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Review

Guarana: Revisiting a highly caffeinated plant from the Amazon

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ABSTRACT

Ethnopharmacological relevance: Guarana (*Paullinia cupana* Kunth var. *sorbilis* (Mart.) Ducke) has been traditionally consumed by indigenous communities of the Amazon region. It is valued mainly for its stimulant property because of its high content of caffeine, which can be up to 6% in the seeds.
Aim of the review: The purpose of this review is to revisit this typically Brazilian plant, addressing economic considerations, the chemical makeup of the seeds and pharmacological properties so far investigated.
Results: Guarana is primarily produced in the Brazilian states of Amazonas and Bahia, and approximately 70% of the production is used by the industry of soft and energy drinks. The other 30% becomes guarana powder for direct consumption in capsules or dilution in water, or it serves as a raw material for the pharmaceutical and cosmetics industries. In addition to its stimulant property, guarana has other therapeutic properties, which have aroused the interest of the scientific community.
Conclusion: This review shows that other guarana properties may be explored and how scarce are the studies regarding agronomic, plant pathology, physiology and breeding. So far, caffeine has been the main reason to study guarana and still will lead the researches because the demand for this alkaloid by food and pharmaceutical industry, and a strongly growing market related with beauty products. However, guarana has other components and there is great interest in studies designed to elucidate the effects of guarana's bioactive components and their potential pharmacological applications. Significant part of the guarana production in Brazil still comes from Indians tribes in the Amazon State, and any improvement in this plant, in any aspect, may propitiate a positive economic impact in their lives.

Contents

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1. Introduction

Guarana, also called *guaraná-da-amazônia*, *guaranaina*, *guaranauva*, *uarana* or *narana*, is a species native to the Amazon region known for its stimulant and medicinal properties and used for centuries by indigenous communities of the Amazon. The first report about the use of guarana as a beverage occurred in 1669 when, during the Jesuit expedition to the Amazon, the missionary João Felipe Bettendorf observed that the Sateré-Mawé Indians consumed a stimulating beverage that had diuretic properties and therapeutic effects against headache, fever and cramps (Maravalhas, 1965; Henman, 1986).

Guarana had two botanical classifications until 1897, at which point *Paullinia cupana* was retained as the scientific name because it was the first recorded, but Ducke (1937) described sufficient morphological differences to distinguish the populations of plants found in the upper Rio Negro from those found in Maués. Ducke's description thus complemented the description by Theodor Martius, who provided a description of *Paullinia sorbilis* as a variety of *Paullinia cupana*: *Paullinia cupana* Kunth var. *sorbilis* (Mart.) Ducke (Atroch, 2009). According to Ducke (1937) *Paullinia cupana* var. Typica is the Venezuelan guarana while var. Sorbillis is the Brazilian guarana, which is economically explored. This review will refer to this variety of guarana, which is the only one that is used commercially and has been the most thoroughly studied.

Fig. 1. Guarana fruits.

2. Characterisation of the species and cultivation of the guarana plant

The family *Sapindaceae* has approximately 140 genera and 2000 species distributed across three subfamilies; the guarana plant belongs to the subfamily *Sapindoideae* (Gentry, 1991; Souza and Lorenzi, 2008). The genus *Paullinia*, with approximately 200 species, is almost entirely restricted to tropical and subtropical America, with the exception of *Paullinia pinnata* L., which is also present in tropical Africa. In the Brazilian Amazon, in addition to guarana, there are more than eight reported species, including *Paullinia seminuda* Radlk., *Paullinia paullinoides* Radlk., *Paullinia verrucosa* Radlk., *Paullinia rufescens* Rich. ex Juss., *Paullinia caloptera* Radlk., *Paullinia selenoptera* Radlk., *Paullinia pinnata* L. and *Paullinia pseudota* Radlk. ex Warm. (Schmidt, 1941; Missouri Botanical Garden, 2012). These species have not been well characterized so far but depending on the phylogenetic relationship with guarana they might become a rich source of genetic variability for breeding purposes (Atroch, 2009).

There are controversies regarding the origin and distribution of the guarana plant (*Paullinia cupana* var. *sorbilis*). However, its natural habitat seems to be limited to the region of the Maués-Açu river basin, which coincides with the territory of the Sateré-Mawé Indians (Schmidt, 1941; Saldaña et al., 2002). The phylogenetic centre of origin of guarana would be, according to Ducke (1937), the upper Rio Negro, although some authors claim that the species follows the distribution of the genus *Hevea* (Pires, 1949).

