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Review

Paullinia cupana Kunth (Sapindaceae): A review of its ethnopharmacology, phytochemistry and pharmacology

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In Western markets, the extract from the seeds of *Paullinia cupana* Kunth, Sapindaceae, popularly known as Guaraná, is most commonly used in high-energy foods and drinks and dietary supplements. However, a broad spectrum of medicinal activities is reported for *P. cupana*, ranging from stimulation of the central nervous system, in cases of physical or mental stress, to appetite suppression. It can also be used as an aphrodisiac and a treatment for impotence, as well as a medication to reduce fever, stimulate metabolism, induce antiplatelet, antioxidant and antibacterial activites. In addtition, *P. cupana* has been used in cosmetic preparations, and it has become a popular soft drink in Brazil. In the last two decades, Guaraná has emerged as a key ingredient in various sports and high-energy drinks. Methylxanthines, including caffeine, cathechins, theophylline and theobromine, and tannins are compounds which are reported for this plant. This article reviews the most up-to-date information on the botanical, chemical and pharmacological aspects of *P. cupana* extract, as well as its miscellaneous uses.

Key words: Ethnopharmacology, Guaraná extract, *Paullinia cupana*, caffeine, pharmacology, morphology.

INTRODUCTION

Paullinia cupana Kunth, Sapindaceae, popularly known as Guaraná, is widely used in Brazil for its medicinal properties, but it is also consumed in European countries (Oliveira et al., 2002). This plant is native to the Central Amazon basin and occurs in Brazil, Colombia, Equador, Peru, Venezuela and the Republic of Guyana (Raldkofer, 1895; Martínez, 1997; Beck, 2005; Acevedo-Rodríguez, 2008; Acevedo-Rodríguez, 2012). Guaraná was domesticated in the interfluvial forests between the lower Tapajós and lower Madeira Rivers in the Brazilian Amazon for its caffeine-rich fruits (Smith and Atroch, 2007).Roasted seed extracts have been used by native Amazonian tribesmen as an herbal beverage, based on its reputation as a stimulant, aphrodisiac, and tonic for headaches (Henman, 1982). Recently, it has been shown to promote weight loss (Andersen and Fogh, 2011), improve cognitive performance (Kennedy et al., 2008), as well as protect against diethylnitrosamine-induced DNA damage and gastric lesions induced by ethanol and indomethacin (Fukumasu et al., 2006). It is used for its antidepressant (Scholey and Haskell, 2008), antioxidant, and antibacterial effects and has been demonstrated to reduce the incidence and multiplicity of preneoplastic lesions induced by diethylnitrosamine in mouse liver

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(Fukumasu et al., 2008). It is also an ingredient in some soft drinks, non-alcoholic beverages and cosmetics.

Chemically, Guaraná seeds mainly consist of methylxanthine derivatives, including caffeine, theophylline and theobromine (Figure 1), which have well-studied effects on the central nervous system. It also contains a high proportion of polyphenols and catechins (Heard et al., 2006) (Figure 2). Based on its broad spectrum of medicinal effects, Guaraná is currently listed in the official Brazilian Pharmacopoeia (Farmacopéia Brasileira, 2000), and among Amazonian species, it is counted as one of the most promising drugs of Brazilian flora (Miranda and Metzner, 2010). The present paper reviews the most current information about this plant's ethnopharmacology, phytochemistry, pharmacology and morfology.

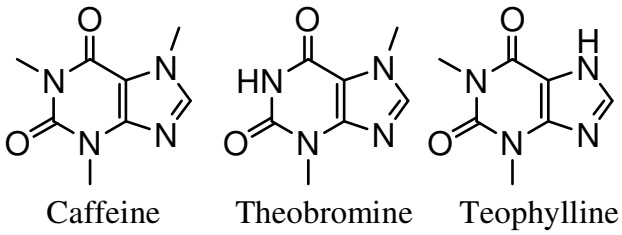

Figure 1. Methylxanthines from seeds of *P. cupana*.

BOTANICAL FEATURES

P. cupana Kunth was described for the first time by Kunth (1821) from a material collected by Humboldt and Bonpland at Venezuela. Later, Mart (1826) described *Paullinia sorbilis* as a new species from Ama-zonas State, Brazil. Ducke (1946) described a variety of Guaraná, *P. cupana* var. *sorbilis*. Then, Acevedo-Rodríguez (2012) synonymyzed *P. sorbilis,* T. Mart. and *P. cupana* var. *sorbilis* Ducke in *P. cupana* Kunth. This study follows the work of Acevedo-Rodríguez (2012).

In Brazil, *P. cupana* is popularly known as Guaraná, Guaraná-uva, Guaraná-cipó, naraná, uaraná, varaná, cupana, Brazilian cocoa and Guaraná Bread. *P. cupana* is a shrub (Figure 4) or liana (Figure 5) up to 5 m long with tendrils. Stems are obtusely pentagonal, puberulent, with stem cross section exhibiting a single vascular cylinder. Its leaves are pinnately 5-foliolate, alternate, chartaceous; its minute stipules are deltoid, 2-3 mm long, tomentulose, persistent; petiole and rachis are unwinged, petiole 11-20 cm long and rachis 7-12.5 cm long. The leaflet blades of *P. cupana* are elliptic or oblong-elliptic, 11 to 30 x 5.7 to 11 cm. The base of distal leaflet is cuneate or attenuate, acute, and obtuse to subrounded on lateral leaflet. The apex narrows into an acute broad apiculum with rounded tip, and its margins are grossly crenate or sinuate dentate with a glandular tooth. The adaxial surface is glabrous, while the abaxial surface is sparsely, minutely pubescent, having microscopic scurfy-like papillae; the tertiary venation is slightly sub-clathrate. Inflorescences are thyrses, axillary, racemiform, solitary, puberulent, with cincinni sessile, 5-8-flowered; bracts and bracteoles are minute deltate, tomentulose. Flowers are unisexual, zygomorphic. The calyx has 5 green sepals , possessing minute glandular hair along the margin; the outer sepals are 2.5-3.2 mm long, while the inner sepals are about 4 mm long, tomentulose. The corolla has 4 white petals, oblong, 4-5.5 mm long., bearing a hood-shaped appendage, these with a fleshy, yellowish apex. The 4 ovate nectariferous lobes are glabrous, each lobe about 1 mm long. The eight stamens are pubescent. The gynoecium is glabrous, the ovary is 3-carpellate, the carpels with a single ovule. The fruit (Figure 6) of P. cupana is a septifragal (marginicidal) capsule, maturing red, unwinged, ellipsoid to subglobose, 6-ridged, apiculate, long stipitate, 1-2-seeded, glabrous. The seeds are ovoid, dark-brown, with a white fleshy sarcotesta on lower 1/2 to 1/3.

