Aqueous extract of Ilex paraguariensis attenuates the progression of atherosclerosis in cholesterol-fed rabbits. (* Abstract - PubMed)

Mosimann AL, **Wilhelm-Filho D**, **da Silva EL**.

Department of Clinical Analysis, Health Sciences Center, Federal University of Santa Catarina, Florianopolis, SC, Brazil.

Ilex paraguariensis aqueous extract (mate) is an antioxidant-rich beverage widely consumed in South American countries. Here we questioned whether mate could reduce the progression of atherosclerosis in 1% cholesterol-fed rabbits. New Zealand White male rabbits (n = 32) were divided into four groups: control (C, n = 5), control-mate (CM, n = 5), hypercholesterolemic (HC, n = 11) and hypercholesterolemic-mate (HCM, n = 11). The daily water and mate extract consumption was approximately 400 ml. After 2 months of treatment, mate intake did not change the lipid profile or hepatic cholesterol content of control or hypercholesterolemic rabbits ($p < 0.05$). However, the atherosclerotic lesion area was considerably smaller in the hypercholesterolemic-mate group (HCM, 35.4% vs. HC, 60.1%; $p < 0.05$). In addition, the aortic cholesterol content was around half that of the HC group (HCM, 36.8 vs. HC, 73.9 microg/mg of protein, $p < 0.05$). 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 ($p > 0.05$). The results showed that Ilex 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.

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Naturally occurring proteasome inhibitors from mate tea (Ilex paraguayensis) serve as models for topical proteasome inhibitors.

(* Abstract - PubMed)

Arbiser JL, **Li XC**, **Hossain CF**, **Nagle DG**, **Smith DM**, **Miller P**, **Govindarajan B**, **DiCarlo J**, **Landis-Piwowar KR**, **Dou QP**.

Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia 30322, USA. jarbise@emory.edu

Proteasome inhibitors have emerged as a clinically important therapy for neoplastic disease, with velcade, an organoboron compound used extensively in multiple myeloma. Recently, (-)-epigallocatechin gallate has been found to be a potent inhibitor of the proteasomal chymotrypsin-like activity. Other compounds that inhibit angiogenesis and are active as chemopreventive agents, such as curcumin, also inhibit proteasome activity. We have screened natural product extracts using ras-transformed endothelial cells (SVR cells) as a bioassay, and found that extracts of mate tea (Ilex paraguayensis) inhibit the growth of these endothelial cells. The extract was fractionated and found to have novel cinnamate esters that inhibit proteasome activity. Based upon the structures of the compounds isolated from mate tea, we examined synthetic analogs of these compounds for proteasome activity. Cinnamic acid amides had no inhibitory activity against proteasomes, whereas cinnamate esters displayed the activity. Based upon these findings, preclinical and clinical trials of topical cinnamate esters as proteasome inhibitors are warranted for psoriasis and other inflammatory disorders.

J Invest Dermatol. 2005 Aug;125(2):207-12.
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Ilex paraguariensis extracts inhibit AGE formation more efficiently than green tea. (* Abstract - PubMed)

Lunceford N, **Gugliucci A**.

Glycation, Oxidation and Disease Laboratory, Division of Basic Medical Sciences, Touro University-California, Mare Island, Vallejo, CA, USA.

Glycation, the nonenzymatic adduct formation between sugar dicarbonyls and proteins, is one key molecular basis of diabetic complications due to hyperglycemia. Given the link between glycation and oxidation, we hypothesized that herbal extracts with a high concentration of antioxidant phenolics might possess significant in vitro antiglycation activities as well. The aim of the present study was to address the hypothesis that polyphenol-rich Ilex paraguariensis (IP) extracts are capable of inhibiting advanced glycation end-products (AGEs) formation and to compare the potency of these extracts with green tea and with the standard antiglycation agent aminoguanidine. When we studied the effects of IP extract on AGE fluorescence generated on bovine serum albumin (BSA) by glycation with methylglyoxal, a dose-dependent effect that reaches 40% at 20 mul/ml of extract was demonstrated. Green tea did not display any significant effect. IP polyphenols are about 2- to 2.5-fold higher in our preparations compared with green tea. The effect of IP, therefore, may be due not only to the higher concentrations but to the different composition in phenolics of the two botanical preparations as well. To better discriminate between an antioxidant or a carbonyl quenching mechanism of action, we explored tryptophan fluorescence and cross-linking by sodium dodecyl sulfate polyacrylamide gel (SDS-PAGE) electrophoresis. The conformational changes induced by glycation and substitution of positive charges in arginine and/or lysine produce a decrease in tryptophan fluorescence. We show that incubation of BSA with methylglyoxal produces dramatic changes in tryptophan fluorescence that are prevented by aminoguanidine. This also prevents the downstream effect of AGE formation. Neither green tea nor IP extracts displayed any significant effect which rules out any significant participation as inhibitors in the first phase of the glycation cascade. The results from the SDS-PAGE serve to confirm the above-mentioned data. The effect is therefore due mainly to an inhibition of the second phase of the glycation reactions, namely the free-radical mediated conversion of the Amadori products to AGE. Taken together our results demonstrate a significant, dose-dependent effect of water extracts of I. paraguensis on AGE adducts formation on a protein model in vitro, whereas green tea displays no significant effect. The inhibition of AGE formation was comparable to that obtained by using millimolar concentrations of the standard antiglycation agent aminoguanidine.