The word *guarana*, *uarana* or *varana* means "vine" in various indigenous dialects, and it refers to the liana growth habit of this perennial plant, which has tendrils that can reach up to 10 m in length in the presence of trees that act as supports (Fig. 1). The stem is ridged and has a yellowish-brown colouring when lignified. The leaves are alternate and odd-pinnate. The well-developed sheaths are approximately 1.5 cm long. The main petiole (rachis) is 8 to 19 cm, and the petioles of the leaflets are very short. The leaflets have a roughly oval shape and a serrated apex, with width ranging from 10 to 14 cm and length from 27 to 33 cm. The leaflets are well spaced and have prominent underside veins. The leaves are dark green with glossy topside. At the base of each leaf, there is a vegetative and a reproductive bud (Lodewijks, 1986).

The guarana plant is a monoecious plant, with a raceme type of inflorescence that can be longer than 30 cm. Its flowers are small and zygomorphic, and they are laid out along the main axis of the inflorescence. The calyx is composed of five sepals, of which two are smaller and external, with the corolla formed by four white petals that have the shape of a hood or gutter and have, internally, crest-shaped coriaceous scales with yellow tips. The flowers are pseudo-hermaphrodites, of which those considered female have seemingly normal rudimentary stamens and indehiscent anthers, whereas those considered male have atrophied ovaries and a regressed stylus and stigma (Escobar, 1985; Souza et al., 1996; Lunguinho, 2007). Although the large number of flowers, approximately 95 per inflorescence, the ratio of male to female flowers is 4.5:1 and it may vary with each bloom. This variation occurs mainly because of genetic and environmental factors, which are directly related to the production of the guarana plant (Henman, 1982; Escobar, 1985; Lunguinho, 2007).

The fruit is a capsule with septicidal dehiscence and a developed peduncle. When immature, it has a dark green colour, and when ripe, its colour ranges from yellow-orange to yellow-red to bright red. The seeds (one to four per fruit) are dark brown with a crustaceous texture, and they are partially enveloped by a chalky white aril, which anatomically represents a sarcotesta that seems to protect the embryo against moisture loss (Polo, 2006). The open mature fruit exposes the white aril (Fig. 1). The dark seed, in contrast with the red colour of the shell, resembles a human eye, which represents a striking feature for the identification of guarana (Schmidt, 1941; Souza et al., 1996; Embrapa Agropecuária Ocidental, 2001; Smith and Atroch, 2007). When dried or roasted, the seeds can be used to produce commercial products with high caffeine content (2.5 to 6%); the caffeine content of guarana seeds is 2 to 5 times higher than that of Arabica coffee seeds (Cabral, 1932; Lyra, 1953; Souza, 2010).

Guarana plant propagation is accomplished by using seeds or cuttings. The use of cuttings is advantageous when the goal is to maintain the traits of cultivars, such as tolerance to pests and

diseases and overall productivity. In addition, plants propagated by cuttings grow faster and thus come into production more quickly (Embrapa Agropecuária Ocidental, 2005; Nascimento Filho et al., 2009).

In the juvenile stage, the seedlings should be kept in the nursery for a period of seven to nine months, with shading and intermittent nebulisation. When taken to the field, they must be kept under partial shading, which is gradually withdrawn. At the time of planting, phosphate fertilisation is performed. Nitrogen, potassium, magnesium and micronutrients fertilisation is distributed over the year. Pruning for maintenance after the production is important to decrease the incidence of pests and diseases in the plantation, while the pruning for fruiting induces the release of new branches, which will be the productive branches of the next harvest. Because of the wide spacing used in planting, the soil can be used for short cycle crops during the first three years of guarana plant growth (Embrapa Agropecuária Ocidental, 2005).

3. Production and marketing

The Sateré-Mawé Indians initiated the process of domesticating guarana in the region of the Maués River and its tributaries. In controlled plantations in open areas, the guarana plant loses the liana morphology and develops as a non-deciduous shrub of 2 to 3 m. Domestication occurred because the properties of the drink made with guarana caught the interest of settlers in the region, who went on to explore commercial production of the plant (Monteiro, 1965).