ANATOMY

Few studies have reported the anatomy of *P. cupana*, and those that have referred only to the leaf and fruit. Sand (1966, 1971) showed some aspects of cell wall fragments of young leaf and highlights anatomical differences between young and mature leaves. Medri et al. (1980) compared diploid and polyploid leaves of Guaraná and found no difference in the size of the epidermal cells, stomatal size and number of stomata per unit area. Gonçalves et al. (2006) studied the anatomy of stomata in two clones and found a significant difference between the clones with respect to stomatal index, as well as ostiolar length and porous area. Milanez (1959) describes in detail the anatomy of the fruit, as well as some parts of the seed, and Mendonça et al. (1992) describe the structures of the seed, the fleshy structure (termed by them as arilódio) of the embryo and seed coats.

CHEMICAL COMPOSITION

Guaraná seeds contain high amounts of methylxanthines and tannins, as well as saponins, starch, polysaccharides, pigments, fats and choline (Dalonso and Petkowicz, 2012; Sousa et al., 2010; Yamaguti-Sasaki et al., 2007; Ushirobira et al., 2007; Edwards et al., 2005; Sombra et al., 2005; Bruneton et al., 1999; Meurer-Grimes et al., 1998; Seidemann, 1998; Carlson and Thompson, 1998; Mattei et al., 1998; Nazaré 1988; Baumann et al., 1995; Henman, 1982) (Table 1). The methylxanthines, especially caffeine, theophylline and theobromine, are found in different plant organs. The seeds of *P. cupana* are known to contain the highest natural dose of caffeine in the world (2 to 8%) (Higgins and Higgins, 2010; Beck, 2005; Schery, 1954), some 3 to

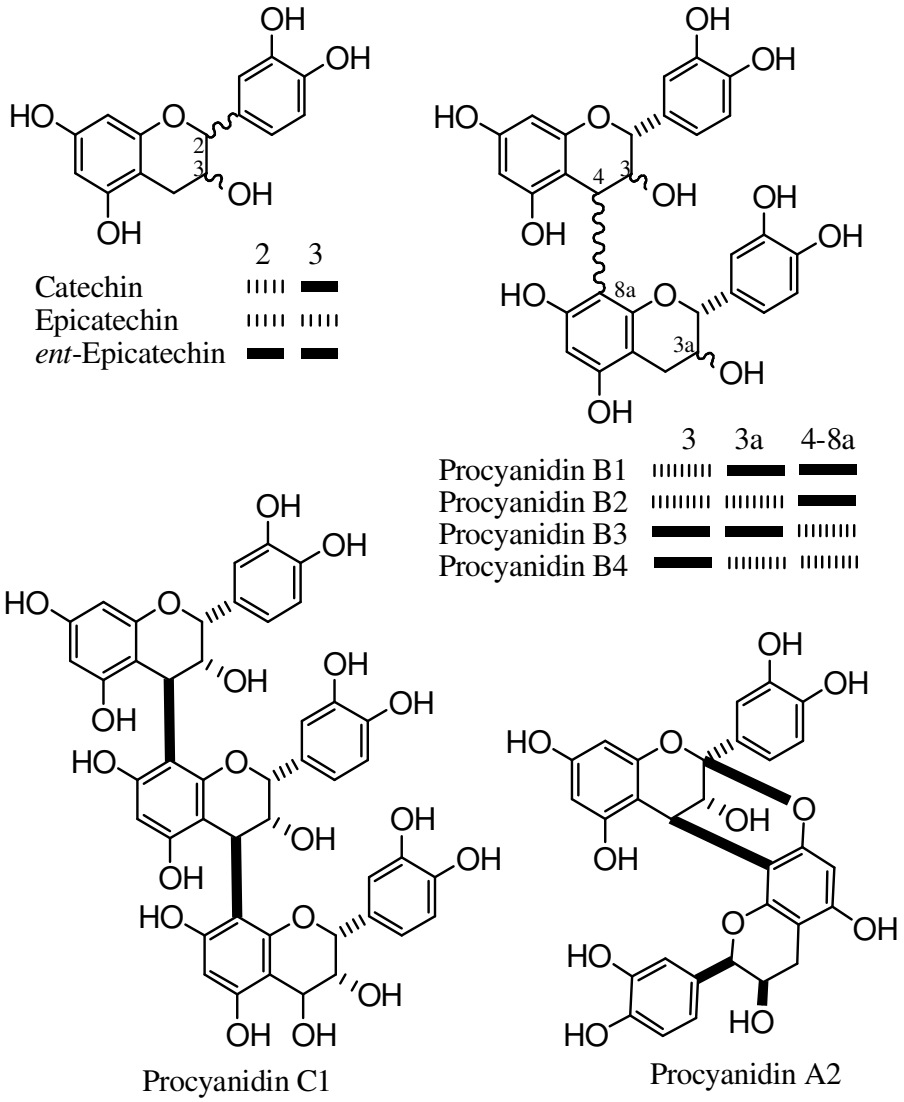

Figure 2. Polyphenols from seeds of *P. cupana*.