Fitoterapia. 2005 Jul;76(5):419-27.
PMID: 15894431 [PubMed - indexed for MEDLINE]

Ilex paraguariensis extracts are potent inhibitors of nitrosative stress: a comparative study with green tea and wines using a protein nitration model and mammalian cell cytotoxicity. (* Abstract - PubMed)

Bixby M, **Spieler L**, **Menini T**, **Gugliucci A**.

Glycation, Oxidation and Disease Laboratory, Division of Basic Sciences, Touro University-California, 1310 Johnson Lane, Mare Island Vallejo, CA 94592, USA.

Due to the increasing importance of nitrosative stress in pathology and the efficacy displayed by flavonoids in cancelling the effects of peroxynitrite, we decided to conduct a comparative study of three commonly used beverages with the highest polyphenol contents and proven antioxidant properties: mate (Ilex paraguariensis); green tea (Camelia sinensis) extracts and white and red wines of the main varietals. We directly evaluated and compared the extracts and wines as protein nitration inhibitors using 3-nitrotyrosine as a biomarker, we studied the extracts as protectors from OONO-induced cytotoxicity in two mammalian cell lines. Both green tea and mate extracts have a high polyphenol content, in the case of Ip, its higher concentration and higher free radical quenching activity on the DPPH assay may be mainly due to the sui generis extraction procedure. When BSA was incubated in the presence of SIN-1, a time and dose dependent nitration of the protein is clearly shown. Co-incubation of BSA with Ip, green tea or red wines led to a dose dependent inhibition of the effect. Ip displayed the highest inhibitory activity, followed by red wines and the green tea. Dilutions as low as 1/1500 produced more than 80% inhibition of albumin nitration. When we studied peroxynitrite-induced cytotoxicity in murine RAW 264.7 macrophages and 31EG4 mammary cells., we found a potent, dose-dependent protective effect that was Ilex paraguariensis > red wines > green tea. Taken together, our results indicate that when the herbal preparations studied here are prepared the way they are usually drunk, Ip displays the highest inhibition of protein nitration, and the highest promotion of cell survival, whereas green tea or red wines display significant but lesser effects at the same concentrations. Further studies aiming at isolation of the active principles and assessment of their bioavailability are warranted.

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Effect of yerba mate (Ilex paraguariensis) tea on topoisomerase inhibition and oral carcinoma cell proliferation. (* Abstract - PubMed)

Gonzalez de Mejia E, **Song YS**, **Ramirez-Mares MV**, **Kobayashi H**.

Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, 228 ERML, MC-051, 1201 West Gregory Drive, Urbana, Illinois 61801, USA. edemejia@uiuc.edu

