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 activities. In addition, **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, catechins, 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 (Fukumatu et al., 2006). It is used for its antidepressant (Shohey 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, Guarana 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, Guarana is currently listed in the official Brazilian Pharmacopoeia (Farmacopeia 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 morphology.

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 *Paulinia sorbilis* as a new species from Ama-zonas State, Brazil. Dudke (1946) described a variety of Guarana, *P. cupana* var. *sorbilis*. Then, Acevedo-Rodriguez (2012) synonymized *P. sorbilis*, T. Mart. and *P. cupana* var. *sorbilis* Dudke in *P. cupana* Kunth. This study follows the work of Acevedo-Rodriguez (2012).

In Brazil, *P. cupana* is popularly known as Guarana, Guaranã-uvá, 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 apiculate, 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-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 deltoid, 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 (marginicial) 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 Guarana 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. Milanetz (1959) describes in detail the anatomy of the fruit, as well as some parts of the seed, and Mendonca 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 (Dalonsco 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).

<table>
<thead>
<tr>
<th>Determination</th>
<th>Content medium (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>4</td>
</tr>
<tr>
<td>Catechutannic acid</td>
<td>5</td>
</tr>
<tr>
<td>Catechic acid</td>
<td>0.6</td>
</tr>
<tr>
<td>Tannins</td>
<td>12</td>
</tr>
<tr>
<td>Starch</td>
<td>30</td>
</tr>
<tr>
<td>Protein</td>
<td>15</td>
</tr>
<tr>
<td>Oil</td>
<td>0.16</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.08</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.01</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.05</td>
</tr>
<tr>
<td>Kalium</td>
<td>0.27</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>amnesic effects</td>
<td></td>
</tr>
<tr>
<td>Inhibition of platelet aggregation</td>
<td>Bydlowski (1991, 1988)</td>
</tr>
<tr>
<td>Protection against gastric lesions</td>
<td>Campos (2003)</td>
</tr>
<tr>
<td>Lower risk of obesity, hypertension and metabolic syndrome</td>
<td>Krewer (2011)</td>
</tr>
<tr>
<td>Antifatigue effects</td>
<td>Campos (2011)</td>
</tr>
</tbody>
</table>

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.) Ducce indicated the presence of cyanolipid-I (1-cyano-2-hydroxymethylprop-2-ene-1-ol diesters) (Avato et al., 2003).

**ETHNOMEDICINAL USES OF SEEDS FROM P. CUPANA**

For centuries, Guaraná seeds have been used by the Sateré-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.
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,
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; Galdouro 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 an 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), Psychotropical olacoides Bentham. (muirapuama; Olaceae) 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 Foght, 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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