Table 1. Basic composition of Guaraná beans (*Paullinia cupana*) (Nazaré, 1998; Medical, 2000).

Determination	Content medium (%)
Caffeine	4
Catechutannic acid	5
Catechic acid	0.6
Tannins	12
Starch	30
Protein	15
Oil	0.16
Calcium	0.08
Phosphorus	0.01
Magnesium	0.05
Kalium	0.27

5 times higher than that found in a *Coffea arabica* bean (Figure 1) (Weckerle et al., 2003; Pagliarussi et al., 2002; Baumann et al., 1995). Tannins are classified into condensed tannins, based on a flavonoid framework, and hydrolysable tannins, which are essentially galloyl esters of glucose. The total content of condensed tannins (procyanidins B1, B2, B3, B4, A2, and C1) in Guaraná seeds has already been described in many papers, but hydrolysable tannins have not yet been described (Mello et al., 2010; Yamaguti-Sasaki et al., 2007). Other phenolic compounds found in Guaraná seeds include epicatechin, catechin and *ent*-epicatechin, and these have been previously described (Dalonso et al., 2012; Sousa et al., 2010; Yamaguti-Sasaki et al., 2007; Edwards et al., 2005; Sombra et al., 2005; Henman, 1982; Seidemann, 1998; Carlson and Thompson, 1998; Baumann et al., 1995) (Figure 2).

Table 2. Pharmacological properties of *P. cupana* seeds.

Activity	Reference
Low toxicity	Vermaak (2011), Mello (2010a,b), Oliveira (2005), Santa Maria (1998), Mattei (1998), and Fonseca (1994)
Antioxidant activity	Bittencourt (2013), Portella (2013), Dalonso (2012), Majhenic (2007), Mendes and Carlini (2007), Yamaguti-Sasaki (2007), Basile (2005), and Mattei (1998)
Antibacterial and antifungal activities	Basile (2013, 2005), Majhenic (2007), Yamaguti-Sasaki (2007)
Antidepressive, anxiolytic and anti-amnesic effects	Roncon (2011), Shahwar (2010), Antonelli (2007), Majhenic (2007), Otobone (2005, 2007), Ushirobira (2007), Basile (2005), Espinola (1997), and Mattei (1998)
Chemoprophylactic in carcinogenesis and antigenotoxic activity	Fukumasu (2011, 2008, 2006a,b), Oliveira (2002, 2011), Leite (2011); Cragg (2006), and Espinola (1997)
Inhibition of platelet aggregation	Bydlowski (1991, 1988)
Protection against gastric lesions	Campos (2003)
Lower risk of obesity, hypertension and metabolic syndrome	Krewer (2011)
Antifatigue effects	Campos (2011)

The seeds of Guaraná also contain acylglycerols and cyanolipids (Figure 3), an unusual class of plant lipids restricted to only a few families, such as Sapindaceae, Hippocastanaceae and Boraginaceae (Moller and Seigler, 1999). The study of the oil from *P. cupana* Kunth var. *sorbilis* (Mart.) Ducke indicated the presence of cyanolipid-I (1-cyano-2-hydroxymethylprop-2-ene-1-ol diesters) (Avato et al., 2003).

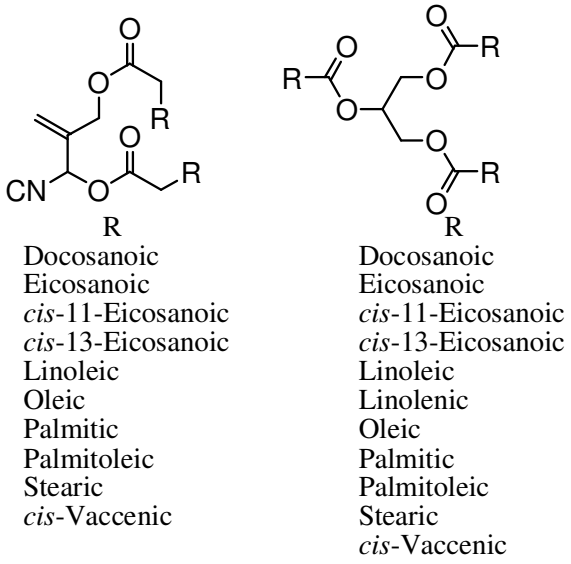

Figure 3. Cyanolipids and acylglycerols from seeds of *P. cupana*.

ETHNOMEDICINAL USES OF SEEDS FROM *P. CUPANA*

For centuries, Guaraná seeds have been used by the Saterê-Maué Indians, natives of the Amazon Region, as a stimulant, medication, beverage, and an antipoison, among other purposes (Beck, 1990). Its seeds are chewed or added to food and drinks. Guaraná is in popular use for a variety of therapeutic purposes, such as a stimulant of the nervous system in cases of physical or mental stress, an antidiarrheal, diuretic, antineuralgic agent, as well as febrifuge and painkiller to treat migraine (Henman, 1982; Rommelspacher, 1995; Galvão et al., 2002; Mendes and Carlini, 2007; Mendes, 2011).

PHARMACOLOGICAL PROPERTIES OF *P. CUPANA*

The extract of Guaraná seeds shows low toxicity (Vermaak et al., 2011; Mello et al., 2010a, 2010b; Oliveira et al., 2005; Santa Maria et al., 1998; Mattei et al., 1998; Fonseca et al., 1994) and different pharmacological activities as detailed in Table 2.

