity, antiviral activity among others have been described in the literature.

The leaves of *I. paraguariensis* contain a significant amount of triterpenoid saponins. Monodesmosidic and bidesmosidic saponins have been isolated from the aerial parts of *yerba maté*, and all compounds contained the ursolic or oleanolic moieties (**Fig. 3**).



Oleanolic acid Ursolic acid

Fig. 3 Oleanolic and ursolic acids: molecular structures.

Saponins may be used as a chemical fingerprint for the authentication of *yerba maté*. Adulteration by variable quantities of leaves of other South American *Ilex* species, showing complete different saponin profile from *yerba maté*, is rather common (Pires *et al*. 1997).

Gosamnn and Schenkel (1989) reported the isolation and elucidation of a new saponin, named matesaponin, from the leaves of *yerba maté* which is a three sugar residue bidesmoside (matesaponin 1: ursolic acid 3-O-[β-D-glucopyranoyl-(1→3)α-L-arabinopyranosyl]-(28→1)-β-D-glucopyranoyl ester). In the sequence, other matesaponins, named metasaponins 2, 3, 4 and 5 were characterized by Gosmann and Guillaume (1995) and by Kraemer *et al*. (1996).

Martinet *et al*. (2001) characterized two minor saponins obtained from the methanolic extract of the leaves of *I. paraguariensis* as oleanolic acid-3-*O*-(β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl)-(28→1)-β-D-glucopyranosyl ester (guaiacin B) and oleanolic acid-3-*O*-(β-D-glucopyranosyl-(1→3)-(α-L-rhamnopyranosyl-(1→2))-α-L-arabinopyranosyl)-(28→1)-β-D-glucopyranosyl ester (nudicaucin C). Both are isomeric forms of the known matesaponins 1 (MSP 1) and 2 (MSP 2) and differ only by the nature of the aglycone: they have oleanolic acid instead of ursolic acid, as found in the matesaponins.

The triterpenoids ursolic acid and its isomer, oleanolic acid, are compounds found widely in the plant kingdom that have many biological effects: anti-inflammatory, antiarthritic, and antitumor activity, hepatoprotective effects in mice, and membrane-stabilizing properties (Liu 1995; Saraswat *et al*. 2000; Martin-Araon *et al*. 2001; Saravanan *et al*. 2006).

Saponins are reported to interfere with cholesterol metabolism and to delay the intestinal absorption of dietary fat via inhibition of pancreatic lipase activity (Hosttetmann and Marston 1995; Han *et al*. 2002, 2005).

Caffeine, saponins and phenolic contents are one of the main targets for *yerba maté* genetic improvement due to their role in the bitter and astringent attributes of the beverages (Sturion *et al*. 2004).

Minerals

Ash content from *yerba maté* leaves ranges from 5.07 to 9% (Sanz and Isasa 1991; Esmerelindo *et al*. 2002). There is little research work available on the mineral content of commercial *yerba maté*, and the data are relative to *chimarrão*-type *yerba maté* leaves and infusions (**Table 4**).

Sanz and Isasa (1991) reported that the mineral extraction from the leaves, during the infusion process, does not show the same behavior. For example: calcium content in the leaves is higher (80-90%) than that found in the infusion, because of its low water solubility. On the other hand, sodium present in the leaves is easily extracted by the infusion process.

According to the data reported by Heinrichs and Malavolta (2001), a *chimarrão* drinker may ingest all the necessary potassium and magnesium from the beverages, while ingesting slow amounts of sodium and aluminum.

The mineral contents from leaves change drastically depending on the agricultural practices. The use of fertilizers and the soil have an important impact in the mineral composition of the leaves and should be taken in account for the production of higher nutritional products.

BIOLOGICAL ACTIVITIES

Antioxidant, antimutagenic and cellular protective actions

It is well established that oxygen radicals are involved in various pathological states such as cancer, cardiovascular disorders, inflammation, and liver diseases (Ames *et al*. 1993; Halliwell 1994). They are ubiquitous in our natural environment but they are also formed in the issue by endogenous mechanisms (Cerutti 1985). The attack of reactive oxygen species (ROS) on DNA generates a multiplicity of DNA damage, including the modification of bases. Besides DNA damage, lipid peroxidation is one of the main deleterious effects of oxidant attack on bimolecules through the disruption of the structural integrity of membranes. The high vulnerability of tissues to lipid peroxidation has been partly attributed to their high content of long-chain polyunsaturated fatty acids (PUFA), such as arachidonic and docosahexaenoic (DHA) acids (Kubo *et al*. 1997). The oxidation

Table 4 The mineral content (mean value) in *yerba maté* products.