Until the 1980s, the town of Maués, in Amazonas, was the undisputed leader in the production of guarana, with 90% of the small producers production in Brazil. However, the expansion of the commercial use of the seed, mainly due to the use of the guarana extract in soft drinks and by the pharmaceutical and beauty industries, prompted thousands of farmers in the south of Bahia, in the cocoa growing area, to plant guarana (Table 1). Guarana expanded rapidly in this region because of the edaphic and climatic conditions, which are similar to those of the plant's natural habitat (high temperature, average annual precipitation between 1500 and 2000 mm and well-drained soil), but particularly because of the absence of pests (thrips) and diseases (anthracnose) and increased soil fertility. Guarana cultivation also expanded to the states of Acre, Pará and Mato Grosso (IBGE-Brazil, 2011).

The states of Amazonas and Bahia together contain 95% of the guarana growth area in Brazil, however, in 2011, the average yield in Bahia was approximately 2.5 times higher than in the state of Amazonas (Table 1). This superior productivity is attributable mainly to the plant health characteristics already mentioned and the number of weedings of invasive plants (2 to 4 weedings per year in Bahia and one weeding in Amazonas). Even with the development of cultivars resistant to major pests and diseases for the Amazon region, productivity remains low. The low productivity is also related to the low technical qualifications of the farmers, who are mostly small-scale producers (Embrapa Agropecuária Ocidental, 2005; Cunha, 2006).

Table 1
Guarana production by Brazilian States—2011.
Source: http://www.ibge.gov.br/home/estatistica/indicadores/agropecuaria, visited in February 2012.

Brazilian state	Planted area (ha)	Harvested area (ha)	Production (ton)	Yield (kg/ha)	Relative production (%)
Acre	27	27	3	111	0.1
Amazonas	6,743	3,349	599	179	16.0
Pará	41	41	21	512	0.6
Bahia	7,054	6,749	2907	431	77.4
Mato-Grosso	600	517	224	433	6.0
Total	**14,465**	**10,683**	**3754**	**351**	**100**

Table 2
Overall Brazilian guarana production—2001 to 2011.
Source: http://www.ibge.gov.br/home/estatistica/indicadores/agropecuaria, visited in February 2012.

Year	Planted area (ha)	Harvested area (ha)	Production (t)	Yield (kg/ha)
2001	11,703	11,668	3935	337
2002	14,332	12,187	4032	331
2003	14,395	12,529	3744	299
2004	14,108	13,015	3844	295
2005	15,540	12,881	2995	233
2006	13,356	13,039	2989	229
2007	13,210	13,144	3388	258
2008	15,321	14,904	3056	205
2009	15,278	15,271	4604	301
2010	13,980	10,552	3739	354
2011	14,465	10,683	3754	351

The difference in productivity between these states is partly compensated by the market price of seed, which is higher in Amazonas, R$ 7.45 kg^{-1} compared to R$ 5.90 kg^{-1} in Bahia (IBGE-Brazil, 2011). The higher price in Amazonas is a result of the producers from Amazonas negotiating directly with the guarana processing industries located exclusively within the state, whereas the product from Bahia has its cost increased by the need to transport it to the industries in Amazonas. After processing, part of the guarana extract remains at these companies for the production of beverages, and part is intended for internal and external markets (Sagri-Brazil, 2010).

Despite the increased interest in guarana for its medicinal and stimulant property, in the last decade, there has been no major growth in the planted area (Table 2). An increase in production can be achieved initially by increasing productivity (Tables 1 and 2).

Small farmers are responsible for meeting the demand for the product in powder or stick (bastão in Portuguese) form in the regional and national markets. There is low international demand for organic guarana, and there are still no certified producers for organic production. The marketing of the product in "ramas" (a Brazilian Amazon term for roasted whole seeds) is dedicated to the processing industries located in the state of Amazonas and supplied by guarana grown across the country (Cunha, 2006; Atroch, 2009).