Tea flavonoids have antitopoisomerase activity and can inhibit cell proliferation. The objectives of this study were to determine the phenolic content of yerba mate tea products (MT) (Ilex paraguariensis) and evaluate their capacity to inhibit topoisomerase I (Topo I) and II (Topo II) activities and oral carcinoma cell proliferation. Total polyphenols of aqueous extracts of dried MT leaves were measured by the Folin-Ciocalteau assay, using chlorogenic (CH) and gallic (GA) acids as standards. Topoisomerase inhibition was determined by a clone-forming assay, which uses yeast (Saccharomyces cerevisiae) strains as a model. Controls included dimethyl sulfoxide (1.66%); camptothecin (50 microg/mL), a Topo I inhibitor; and amsacrine (100 microg/mL), a Topo II inhibitor. Cytotoxicity studies were conducted using a nontumorigenic human keratinocyte cell line HaCaT and two human squamous cancer cell lines (SCC-61 and OSCC-3). MT was found to be a rich source of phenolic compounds. Total polyphenol content of various commercially available traditional MT products ranged from 236 to 490 mg equiv of CH/g of dry leaves. Such levels were significantly different among products depending on their origin ($P < 0.001$). Higher anti-topoisomerase II activity was observed against JN394t(2-4) strain for Nobleza Gaucha MT (IC50 = 0.43 microg equiv of CH) in comparison to GA (IC50 = 112 mM) and CH (IC50 > 1500 mM). MT showed catalytic anti-topoisomerase activity against Topo II but not against Topo I. In addititon, MT exhibited dose-dependent cytotoxicity against all squamous cell lines tested. In comparison to premalignant cell line HaCaT [28 microg equiv of (+)-catechin mL(-1)], the cell line SCC-61 [21 microg equiv of (+)-catechin mL(-1)] was the most sensitive to MT, resulting in 50% inhibition of net cell growth. It is concluded that MT is rich in phenolic constituents and can also inhibit oral cancer proliferation. The effect on cancer cell proliferation may be mediated via inhibition of topoisomerase II. The lack of correlation between polyphenol content and the inhibition of topoisomerases suggests that the effect of MT on topoisomerase inhibition may be due to other still unidentified biologically active phytochemicals constituents.

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Aqueous extract of Ilex paraguariensis decreases nucleotide hydrolysis in rat blood serum. (* Abstract - PubMed)

Gorgen M, **Turatti K**, **Medeiros AR**, **Buffon A**, **Bonan CD**, **Sarkis JJ**, **Pereira GS**.

Laboratorio de Bioquimica, UNIVATES Centro Universitario, Lajeado, Rua Avelino Tallini, 171 CEP: 95900-000 Caixa Posta 155, Lajeado, RS, Brazil.

Mate is a xanthine-containing beverage, which is prepared as an infusion of the dried and ground leaves of Ilex paraguariensis St. Hil. (Aquifoliacea). Previous reports have shown that Ilex paraguariensis has the highest levels of caffeine and theobromine when compared to other Ilex species. Furthermore, mate is able to interfere in the circulatory system, acting as a diuretic and hypotensive agent. Many processes of vascular injury result in the release of adenine nucleotides, which exert a variety of effects. Nucleoside 5' tri- and diphosphates may be hydrolyzed by members of the ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase) family. The synchronic action of a NTPDase and a 5'-nucleotidase promotes the catabolism of ATP to adenosine, which is able to control the extracellular nucleotides/nucleosides ratio. The chronic ingestion of aqueous extract of Ilex paraguariensis by rats during 15 days significantly decreased ATP (55%), ADP (50%) and AMP (40%) hydrolysis in blood serum. These results suggest changes in the balance of purine levels induced by Ilex paraguariensis ingestion. Considering the potential effects of Ilex paraguariensis in the circulatory system, these results may be relevant since NTPDases are a novel drug target for the treatment of cardiovascular diseases.

J Ethnopharmacol. 2005 Feb 10;97(1):73-7. Epub 2004 Dec 22.
PMID: 15652278 [PubMed - indexed for MEDLINE]

Phenolic compounds in seven South American Ilex species. (* Abstract - PubMed)

Filip R, **Lopez P**, **Giberti G**, **Coussio J**, **Ferraro G**.

Catedra de Farmacognosia, Facultad de Farmacia y Bioquimica, IQUIMEFA (UBA-CONICET), Junin 956, 1113, Buenos Aires, Argentina. rfilip@ffyb.uba.ar

Ilex paraguariensis (common name: 'mate' or 'yerba mate') is used for the preparation of the most popular tea-like beverage of South America. Choleretic, hypocholesteremic, antioxidant, hepatoprotective and bitter taste properties of mate are attributed to the phenolic constituents of the leaves. I. paraguariensis has seven local congeneric substitutes or adulterants: I. brevicuspis; I. theezans; I. microdonta; I. dumosa var. dumosa; I. taubertiana; I. pseudobuxus; I. integerrima; and I. argentina. An HPLC method using UV with Photodiode Array Detector was developed for the identification and quantification of caffeoyl derivatives (caffeic acid, chlorogenic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid) and flavonoids (quercetin, rutin and kaempferol) in these species. I. paraguariensis showed a higher content of flavonoids and caffeoyl derivatives than the other assayed species.