Mineral	Aqueous infusion [b] mg/L	Commercial Yerba maté [a] *g/Kg ** mg/Kg	Commercial Yerba mate[d] mg/100g	Aqueous infusion [d] mg/100g	Resinous material [c] *mg/100 g **mg/L *** mg/Kg
N	11	16 *	---	---	
P	41	0.9 *	---	---	152.25 *
K	683	13 *	915.4	539.3	
Ca	44	6.3 *	622.5	79.6	239.8 *
Mg	188	4.9 *	456.5	170.8	75.75 *
$S - SO_4$	58	0.9 *	---	---	---
B	2,2	32 **	---		---
Cu	0.28	8.9 **	1.0	0.9	---
Fe	0.33	185 **	12.8	0.3	---
Mn	34	880 **	43.1	26.2	---
Ni	0.03	1.9 **	---	---	---
Zn	0.20	40 **	2.6	0.5	---
Al	3.43	403 **	---	---	---
Ba	1.25	---	---	---	---
Cd	0.00	<0.01 **	---	---	0.01 **
Co	---	<0.01 **	---	---	
Cr	0.04	1.5 **	---	---	<0.05 ***
Na	3.23	39 **	17.6	16.1	151.38 *
Pb	0.00	<0.03 **	---	---	---
Si	6.31	---	---	---	---

[a] 70% leaves 30% sticks (Heinrichs and Malavolta 2001).
[b] prepared with 70 g commercial *yerba mate* /1L water (Heinrichs and Malavolta 2001).
[c] *yerba maté* collected in Irati, Paraná, Brazil (Efing *et al*. 2006).
[d] commercial samples purchased in Spain (Sanz and Isasa 1991).

Table 5 Antioxidant and cellular protective actions summary data.

Sample	Analytical Methodology	Results	Reference
In vitro	TBARS production	Inhibit LDL oxidation	Gugliucci and Stahl 1995
In vivo – heath human plasma	TBARS production	Inhibit LDL oxidation	Gugliucci 1996
In vitro – liposomes	TBARS production	Inhibit LDL oxidation	Filip *et al*. 2000
In vivo – rat liver and red blood cells	Lipid peroxidation induced; erythrocyte membrane peroxidation and free radical generation.	Inhibit LDL oxidation; Free radical scavenging properties	Schinella *et al*. 2000
In vivo – human plasma	TBARS production, diene conjugates formation and total polyphenols	Inhibit LDL oxidation	Gugluicci and Menini 2002
In vivo – *Saccharomyces cerevisiae* and human plasma	Double strand breaks determination (TAFE), TBARS production, diene conjugates formation and 1,1-diphenyl-2-picrylhydrazyl assay (DPPH).	Decrease DNA breaks; Inhibit LDL oxidation	Bracesco *et al*. 2003
In vitro - HepG2 cells and *Saccharomyces cerevisiae*	Cytotoxicity, TPA-induced ornithine decarboxylase, quinone reductase and topoisomerase activities	Cytotoxic activity; inhibition of topoisomerase	Ramirez-Mares *et al*. 2004
In vitro – murine hepatoma cells	Total antioxidant capacity (ORAC) and quinine reductase assay	Antioxidant and chemopreventive activities	Chandra and Mejia 2004
In vitro – murine RAW264.7 macrophages	1,1-diphenyl-2-picrylhydrazyl assay (DPPH), nitration of BSA, and LDH cytotoxicity	Inhibition of protein nitration and cytoprotective effects	Bixby *et al*. 2005
In vivo – rabbits	Lipid profile; TBARS production and antioxidant enzymes	Reduced atherosclerotic lesion	Mosimann *et al*. 2006
Ex vivo – Wistar rat submandibular glands	Peroxidase secretion	Prevention of oral pathologies and potential chemopreventive action on oral cavity	Filip *et al*. 2007

of PUFAs in cell membranes has received considerable attention because of its contribution to potential damage to biological systems. Additionally, it has been reported that a high content of unsaturated fatty acid may increase the oxidative stress (Cosgrove *et al*. 1987).