Antioxidant activity

The extract of Guaraná seeds exerts an antioxidant effect by inhibiting the process of spontaneous peroxidation (Basile et al., 2005; Mattei et al., 1998). Moreover, it possesses free radical-scavenging and antioxidant activities, as analyzed by the diphenylpicrylhydrazyl (DPPH) assay, the β-carotene–linoleic acid system, and the relative antioxidant capacity (RAC) assay (Portella et al., 2013; Dalonso et al., 2012; Majhenic et al., 2007; Yamaguti-Sasaki et al., 2007), and it protects against cadmium-induced damage (Leite et al., 2011). Guaraná extract has an antioxidant effect on nitric oxide (NO) metabolism in situations with higher cellular NO levels(Bittencourt et al., 2013). Its antioxidant activities may be related to the high concentrations of tannins

Figure 4. Plantation of *Paullinia cupana* shrubs.

Figure 5. Liana with mature fruits.

Figure 6. Detail of the opening fruits, showing the black seeds and sarcotesta.

present in the Guaraná seeds and may suggest a possible adaptogenic effect of the plant (Mattei et al., 1998; Mendes and Carlini, 2007).

Antibacterial and antifungal activities

The alcoholic Guaraná seed extract displays strong antimicrobial activity against fungi, including *Aspergillus niger*, *Trichoderma viride* and *Penicillium cyclopium*, and health-damaging bacteria, such as *Escherichia coli*, *Pseudomonas fluorescens*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Proteus vulgaris*, and *Streptococcus mutans* (Majhenic, 2007; Yamaguti-Sasaki, 2007; Basile, 2005).

Stimulant of the nervous system

The extracts of *P. cupana* show antidepressive, anxiolytic and anti-amnesic effects (Roncon et al., 2011; Shahwar et al., 2010; Antonelli et al., 2007; Otobone et al., 2007, 2005; Ushirobira et al., 2007; Basile et al., 2005; Majhenic et al., 2007; Espinola et al., 1997; Mattei et al., 1998). Different from caffeine, its antidepressant action, particularly after long-term treatment, is comparable to that of the tricyclic antidepressant imipramine (Tofranil), and it has a beneficial effect on cognition without altering locomotor activity (Scholey and Haskell, 2008; Otobone et al., 2005, 2007; Kennedy et al., 2004; Roncon et al., 2011; Carlini, 2003).

Chemopreventive and other activities

Guaraná seeds have been investigated for their potential effect as a chemoprophylactic in carcinogenesis and antigenotoxic activity *in vivo* (Fukumasu et al., 2011,

2008, 2006a, 2006b; Oliveira et al., 2011, 2002; Leite et al., 2011; Cragg et al., 2006; Espinola et al., 1997), such as the inhibition of platelet aggregation *in vitro* and *in vivo* (Bydlowski et al., 1991, 1988), protection against gastric lesions induced by ethanol and indomethacin *in vivo* (Campos et al., 2003) and the treatment of inflammatory allergic diseases (Jippo et al., 2009). An *in vivo* study to investigate the association between habitual Guaraná ingestion and the prevalence of metabolic disease exhibited a possible protective effect against obesity, hypertension and metabolic syndrome, all of which are related to a higher risk of cardiovascular disease (Krewer et al., 2011). In another study, the Guaraná extract (50 mg by mouth twice daily) showed antifatigue effects in patients with breast cancer undergoing systemic chemotherapy (Campos et al., 2011).

USE OF *P. CUPANA* IN FOOD, DRINKS AND DIETARY SUPPLEMENTS

An extensive range of products that include Guaraná seed extracts as ingredients is commercially available. Examples include confections (e.g., chocolate products), fruit-juice-based drinks, “energy drinks”, dietary supplements, comestics, and most controversially, natural weight loss products (Boozer et al., 2001; Andersen and Fogh, 2001; Carlini, 2003; Galduroz and Carlini, 1994). The main commercial use of Guaraná in Brazil is a carbonated soft drink (Miura et al., 1998; Freitas et al., 2007), Guaraná Antarctica being the most popular brand.

Guaraná is classified as a thermogenic agent (metabolic stimulant), because of its caffeine contents. Energy drinks typically comprise high levels of caffeine, as the dose of caffeine from high-energy drinks is typically up to 500 mg. Guaraná, taurine and sugar with various other amino acids are often also included in these formulations (Gray et al., 2012). Guaraná high-energy beverages are recognized as a safe food by the US Food and Drug Administration (FDA) and by the Brazilian agency that regulates and registers medicines and foods, Agência Nacional de Vigilância Sanitária (ANVISA) (Ducan et al., 2010; Heneman and Zidenberg-Cherr, 2007). The presence of flavonoids has been identified in Guaraná, and flavonoids are known to exert an antistress/adaptogenic activity (Carlson and Thompson, 1998).

It should be noted that a number of case reports in the literature have highlighted multiple potentially fatal cardiac side effects from high-energy drinks in the general population; consequently, the overall toxic effects of energy drinks is increasingly investigated and reported (Gray et al., 2012; Smith and Atroch, 2007).

Guaraná seed extract exhibits a powerful antioxidant activity, and in combination with vitamins and minerals, it improves cognitive task performance and attenuates increased mental fatigue associated with extended cognitive task performance (Bulku et al., 2010; Kennedy et al., 2008). Guaraná seed products are increasingly being used as a weight loss product in the form of powder, tablets and jams (Basile et al., 2005; Henman, 1982; Seidemann, 1998), and it is widely consumed by athletes who believe that it presents ergogenic and “fat burning” effects (Lima et al., 2005).