Fitoterapia. 2001 Nov;72(7):774-8.
PMID: 11677016 [PubMed - indexed for MEDLINE]

Comparative study on the antioxidant capacity of wines and other plant-derived beverages. (* Abstract - PubMed)

Actis-Goretta L, Mackenzie GG, Oteiza PI, Fraga CG.

Physical Chemistry-PRALIB, School of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina.

Consistent epidemiological data point to a reduced morbidity and mortality from coronary heart disease and atherosclerosis in people consuming plant-derived beverages such as tea or wine. We studied the antioxidant capacity of three red wines (W) and compared it those of tea and herbal "mate" tea infusions. The antioxidant capacity was evaluated measuring: (1) the inhibition of the luminol-induced chemiluminescence assay (TRAP); (2) the inhibition of 2.2'-thiobarbituric-reactive substances (TBARS) formation in liposomes by fluorescence; (3) the protection of Jurkat cells from AMVN-induced oxidation, measuring the oxidation of 5-(and-6)-carboxy-2'7'-dichlorodihydrofluorescein diacetate to a fluorescent derivative. The polyphenolic content was estimated spectrophotometrically and by HPLC with electrochemical detection. All three beverages provided antioxidant protection in the three assays in a dose-dependent manner. Significant and positive correlations were found between antioxidant capacity and total polyphenol content, especially in the Jurkat cell oxidation assay ($r: 0.96$, $p < 0.01$). Results suggest that these dietary components could be a source of antioxidants that protect from oxidative stress. Further studies of absorption and metabolism of the active compounds will judge the physiological relevance of these results for human health.

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PMID: 12074981 [PubMed - indexed for MEDLINE]

Antioxidant effects of an aqueous extract of Ilex paraguariensis.

(* Abstract - PubMed)

Schinella GR, **Troiani G**, **Davila V**, **de Buschiazzo PM**, **Tournier HA**.

Catedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, CIC Pcia. de Buenos Aires, 60 y 120, La Plata Buenos Aires, 1900, Argentina.

In this work we investigate the antioxidant properties of an aqueous extract prepared from an infusion of Ilex paraguariensis (Aquifoliaceae) using free radical-generating systems. The extract inhibited the enzymatic and nonenzymatic lipid peroxidation in rat liver microsomes in a concentration-dependent fashion, with IC(50) values of 18 microg/ml and 28 microg/ml, respectively. The extract also inhibited the H(2)O(2)-induced peroxidation of red blood cell membranes with an IC(50) of 100 microg/ml and exhibited radical scavenging properties toward superoxide anion (IC(50) = 15 microg/ml) and 2,2-diphenyl-1-picrylhydrazyl radical. In the range of concentrations used, the extract was not a scavenger of the hydroxyl radical. Our results suggest that ingestion of extracts of Ilex paraguariensis could contribute to increase the antioxidant defense of an organism against free radicals attack.

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Antioxidant effects of Ilex paraguariensis: induction of decreased oxidability of human LDL in vivo. (* Abstract - PubMed)

Gugliucci A.

Department of Anatomy, University of Montreal, Quebec, Canada.
gugliuca@alize.ere.umontreal.ca

We have recently demonstrated that Ilex paraguariensis extracts inhibit LDL oxidation in vitro exhibiting a potency comparable to that of ascorbic acid (Gugliucci, A. and Stahl, A.J.C. 1995; Biochem Mol Biol Int 35, 47-56). In the present work we extend our observations to the in vivo situation. We first examined the oxidability of LDL in whole plasma from healthy fasted human subjects before and after intake of Ilex paraguariensis. Intake of water extracts of Ilex paraguariensis inhibit copper-induced autoxidation of LDL in whole plasma as shown by the end-term production of TBARS, and as a consequence are able to impair the appearance of Schiff base induced fluorescence, higher electrophoretic mobility and fragmentation of apoB. When LDL was isolated from plasma prior to oxidation no significant differences in lag-time, slope or maximum rate of oxidation could be detected. We then conclude that antioxidants in Ilex paraguariensis are absorbed and reach sufficient high levels in plasma to inhibit copper-induced LDL autoxidation by increasing aqueous-phase antioxidant capacity.

Biochem Biophys Res Commun. 1996 Jul 16;224(2):338-44.
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