Guarana seed processing involves roasting and grinding, and these processes vary between large and small producers. However, the maturation of harvested seeds is uniform because the harvest is performed manually due to the non-uniform ripening of the fruit. The entire raceme can be harvested when most of the fruits are mature (open and intense red colour), or the ripe berries can be individually harvested (Schmidt, 1941; Embrapa Agropecuária Ocidental, 2005; CEPLAC-Brazil, 2012). This happens because there is no flowering pattern in guarana, and even though they are present in the same inflorescence, the flowering periods of male and female flowers appear to be unsynchronised, occurring from two to five days and from one to thirty days, respectively. In addition, more than one period of female flowering can occur (Henman, 1982; Embrapa Agropecuária Ocidental, 2001). As a consequence, fruits at different stages of maturation are found in the same inflorescence, causing the harvest to continue for up to three months and requiring expensive manual harvesting. Fruit production is annual, and the first harvest occurs after the third year of life of the plant, but beginning in the sixth year, the

production becomes more prolific (Henman, 1982; Embrapa Agropecuária Ocidental, 2001).

In manual processing, seeds are retrieved from the fruits after three days of fermentation, but when processing is performed mechanically by pulping machines, the seeds are collected immediately after harvesting. The seeds are then washed to remove the aril as much as possible (Fig. 1), and they are dried in iron or clay pots (2 m in diameter) for three to five hours while stirring to reduce the chances of burning the product. Drying facilitates removing the seed coat. On an industrial scale, the removal of water from the seeds is performed with dryers, and at the end of the process, crude guarana is obtained. At this stage, the seeds can be crushed or macerated until powder is obtained. At industrial scale grinders are used to obtain a fine powder. The powder can be used to manufacture extract, syrup or sticks, the latter being the form the Sateré-Maué Indians use to store and preserve guarana (Schmidt, 1941; Walker et al., 2000).

For the preparation of the sticks, the Sateré-Maué Indians grind the seeds in a wooden pestle and add water to form a soft paste, which is shaped into a cylinder. The sticks are dried in the sun and can last up to a year when smoked, preserving the characteristics of the product better than powder. The drink traditionally prepared with guarana is made from the powder or the grated stick (traditionally with the tongue of a fish from the Amazon region, the pirarucu—*Arapaima gigas*). The powder is mixed in water and may be sweetened (Schmidt, 1941; Henman, 1982; Walker et al., 2000).

There are records of guarana consumption in Europe and the United States in the 18th and 19th centuries (Smith and Atroch, 2007). In the 18th century guarana was popular in a few Brazilian states, being consumed as a beverage prepared with the powder obtained from the sticks made with roasted seeds. Because its stimulant property, guarana was consumed by Brazilians to endure long voyages across the country. Nowadays, formulations containing guarana have been sold as energetics and stimulants, and they have become components of phytopharmacons (Cunha, 2006; Atroch, 2009). However, in Brazil, guarana became thoroughly popular at the beginning of the 20th century, when it went from being a homemade elixir to being added to carbonated soft drinks. Currently, the word “guaraná” is a synonym for several brands of carbonated soft drinks.

Approximately 70% of the national production of guarana seeds is absorbed by the beverage industries of Amazonas, which includes a vast range of drinks. Of this portion, an average of 45% goes to the production of the carbonated “guaraná”. The remaining 25% goes to the production of guarana extract and guarana syrup, which are used mainly to supplement the caffeine content of beverages. Guarana powder is also sold, but in smaller amounts (10% of the total produced) for consumption in homemade energy drinks or for direct ingestion as a tonic packed in gelatinous capsules or packets. The remaining 20% is used for the production of pharmaceuticals and cosmetics (Anvisa-Brazil, 1997; Kuri, 2008).

4. Chemical composition of the seed

The therapeutic properties of guarana as a stimulant, tonic and aphrodisiac have become known worldwide since the first reports of its indigenous use, which led to the inclusion of guarana in the group of medicinal plants and its increased use and commercialisation. The seeds are the commercially useful part of the plant because of their content of purinic alkaloid caffeine (1,3,7-trimethylxanthine), to which the stimulant property of guarana is attributed (Henman, 1982, 1986; Kofink et al., 2007).

Caffeine was first isolated by Friedlieb Ferdinand Runge in 1820 (Mazzafera et al., 2009). Shortly thereafter, in 1826, Theodor Martius conducted the first chemical study of guarana. The pharmacologist had received the material for analysis from his brother, the botanist Carl Martius, who had collected the seeds during his visit to Brazil. Theodor Martius described the guarana mass as consisting of green fatty oil, resin, cellulose gum, starch and a crystalline material that was white and bitter, which he called guaranine (Corrêa, 1926). Years later, guaranine was described as identical to caffeine, but its association with tannins led Theodor Martius to believe it was a new substance. Subsequently, a series of analyses has been conducted on the caffeine content in guarana samples, although the values differed because of the various methods employed, the genetic variability of plant material analysed and even the type of solvent used in the extraction (Corrêa, 1926; Majhenic et al., 2007).