As alternative to synthetic products, mixed herbal preparations have been used in numerous over-the-counter products. In Brazil, an herbal medicinal extract named Catuama® containing a mixture of *P. cupana* (Guaraná; Sapindaceae), *Trichilia catigua* A. Juss. (catuaba; Meliaceae), *Ptychopetalum olacoides* Benth. (muirapuama; Olacaceae) and *Zingiber officinale* Roscoe (ginger; Zingiberaceae) is used as a body stimulant, ergogenic, tonic and aphrodisiac (Oliveira et al., 2005). Kennedy et al. (2008) concluded that multivitamin-mineral food supplements fortified with Guaraná can improve cognitive performance and reduce the mental fatigue with sustained mental effort. Another dietary supplement, which is composed of three well-known phytochemicals, namely, *Salvia officinalis* L. (sage) extract, *Camellia sinensis* (L.) Kuntze (oolong tea) extract, and *P. cupana* (Guaraná) extract, and two prominent vitamins (thiamine and niacin), was designed to provide nutritional support by enhancing metabolism and maintaining healthy weight and energy (Bulku et al., 2010). The mixed herbal preparation “YGD,” which contains Yerbe Maté (leaves of *Ilex paraguayensis* Hook), Guaraná (seeds of *P. cupana*) and Damiana (leaves of *Turnera diffusa* Willd. var. *aphrodisiaca* (Ward) Urb.), has long been used in folk medicine in South America and Mexico as herbs with diverse effects (Schery, 1954). YGD significantly delayed gastric emptying, reduced the time of perceived gastric fullness and induced significant weight loss over 45 days in overweight patients treated in a primary health care context (Andersen and Foght, 2001). The herbal preparations of *Ephedra sinica*, and Guaraná (caffeine) have both anorectic and thermogenic effects, and therapy produces about 10% loss of initial body weight over 6 months (Andersen and Fogh, 2001). No studies have been found that report the use of Guaraná alone as promoting weight loss.

Cosmetic uses

In the cosmetics industry, the Amazon is recognized as an invaluable resource, providing rich ingredients used in personal care products and fragrances (Bolan, 2005). Seed extracts of Guaraná possess strong antimicrobial and antioxidant properties and can therefore be used as a natural additive in cosmetics (Majhenic et al., 2007). Furthermore, it can be used in the manufacture of products for both skin and hair (http://www.advanstar.com). It is indicated in products for the treatment of cellulitis based on its high content of

alkaloids, in particular, caffeine (Marchei et al., 2012). It can also be used in anti-aging creams (Peirano et al., 2011), cleansing lotions or soaps, shampoos and conditioners (www.natura.com.br).

CONCLUSION

P. cupana has the luster of an interesting rainforest liana with a long history of use as a medicinal plant. For a long time, *P. cupana* has been used in traditional medicines for the treatment of headache, dysmenorrhea, and as a stimulant. *P. cupana* has recently been shown to have antimicrobial, chemoprophylactic and antigenotoxic activities, in addition to antidepressive, anxiolytic and anti-amnesic effects. This plant warrants further study of its antioxidant and antidepressive effects.

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REFERENCES

Acevedo-Rodríguez P (2008). Sapindaceae. In: Daly, D.C., Silveira, M. & colaboradores. Primeiro Catálogo da Flora do Acre, Brasil. Rio Branco, AC:EDUFAC. pp. 337-343.

Acevedo-Rodríguez P (2012). Sapindaceae. In Oliveira SM, Flora of the Guianas, Royal Botanic Gardens, Kew. p. 196.

Andersen T, Fogh J (2001). Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. J. Hum. Nutr. Dietet. 14:243-250.

Antonelli UTM, Yamaguti E, Uemura LM, Nakamura CV, Dias Filho BP, De Mello JCP (2007). Chemical and microbiological study of extract from seeds of Guaraná (*Paullinia cupana* var. sorbilis). Lat. Am. J. Pharm. 26:5-9.

Avato P, Pesante MA, Fanizzi FP, Santos CAD (2003). Seed oil composition of *Paullinia cupana* var. *sorbilis* (Mart.) Ducke. Lipids. 38:773-780

Basile A, Ferrara L, Del Pezzo M, Mele G, Sorbo S, Bassi P, Montesano D (2005). Antibacterial and antioxidant activities of ethanol extract from *Paullinia cupana* Mart. J. Ethnopharmacol. 102:32-36.

Basile A, Rigano D, Conte B, Bruno M, Rosselli S, Sorbo S (2013). Antibacterial and antifungal activities of acetonic extract from *Paullinia cupana* Mart. Seeds. Nat. Prod. Res. In press.

Baumann TW, Schulthess BH, Hanni K (1995). Guaraná (*Paullinia cupana*) rewards seed dispersers without intoxicating them by caffeine. Phytochem. 39:1063-1070.

Beck HT (2005). *Paullinia*. In: Steyermark, JA, Berry P & Holts B, eds). Flora of the Venezuelan Guayana V. 9. Missouri Bot. Gard. Press.

Beck HT (1990). A survey of the useful species of *Paullinia* (Sapindaceae). Adv. Econ. Bot. 8:41-56.

Beck HT (2005). Caffeine, alcohol, and sweeteners. In G. Prance and M. Nesbett, eds., Cultural History of Plants. New York: Routledge.

Bolan C (2005). Natura sustains its growth. Global Cosmetic Industry. 173:22-23.

Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL (2001). An herbal supplement containing MA Huang-Guarana for weight loss: a randomized, double-blind trial. Int. J. Obes. 25:316-324.

Bruneton J (1999). "Pharmacognosy, Phytochemistry and Medicinal Plants", 2nd Edition, intercept LTd., Hampshire, U.K. p 1119.