I. paraguariensis extracts are very potent inhibitors of low-density lipoproteins (LDL) oxidation and have antimutagenic effects (**Table 5**). In 1995 Gugliucci and Stahl demonstrated that *I. paraguariensis* extract was able to inhibit LDL oxidation *in vitro*. The inhibition of lipid peroxidation was monitored by diene conjugates and thiobarbituric acid-reactive substances (TBARS), as well as LDL apoB modification. The authors showed that this inhibition has a concentration-dependent effect. Subsequently Gugliucci (1996) extended these observations *in vivo* demonstrating that the antioxidants present in *I. paraguariensis* are absorbed and reach sufficient high levels in whole plasma from healthy humans to inhibit copper-induced LDL autooxidation as shown by end-term production of TBARS. These results were further corroborated by Gugliucci and Menini (2002) employing three different oxidation systems (copper, peroxynitrite and lipoxygenase) on human LDL.

The antioxidant activity of *Ilex* species were also evaluated by Filip *et al*. (2000). The results presented by these authors showed an antioxidant potential of the *Ilex* extracts inhibiting a chemically initiated oxidation of synthetic membranes (liposomes) measured by TBARS production. Schinella *et al*. (2000) investigated the antioxidant properties of an aqueous extract of *I .paraguariensis*, in rats, using a free radical-generating system. They were able to demonstrate an inhibition in the lipid peroxidation in rat liver microsomes in a concentration-dependent way. Additionally, the extract was also able to inhibit the H_2O_2-induced peroxidation in red blood cell membranes exhibiting radical scavenging properties to ward superoxide anion.

Bracesco *et al*. (2003) evaluated the antioxidant properties of *I. paraguariensis* infusion by means of induction of DNA double-strand breaks by H_2O_2 in *Saccharomyces cerevisiae* as well as peroxide and lipoxygenase-induced human LDL oxidation. Their results suggested that *maté* infu-

sion decreased, in a dose dependent way, the number of DNA double strand-breaks, and peroxynitrite and lipoxygenase-induced human LDL oxidation are inhibited by the extracts in a potent, dose-dependent fashion.

Ramirez-Mares *et al*. (2004) studied the *in vitro* chemopreventive activity of *maté* tea evaluating cytotoxicity, TPA-induced ornithine decarboxylase and quinone reducetase activities using HepG2 cells. The topoisomerase inhibitory activity was also tested using *Saccharomyces cerevisiae*. The results presented by the authors suggest that cytotoxic activity and the inhibition of topoisomerase II may contribute to the overall chemopreventive activity of *maté* extracts. *Maté* quinone reductase activity was also tested by Chandra and Mejia (2004), but they found no induction of this enzyme in Hepa1 c1 c7 murine hepatoma cells at the concentration range tested (0.5-10.5 mg/mL).

Bixby *et al*. (2005) showed the *in vitro* protective effects of *I. paraguariensis* against peroxynitrite-induced cytotoxicity, which is implicated in the pathogenic mechanisms of stroke, myocardial ischemia, diabetes and diabetes-associated cardiovascular dysfunction (Szabo 2003). *I. paraguariensis* extracts proved the highest inhibition of protein nitration, and the highest promotion of cell survival, being over 60% at dilutions of 1/1200, whereas green tea or red wines displayed modest effects at the same concentrations.

The ability to inhibit the oxidation of LDL demonstrates their potential as chain-breaking antioxidants (Mangiapane *et al*. 1992; Miura *et al*. 1995; Vinson *et al*. 1995; Salah *et al*. 1995). It was suggested that the antioxidant activity may be related to the presence of polyphenolic compounds that might inhibit free radical formation and propagation of free radical reactions though the chelation of transition-metal ions (Morel *et al*. 1993; van Acker *et al*. 1996; Paganga *et al*. 1996). The ursolic and oleanolic acids, the main saponin derivatives in *I. paraguariensis* (Pires *et al*. 1997) might also play an important role as antioxidants.

Anesini *et al*. (2005) demonstrated that *maté* infusions may also act as peroxidase, what was further reinforced by Filip *et al.* (2007) that investigated the activity of aqueous extracts of *I. paraguariensis* (herbarium specimen) and commercial *yerba maté* on peroxidase secretion in female rat submandibular glands. Spectrophotometrical determination of peroxidase activity showed that both extracts produced a significant increase in both secreted and total peroxidase activity. Caffeine and CGA were proved to play an important role in the induction of peroxidase secretion induced by the extracts. As peroxidase is an oral enzyme involved in the defense of the oral cavity, it seems that the ingestion of the infusions might play an important role in protection against pathogenic process.

Thermogenic effects and weight loss

Martinet *et al*. (1999) studied various commercially-available plant preparations that have claimed to possess anti-obesity action. No significant increase in energy expenditure (EE) was noted after treatment with any of the preparations. In addition, no change in respiratory quotient (RQ) was shown, except after treatment with *I. paraguariensis* extract, where a drop in RQ was observed, indicating a rise in the proportion of fat oxidized. The results suggested the poor potential of these plant preparations in the treatment of obesity, except possibly for the *maté* extract.