Table 3 lists the various studies that have analysed the caffeine content in different tissues of the guarana plant in materials collected from different growth locations. Such variations are certainly related to genetic variability as well as to the edaphic and climatic conditions of cultivation. In any case, high caffeine content has been an important feature in the process of selecting varieties for improvement and in the introduction of clones for commercial cultivation (Angelucci et al., 1978; McCusker et al., 2003; Embrapa Agropecuária Ocidental, 2005; Heckman et al., 2010).

Despite the wide variation in the caffeine content of guarana seeds, the values found, from 2.5 up to 6%, are still high when compared with any other species, including coffee (*Coffea arabica* L.), tea (*Camellia sinensis* (L.) Kuntze.) and mate (*Ilex paraguariensis* A. St.-Hil.) (Heckman et al., 2010).

In addition to caffeine, other purinic alkaloids were found in smaller proportions (below 0.3%) in guarana plants, including theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) (Wisniewski, 1955; Oliveira, 2010).

Within the genus *Paullinia*, aside from *Paullinia cupana*, only *Paullinia yoco* R.E. Schult. & Killip contains caffeine and theobromine (*Paullinia pachycarpa* Benth. contains theobromine in the leaves and stem). However, unlike guarana (*Paullinia cupana*), the highest purinic alkaloid content in *Paullinia yoco* was found in the stem cortex, which could be related to the use of this part of the plant for the preparation of a drink by the indigenous peoples of Colombia and Peru (Henman, 1982; Werckerle et al., 2003).

The differential distribution of caffeine in the organs and tissues of the plant represents a directed strategy of chemical defence (phytochemical architecture). For example, the high caffeine content in young tissues and the build-up of caffeine in the edge of the leaf help to guard tissues that are preferentially attacked by herbivores (Werckerle et al., 2003).

In the guarana fruit, purine alkaloid allocation is also tissue and organ specific. The high caffeine content in the seed, in contrast with the total lack of caffeine, theobromine and theophylline in the aril, is related to the dispersal of seeds by birds (Baumann et al., 1995). To take advantage of the sugars of the aril, birds ingest the guarana seeds, but without crushing or breaking them, such that the amount of caffeine released is minimal and intoxication is avoided. When expelled, the intact seed is dispersed (Baumann et al., 1995).

In 2008, a Brazilian initiative was put forward to obtain genomic information on the guarana fruit to expand the body of knowledge about this plant (Ângelo et al., 2008). In this project, the annotations of 15,387 expressed sequence tags (ESTs) from guarana seeds in three stages of maturation were described and discussed. Approximately 4% of the ESTs were related to secondary metabolism, including flavonoid metabolic pathways (catechin and anthocyanin synthesis) and caffeine, with 94 notes referring

Table 3
Caffeine content in seeds and other guarana tissues/organs.

Tissue	Caffeine (%)	Place	Reference
Leaves	1.6	Maués-AM (Brazil)	Pires (1949)
Stem (wood)	0.2	Maués-AM (Brazil)	Pires (1949)
Stem (bark)	1.8	Maués-AM (Brazil)	Pires (1949)
Fruit pericarp	0.0	Costa Rica	Baumann et al. (1995)
Fruit pericarp	0.5	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)
Septa	0.7	Costa Rica	Baumann et al. (1995)
Sarcotesta (arilo)	0.0	Costa Rica	Baumann et al. (1995)
Testa	1.1	Pariquera-Açu-SP (Brazil)	Spoladore et al. (1987)
Testa	1.6	Costa Rica	Baumann et al. (1995)
Testa	2.0	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)
Testa	2.9	Maués-AM (Brazil)	Maravalhas (1965)
Seed	2.3	Pariquera-Açu-SP (Brazil)	Spoladore et al. (1987)
Seed	2.3	Maués-AM (Brazil)	Pires (1949)
Seed	3.0	Maués-AM (Brazil)	Meurer-Grimes et al. (1998)
Seed	3.1	Maués-AM (Brazil)	Maravalhas (1965)
Seed	3.7	Maués-AM (Brazil)	Meurer-Grimes et al. (1998)
Seed	4.3	Costa Rica	Baumann et al. (1995)
Seed	6.1	Alta Floresta-MT (Brazil)	Antonelli-Ushirobira et al. (2007)
Seed	7.8	Maués-AM (Brazil)	Antonelli-Ushirobira et al. (2007)
Cotyledons	3.3[1]	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)
Cotyledons	3.7[2]	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)
Cotyledons	4.8[3]	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)
Cotyledons	5.3[4]	Pres. Figueiredo-AM (Brazil)	Oliveira (2010)