Bulku E, Zinkovsky D, Patel P, Javia V, Lahoti T, Khodos I, Stohs, JM, Ray SD (2010). A novel dietary supplement containing multiple phytochemicals and vitamins elevates hepatorenal and cardiac antioxidant enzymes in the absence of significant serum chemistry and genomic changes. Ox. Med. Cell. Longev. 3:129-144.

Bydlowski SP, Damico EA, Chamone DAF (1991). An aqueous extract of Guaraná (*Paullinia cupana*) decreases platelet thromboxane synthesis. Braz. J. Med. Biol. Res. 24:421-424.

Bydlowski SP, Yunker RL, Subbiah MTR (1988). A novel property of an aqueous Guaraná extract (*Paullinia cupana*) - inhibition of platelet-aggregation *in vitro* and *in vivo*. Braz. J. Med. Biol. Res. 21:535-538.

Campos MPD, Riechelmann R, Martins LC, Hassan BJ, Casa FBA, Del Giglio A, (2011). Guarana (*Paullinia cupana*) Improves Fatigue in Breast Cancer Patients Undergoing Systemic Chemotherapy. J. Altern. Complement. Med. 17:505-512.

Campos AR, Barros AIS, Santos FA, Rao VSN (2003). Guaraná (*Paullinia cupana* Mart.) offers protection against gastric lesions induced by ethanol and indomethacin in rats. Phytother. Res. 17:1199-1202.

Carlini EA (2003). Plants and the central nervous system. Pharmacol. Biochem. Behav. 75:501-512.

Carlson M, Thompson RD (1998). Liquid chromatographic determination of methylxanthines and catechins in herbal preparations containing Guaraná. J. AOAC Int. 81:691-701.

Cragg GM, Newman DJ, Yang SS (2006). Natural product extracts of plant and marine origin having antileukemia potential. The NCI experience. J. Nat. Prod. 69:488-498.

Dalonso N, Petkowicz CLO (2012). Guaraná powder polysaccharides: Characterisation and evaluation of the antioxidant activity of a pectic fraction. Food Chem. 134:1804-1812.

Ducan E, Patel ND, Feucht C (2010). Energy drinks: a review of use and safety for athletes. Phys. Sportsmed. 28:171-179.

Edwards HGM, Farwell DW, de Oliveira LFC, Alia JM, Le Hyaric M, de Ameida MV (2005). FT-Raman spectroscopic studies of Guaraná and some extracts. Anal. Chim. Acta. 532:177-186.

Espinola EB, Dias RF, Mattei R, Carlini EA (1997). Pharmacological activity of Guaraná (*Paullinia cupana* Mart) in laboratory animals. J. Ethnopharmacol. 55:223-229.

Farmacopéia Brasileira (2000). Fourth Ed. Editora Atheneu, São Paulo.

Fonseca CAS, Leal J, Costa SS, Leitao AC (1994). Genotoxic and mutagenic effects of Guaraná (*Paullinia cupana*) in prokaryotic organisms. Mutat. Res. 321:165-173.

Freitas RS, Moreno SRF, Lima-Filho GL, Fonseca AS, Bernardo-Filho M (2007). Effect of a commercial extract of *Paullinia cupana* (guarana) on the binding of 99mtc-DMSA on blood constituents: An *in vivo* study. App. Radiat. Isto. 65:528-533.

Fukumasu H, Avanzo JL, Heidor R, Silva TC, Atroch A, Moreno FS, Dagli MLZ (2006a). Protective effects of Guaraná (*Paullinia cupana* Mart. var. *Sorbilis*) against DEN-induced DNA damage on mouse liver. Food Chem. Toxicol. 44:862-867.

Fukumasu H, Avanzo JL, Nagamine MK, Barbuto JA, Rao KV, Dagli MLZ (2008). *Paullinia cupana* Mart var. sorbilis, Guaraná, reduces cell proliferation and increases apoptosis of B16/F10 melanoma lung metastases in mice. Braz. J. Med. Biol. Res. 41:305-310.

Fukumasu H, da Silva TC, Avanzo JL, de Lima CE, Mackowiak, II, Atroch A, Spinosa HD, Moreno FS, Dagli MLZ (2006b). Chemopreventive effects of *Paullinia cupana* Mart var. *sorbilis*, the Guaraná, on mouse hepatocarcinogenesis. Cancer Lett. 233:158-164.

Fukumasu H, Latorre AO, Zaidan-Dagli ML (2011). *Paullinia cupana* Mart. var. *sorbilis*, Guaraná, increases survival of Ehrlich Ascites Carcinoma (EAC) bearing mice by decreasing Cyclin-D1 expression and inducing a G0/G1 cell cycle arrest in EAC Cells. Phytother. Res. 25:11-16.

Galduroz JC, Carlini de EA (1994). Acute effects of the *Paullinia cupana*, "Guaraná" on the cognition of normal volunteers. São Paulo Med. J. 112:607-611.

Galvão SMP, Marques LC, Oliveira MGM, Carlini EA (2002). Heteropterys aphrodisiaca (extract BST0298): a Brazilian plant that improves memory in aged rats. J. Ethnopharmacol. 79:305-311.

Gray B, Das KJ, Semsarian C (2012). Consumption of energy drinks: A new provocation test for primary arrhythmogenic diseases? Int. J.