In 2001, a research team studying obesity at the Charlottenlund Medical Center in Denmark tested a herbal preparation of *yerba maté*, *guaraná*, and damiana (YGD) for gastric emptying and subsequent weight loss (Andersen and Fogh 2001). They concluded that the herbal preparation, YGD capsules, significantly delayed gastric emptying, reduced the time to perceived gastric fullness and induced significant weight loss over 45 days in overweight patients treated in a primary health care context. In addition, maintenance treatment given in an uncontrolled context resulted in no further weight loss, nor weight regain in the group as a whole.

Among several plants used with weight loss purpose, reported by 14 herb sellers in Porto Alegre, Brazil, *I. paraguariensis* was cited twice (Dickel *et al*. 2007).

Anti-diabetic actions

Yerba maté has been shown to inhibit the formation of advanced glycation end products (AGEs), with an effect comparable to that of two pharmaceutical grade AGE inhibitor drugs. Lunceford and Gugliucci (2005) reported that polyphenol-rich *I. paraguariensis* extracts are capable of inhibiting AGEs (or Maillard reaction products) on a protein model *in vitro*, whereas green tea displays no significant effect. Glycation, the nonenzymatic adduct formation between sugar aldehydes and proteins, is one key molecular basis of diabetic complications due to hyperglycemia. The AGEs, which are irreversibly formed, accumulate with aging, atherosclerosis, and diabetes mellitus (Wiemsperger 2004). Phenolics, such as chlorogenic acids, have been claimed to modulate the activity of glucose-6-phosphatase involved in glucose metabolism (Hemmerle *et al*. 1997).

Digestion improvement

Research conducted by a team at Catedra de Farmacologia in Buenos Aires, Argentina found that *yerba maté* does induce an increase in bile flow and enhance intestinal transit (Gorzalczany *et al*. 2001). According to the results obtained with the four species of *Ilex* studied, the choleretic activity of *I. paraguariensis* was slow, gradual and sustained, while that *I. brevicuspis* is rapid, reaches a maximum and decreases rapidly.

Anti-fatigue and stimulant actions

Yerba maté is a CNS stimulant. The metabolic effects of *maté* appear to include the ability to maintain aerobic breakdown of carbohydrates during exercise for long periods of time. As a result, more calories are burned, thereby increasing cardiac efficiency and delaying the build-up of lactic acid.

In fact, a US Patent in 2002 cites *yerba maté* as inhibiting monoamine oxidase (MAO) activity by 40-50% *in vitro*. The underlying study suggests that *maté* might be useful for treating a variety of disorders such as “depression, disorders of attention and focus, mood and emotional disorders, Parkinson’s disease, extrapyramidal disorders, hypertension, substance abuse, eating disorders, withdrawal syndromes, and the cessation of smoking”.

Circulatory system action and hypocholesterolemic effect

Stein *et al*. (2005) verified that the aqueous extract and an acid *n*-butanilic extract from *I. paraguariensis* induced vasodilatation in the mesenteric arterial vascular beds from standard-diet rats in a dose dependent manner, what was not observed with a hypercholesterolemic-diet. These authors observed that chronic oral administration of *yerba maté* in hypercholesterolemic-diet rats resulted in a significant reduction in serum levels of cholesterol (30% reduction) and tryglicerides (60.4% reduction). These authors suggest that the antioxidant activity of *yerba maté* infusions might be responsible, in part, for the decrease in plasma levels of cholesterol and triglycerides and that the induced vasodilatation observed for both aqueous and acidified butanol fraction from *yerba maté* are mediated by release of endothelium-derived substances.

Gorgen *et al*. (2005) suggest than *I. paraguariensis* is able to interfere in the circulatory system, acting as a diuretic and hypotensive agent. The chronic ingestion of aqueous extract of *I. paraguariensis* promoted a decrease of ATP, ADP and AMP hydrolysis in rat blood serum. Thus, it seems that this treatment can alter the nucleotidase pathway,

modulating the balance in the purine levels which can induce relevant effects, for example in the cardiovascular system.