Mean value for cultivars ([1]) BRS-87; ([2]) BRS-619; ([3]) BRS-300; ([4]) BRS-608. Cotyledon refers to cotyledon plus embryo.

to genes encoding caffeine synthase, which is an enzyme that acts at the last step of the caffeine biosynthesis pathway (Ashihara et al., 2008).

Based on the EST annotations referring to caffeine synthase, Figueiredo et al. (2011) recently identified three complete sequences of caffeine synthase through *in silico* studies, with subsequent confirmation by isolation and sequencing of the gene. Additionally, proteomics studies during fruit maturation showed little variation in protein levels, except when the seeds are ripe and a characteristic proteomic profile was observed (Souza, 2010).

Despite the availability of gene sequences related to the biosynthesis of caffeine in guarana, until now, no effort has been made to describe the caffeine biosynthetic pathway in this plant (Ashihara and Suzuki, 2004; Ashihara et al., 2008). Nevertheless, the pathway likely follows the main route of biosynthesis identified in coffee and tea (*Camellia sinensis*), which, with the exception of certain variations, is highly conserved (Ashihara and Suzuki, 2004; Mazzafera, 2004; Ashihara et al., 2008).

Studies of the chemical composition of guarana have not been limited to methylxanthines. The first and most thorough analysis of the species was performed by Peckolt (1868). Other studies complemented the composition data, but information is still incomplete since some substances were not properly identified and chemically characterized so far (Angelucci et al., 1978; Okada et al., 1977; Tocchini, 1977). Table 4 shows the composition of guaraná according Angelucci et al. (1978).

The tannin in present in guaraná in considerable amounts and is primarily in the form of condensed tannins or proanthocyanidins (flavan-3-ol polymers), with a higher prevalence of catechins and epicatechins (Marx, 1990; Ushirobira et al., 2004; Basile et al., 2005). Additionally, Antonelli-Ushirobira et al. (2007) have identified small variations in the monomers constituting this fruit's tannins.

Mattei et al. (1998) attributed the strong antioxidant activity of the guarana extract to the presence of flavonoids (primarily catechins) and saponins, although they have not analysed the composition of the extracts they used. Saponins were identified in guarana in small amounts (Peckolt, 1868).

Among the compounds found in guarana seeds, the methylxanthines and tannins represent the most scientifically interesting compounds, mainly because of their potential for applications in the pharmaceutical, food and cosmetics industries. However, other studies are also notable, such as those that have investigated the composition of guarana oil, in which a variety of methylbenzenes, cyclic monoterpenes, sesquiterpenes, oleic acid, paullinic acid and methoxyphenyl propene have been identified (Avato et al., 2003).

Table 4
Chemical composition of guarana seeds from Maués (Amazon state) and Pariquera-Açu (São Paulo State) according Angelucci et al. (1978). Data are presented as g $100\ g^{-1}$.

Substance	Maués	Pariquera-Açu
Starch	60.88	59.79
Tannin	9.6	8.45
Protein	8.56	7.6
Total soluble sugars	7.97	7.81
Reducing sugars	4.89	2.3
Caffeine	3.79	3.22
Fiber	3.15	2.42
Pentosan	0.21	0.57
Ash	1.46	2.13
Humidity	10.46	8.75

5. Production of guarana extracts

After the seeds are processed, depending on the treatment applied, the caffeine content can be concentrated; in guarana extract, the caffeine content can be double or triple that found in seeds, with levels described at approximately 9.8 to 11.0% (Meurer-Grimes et al., 1998). Such information is the result of analyses using more than 40 samples of guarana and their by-products, such as seeds, powder, syrup, sticks, gelatine capsules and carbonated beverages. These authors reported the varying levels of caffeine, theobromine and theophylline found in guarana products. In carbonated drinks, the caffeine content varies from 8 to 56 mg $100\ ml^{-1}$.