Cardiol. 159:77-78.
Gruenwald J, Brendler T, Jaenicke C (2000). PDR for Herbal Medicines, 2nd ed. Montvale, NJ: Medical Economics. Please provide page number
Heard CM, Johnson S, Moss G, Thomas, CP (2006). In vitro transdermal delivery of caffeine, theobromine, theophyline and catechin from of guarana, *Paullinia cupana*. Int. J. Pharm. 317:26-31.
Heneman K, Zidenberg-Cherr S (2007). Nutrition and Health Info-Sheet for Health Professionals University of California, Davis. Retrieved May 15, from http://nutrition.ucdavis.edu/content/infsheets/EnergyDrinks.pdf
Henman AR (1982). Guaraná (*Paullinia cupana* var *sorbilis*) - ecological and social perspectives on an economic plant of the central amazon basin. J. Ethnopharmacol. 6:311-338.
Higgins JP, Higgins CL (2010). Energy Beverages: Content and Safety. Mayo Clin. Proc. 85:1033-1041.
Jippo T, Kobayashi Y, Sato H, Hattori A, Takeuchi H, Sugimoto K, Shigekawa M (2009). Inhibitory effects of Guaraná seed extract on passive cutaneous anaphylaxis and mast cell degranulation. Biosci. Biotechnol. Biochem. 73:2110-2112.
Kennedy DO, Haskell CF, Robertson B, Reay J, Brewster-Maund, Luedmann J, Maggini S, Ruf, M, Zangara A, Scholey AB (2008). Improved cognitive performance and mental fatigue following a multi-vitamin and mineral supplement with added guaraná (*Paullinia cupana*). Appetite 50:506-513.
Kennedy DO, Haskell CF, Wesnes KA, Scholey AB (2004). Improved cognitive performance in human volunteers following administration of Guaraná (*Paullinia cupana*) extract: comparison and interaction with *Panax ginseng*. Pharmacol. Biochem. Behav. 79:401-411.
Krewer CD, Ribeiro EE, Ribeiro EAM, Moresco RN, da Rocha MIDM, Montagner GFFD, Machado MM, Viegas K, Brito E, da Cruz IBM (2011). Habitual Intake of Guarana and Metabolic Morbidities: An Epidemiological Study of an Elderly Amazonian Population. Phytother. Res. 25:1367-1374.
Kunth KS (1821). Nova genera et species plantarum equinoctialum uas in peregrinatione ad plagam aequinoctialem orbis novi collegerunt Bonpland ET Humboldt. Paris: Librairie Grècque-Latine-Allemande. pp. 1815-1825.
Leite RP, Wada RS, Monteiro JC, Predes FS, Dolder H (2011). Protective Effect of Guaraná (*Paullinia cupana* var. *sorbilis*) Pre-treatment on cadmium-induced damages in adult wistar testis. Biol. Trace Elem. Res. 141:262-274.
Lima WP, Carnevali-Junior LC, Eder R, Rosa LFBPC, Bacchi EM, Seelaender MCL (2005). Lipid metabolism in trained rats: Effect of guarana (*Paullinia cupana* Mart) supplementation. Clin. Nutr. 24:1019-1028.
Majhenic L, Skerget M, Knez Z (2007). Antioxidant and antimicrobial activity of Guaraná seed extracts. Food Chem. 104:1258-1268.
Marchei E, Orsi D, Guarino C, Dorato S, Pacifici R, Pichini S (2012). Measurement of iodide and caffeine content in cellulite reduction cosmetic products sold in the European Market. Anal. Methods. 5:376-383
Martínez RV (1997). Sapindaceae. Flórula de las Reservas Biológicas de Iquitos, Perú. Missouri Bot. 63:651-657.
Mattei R, Dias RF, Espinola EB, Carlini EA, Barros SBM (1998). Guaraná (*Paullinia cupana*): toxic behavioral effects in laboratory animals and antioxidant activity in vitro. J. Ethnopharmacol. 60:111-116.
Mello J, Klein T, Lopes G (2010). Application of an HPLC method for analysis of the extract from *Paullinia cupana* var. sorbilis (Mart.) Ducke. Planta Med. 76:1259-1259.
Mello JRB, de Mello FB, Langeloh A (2010a). Pre-clinic toxicity of a phytoterapic containing *Anemopaegma mirandum, Cola nitida, Passiflora alata, Paullinia cupana, Ptychopetalum olacoides* and thiamin chlorhydrate. Lat. Am. J. Pharm. 29:57-63.
Mello JRB, de Mello FB, Langeloh A (2010b). Toxicity study of a phytotherapic with *Anemopaegma mirandum, Cola nitida, Passiflora alata, Paullinia cupana, Ptychopetalum olacoides* and thiamin in rabbits. Lat. Am. J. Pharm. 29:1431-1435.
Mendes FR (2011) Tonic, fortifier and aphrodisiac: adaptogens in the Brazilian folk medicine. Rev. Bras. Farmacogn. 21:754-763.
Mendes FR, Carlini EA (2007). Brazilian plants as possible adaptogens: An ethnopharmacological survey of books edited in Brazil. J. Ethnopharmacol. 109:493-500.
Meurer-Grimes B, Berkov A, Beck H (1998). Theobromine, theophylline, and caffeine in 42 samples and products of Guaraná (*Paullinia cupana*, Sapindaceae). Econ. Bot. 52:293-301.
Milanez FR (1959). Anatomia do fruto do guaraná. Arq. Jard. Bot. Rio de Janeiro. 16:57-100.
Miranda MV, Metzner BS (2010). *Paullinia cupana*: revisão da materia médica. Revista de Homeopatia 73:1-17.
Medri ME, Lleras E, Valois ACC (1980). Comparação anatômica entre folhas diplóides e poliplóides do guaraná (*Paullinia cupana* var *sorbilis* (Mart.) Ducke). Acta Amazonica 10:283-288.
Mendonça MS, Noda H, Corrêa MPF (1992). Aspectos morfológicos da semente e da germinação do guaraná (*Paullinia cupana* var. *sorbilis* (Mart.) Ducke). Rev. U.A.Série: Ciências Agrárias. 1(2):71-82.
Moller BL, Seigler DS (1999). Biosynthesis of Cyanogenic Glycosides, Cyanolipids, and Related Compounds, in Plant Amino Acids. Biochemistry and Biotechnology (Singh, B.K., ed.), Marcel Dekker, New York. pp. 563-609.
Nazaré RFR (1998). de. Processamento de guaraná em pó solúvel. Belém: Embrapa-CPA TU. (Embrapa - CPA TU. Documentos, 95). p. 24.
Oliveira CH, Moraes MEA, Moraes MO, Bezerra FAF, Abib E, De Nucci G (2005). Clinical toxicology study of an herbal medicinal extract of *Paullinia cupana, Trichilia catigua, Ptychopetalum olacoides* and *Zingiber officinale* (Catuama®) in healthy volunteers. Phytother. Res. 19:54-57.
Oliveira CMP, Hassan BJ, Riechelmann R, del Giglio A (2011). Cancer-related fatigue: a review. Rev. Assoc. Med. Bras. 57:211-219.
Oliveira JF, Avila AS, Braga ACS, de Oliveira MBN, Boasquevisque EM, Jales RL, Cardoso VN, Bernardo M (2002). Effect of extract of medicinal plants on the labeling of blood elements with Technetium-99m and on the morphology of red blood cells: I - a study with *Paullinia cupana*. Fitoterapia. 73:305-312.
Otobone FJ, Sanches AC, Nagae RL, Martins JVC, Obici S, Mello JCP, Audi EA (2005). Effect of crude extract and its semi purified constituents from Guaraná seeds (*Paullinia cupana* var. *sorbilis* (Mart.) Ducke) on cognitive performance in morris water maze in rats. Braz. Arch. Biol. Technol. 48:723-728.
Otobone FJ, Sanches AC, Nagae RL, Martins JVC, Sela, VL, Mello JCP, Audi EA (2007). Effect of lyophilized extracts from Guaraná seeds (*Paullinia cupana* var. *sorbilis* (Mart.) Ducke) on behavorial profiles in rats. Phytother. Res. 21:531-535.
Pagliarussi RS, Freitas LAP, Bastos JK (2002). A quantitative method for the analysis of xanthine alkaloids in *Paullinia cupana* (Guaraná) by capillary column gas chromatography. J. Sep. Sci. 25:371-374.
Portella RD, Barcelos RP, da Rosa EJF, Ribeiro EE, da Cruz IBM, Suleiman L, Soares FAA (2013). Guarana (*Paullinia cupana* Kunth) effects on LDL oxidation in elderly people: an in vitro and in vivo study. Lipids Health Dis. 12:1-9.
Raldkofer L (1895). *Paullinia sapindacearum* genus monographice descriptum. Monographie de Sapindaceen-gattung. *Paullinia*. Verlag der K. Akademie, Munchen. 19(I-II):71-315.
Rommelspacher H (1995). Guaraná (*Paullinia cupana* Knutz). Dtsch. Med. Wochenschr. 120:384-384.
Roncon CM, de Almeida CB, Klein T, Palazzo de Mello JC, Audi EA (2011). Anxiolytic effects of a semipurified constituent of Guaraná seeds on rats in the elevated T-maze test. Planta Med. 77:236-241.
Santa Maria A, Lopez A, Diaz MM, Munoz-Mingarro D, Pozuelo JM (1998). Evaluation of the toxicity of Guaraná with in vitro bioassays. Ecotoxicol. Environ. Saf. 39:164-167.
Schery RW (1954). Plants for Man. London: George Allen and Unwin. pp. 518:519.
Scholey A, Haskell C (2008). Neurocognitive effects of Guaraná plant extract. Drugs Future. 33:869-874.
Seidemann J (1998). Guaraná (*Paullinia cupana* HB.K.) an active agent from the tropical rain forest. Tropenlandwirt. 1:49-63.
Shahwar D, Raza MA, Mughal MAS, Abbasi MA, Ahmad VU (2010). Comparative study on the antioxidant and antimicrobial activities of stem-bark extract of litchi chinensis and its organic fractions. J. Chem. Soc. Pak. 32:357-362.
Smith N, Atroch, AL (2007). Guaraná's Journey from Regional Tonic to