Mossiman *et al*. (2006) evaluated whether *maté* infusions could reduce the progression of atherosclerosis in 1% cholesterol-fed rabbits. After 2 months of treatment, *maté* intake did not change the lipid profile or hepatic cholesterol content of control or hypercholesterolemic rabbits. However, the atherosclerotic lesion area was considerably smaller in the hypercholesterolemic-*maté* group, and the aortic cholesterol content was around half that of the HC group. In spite of this, the thiobarbituric acid-reactive substances (TBARS) in the atherosclerotic aorta, liver and serum, and the activity of the antioxidant enzymes in liver and aorta did not differ among groups. The results showed that *I. paraguariensis* extract can inhibit the progression of atherosclerosis in cholesterol-fed rabbits, although it did not decrease the serum cholesterol or aortic TBARS and antioxidant enzymes.

Chimarrão ingestion and cancer incidence

The high esophagus cancer incidence in some South America localities where population traditionally consumes *chimarrão* was the concern of several epidemiological studies published during the 1980s-1990s (Vassalo *et al*. 1985; Muñoz *et al*. 1987; Victoria *et al*. 1987; de Stefani *et al*. 1991, 1996, 1998; Dietz *et al*. 1998; Barros *et al*. 2000; Castellsagué *et al*. 2000). These studies could not find a positive correlation between *chimarrão* drinking and cancer. The main issue may be the temperature in which *chimarrão* is drunk, that leads to lesions in the tissues. Confusion factors, such as smoking, expressive alcohol and meat barbecue consume, were revealed in these studies.

One important problem in the *yerba maté* production chain is the contamination of *maté* products with policyclic aromatic hydrocarbons (PAH) that are potential carcinogenic compounds. They are originated from the burning of the wood, which is traditionally used in the drying process of *maté* leaves. These compounds are hydrophobic and its content in *maté* beverages is usually very low, but becomes important due to the large amount usually drunk/day/person. Fagundes *et al*. (2006) evaluated the degree and sources of PAH exposure of the inhabitants of the region of southern Brazil. They measured a PAH metabolite:1-hydroxypyrene glucuronide (1-OHPG) from two hundred healthy adults (half smokers, half non smokers, half male and half female) urine. They suggested that both tobacco smoke and maté both contribute to high levels of benzo[α]pyrene exposure in the people of southern Brazil, what might contribute to the high rates of ESCC observed in this population. The authors stated that the increased urine 1-OHPG concentrations associated with *maté* suggest that contaminants, not just thermal injury, may help explain the increased risk of ESCC previously reported for *maté*.

In a case-control study aiming to investigate bladder cancer and *maté* consumption in Argentina, involving 114 Argentinean case-control pairs concluded that *maté* with pump, consumed from the last 20 years by the subjects, was associated with bladder cancer in ever-smokers but not in never-smokers. *Maté cocido* (green *maté* in bags) was not associated with bladder cancer (Bates *et al*. 2007).

CHALLENGES AND PERSPECTIVES

The scientific interest in *yerba maté* as a functional food or a medicinal plant may be considered recent if compared with other plant products, like *Camellia sinensis*, that similar to *maté*, were traditionally consumed by the indigenous populations in Asia before the European people arrival. The extension of this scientific interest delay may be well visualized by the fact that *maté* was not described as a source of caffeine or phenolics (in South America) in the main scientific reviews published on this subject.

Although there are yet few results from *in vivo* studies relating to the popular therapeutic attributes of this product, they seem to corroborate the pharmacological properties popularly attributed to this plant. Antioxidant activity, tested by different methodologies in different *in vitro* and *in vivo* systems, is the same or even superior of some plants/foods that are usually recognized as health promoters.

I. paraguariensis beverages have almost the same profile of purine alkaloids and phenolic compounds from coffee, another stimulant beverage with other recognized potential application in public health field, as diabetes.

Nowadays, the search for foods that bring, within the regular diet, bioactive substances, as phenolic compounds, phytoestrogens or probiotics, is a may concern in the nutrition field. *Yerba maté*, besides its stimulant activity, long known by the indigenous South American inhabitants, seems to fulfill the requirements as a functional food. In spite of it, there is yet much to be done: there are not enough human based studies to support the properties verified *in vitro* and *in vivo* models with animals. Besides, there is a necessary effort towards the improvement of the production chain, what might result in a raw product with certificated quality. Nowadays, most of the *maté* products lack quality in one or another way: huge differences in chemical composition from one harvest to another, the possible contamination with aromatic polycyclic hydrocarbons and the lack of microbiological control.

The increasing number of *maté* products patents, as well as the growing interest in this product, by countries whose population do not traditionally consume *maté* beverages, and the increasing number of published papers about *I. paraguariensis* pharmacological properties may impulse a new era for this traditional product that is considered by the producers and consumers as "environmentally correct, socially fair and economically feasible".

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