Aphrodisiac and Global Energy Drink. Evid. Based Complement. Altern. Med. Adv. 7(3):279-282.
Sombra LL, Gomez MR, Olsina R, Martinez LD, Silva MF (2005). Comparative study between capillary electrophoresis and high performance liquid chromatography in 'Guaraná" based phytopharmaceuticals. J. Pharm. Biomed. Anal. 36:989-994.
Sousa SA, Alves SF, de Paula JAM, Fiuza TS, Paula JR, Bara MTF (2010). Determination of tannins and methylxanthines in powdered Guaraná (*Paullinia cupana* Kunth, Sapindaceae) by high performance liquid chromatography. Rev. Bras. Farmacogn. 20:866-870.
Ushirobira TMA, Yamaguti E, Uemura LM, Nakamura CV, Dias Filho BP, Mello JCP (2007). Chemical and microbiological study of extract from seeds of Guaraná (*Paullinia cupana* var. *sorbilis*) Lat. Am. J. Pharm. 26:5-9.
Vermaak I, Viljoen AM, Hamman JH (2011). Natural products in anti-obesity therapy. Nat. Prod. Rep. 28:1493-1533.
Weckerle CS, Stutz MA, Baumann TW (2003). Purine alkaloids in *Paullinia*. Phytochem. 64:735-742.
Yamaguti-Sasaki E, Ito LA, Canteli VCD, Ushirobira TMA, Ueda-Nakamura T, Filho BPD, Nakamura CV, De Mello JCP (2007). Antioxidant capacity and in vitro prevention of dental plaque formation by extracts and condensed Tannins of *Paullinia cupana*. Mol. 12:1950-1963.