The traditional way to produce guarana extract in Brazil uses hot water or hydro-alcoholic solutions as solvents. When alcohol is used the solution is concentrate by evaporation and then diluted

or not with water for further use. One of the uses of concentrate extracts is to produce guarana-based energetic tonics, known in Brazil as "rebites", a popular denomination given for beverages ingested to keep the consumer awaken. "Rebites" are produced by Amazon people living on the trade of medicinal herbs and extracts sold in popular markets or by small local companies, where guarana seeds are extracted without a well-defined control and usually not following legal law requirements. Other plant extracts may also be included in the "rebites".

Detailed information on a process to produce extracts from guarana seeds is given by a patent from Coca-Cola Company (Turano, 2006). Besides the industrial plant, this patent also describes temperatures, pressure, concentration procedure, etc, for each extraction step. These can be summarized as follows: the seeds are depulped and then dried under controlled heat until they reach 8–10% humidity. The industrial process starts by grinding the seeds at most to 6 mm in diameter followed by extraction with 40–60% ethanol, in a ratio of 1:4 (weight/volume), at 50–70 °C for 1–8 h, when most of the alcohol is evaporated. The seeds are separated and then washed to remove remaining active substances. The extract and washing solutions are combined and then concentrated under reduced pressure (500–711 mm Hg column) at 50–70 °C. In a precipitation tank the concentrated solution receives neutral ethanol to adjust to a minimum of 40% and containing a minimum of 1.6% caffeine. After cooling at 2–5 °C for 24–72 h, when insoluble and undesirable components are eliminated by precipitation, the extract is filtered. The extract is analysed and adjustments are made according specifications required by law and by the client. Then this final extract is filtered in 5 μm filters.

However, most of the guarana-based energetic tonics have brown color, indicating oxidation. Guarana sticks also have the same color (see Section 3). Guarana seeds are rich in tannins (Marx, 1990; Basile et al., 2005; Antonelli-Ushirobira et al., 2007) and it is believed that this color is a result of hydrophobic interaction and a hydrogen bond formed between the non methylated nitrogen in the imidazole ring of caffeine and the hydroxyl group of tannins (Spencer et al., 1988; Edwards et al., 2005).

Attempts to overcome this problem are found in a patent by the Japanese company Mie Kariyou Corporation (Watanabe et al., 2000) and Ribeiro et al. (2012). In both cases guarana seeds were treated with enzymes able to degrade polysaccharides in order to obtain non-alcoholic extracts low in tannins and rich in caffeine. In the first case the extract obtained had 5% of caffeine and 13.4% of tannin on the basis of dried guarana extract. The best result obtained by Ribeiro et al. (2012) was a combination of cellulase, hemicellulose, alpha-amylase, pectinase and glucoamylase. Additionally, they tested a post-processing step where among different adsorption systems to remove tannins, magnesium oxide was the most efficient. The final product had a ratio between caffeine and tannin of 7.3, 10 times higher than the ratio found in the initial extract, obtained with water (1:5, weight/volume).

6. Local and traditional uses of guarana

Part of the guarana produced in Brazil is internally consumed by the Amazon population. The powder, usually obtained from the ground stick, is mixed in water and sweetened with sugar or honey (Schmidt, 1941; Henman, 1982; Walker et al., 2000).

Guarana has long been admired for its energetic property. The Amazon Indians from Maués used to drink guarana for hunting over long periods of time, what surely is related with the excitement provided by caffeine (Smith and Atroch, 2007). When guarana reached the large urban centres, the popular use of guarana as a medicinal plant was also based on its physical and mental stimulant properties and promotion of weight loss (Sousa et al., 2011). But once adopted as a medicinal plant by the urban Brazilian population it started to be indicated for several physiological disorders and diseases, such as a tonic for the kidneys, muscles, heart, to keep youth, for high cholesterol, stomach and intestine functioning, control of appetite, sexual impotency, for the treatment of migraine and headache, neuralgia, leucorrhoea, arteriosclerosis and menstrual cramps, etc, as it can be easily verified in seller internet websites from Brazil and several other countries, including U.S and European countries. However, much of these effects may be only a strategy to increase the sales and not necessarily can be classified as a long known traditional use. Guarana has also been indicated as a diuretic, calming aphrodisiac and tonic (Henman, 1982; Carlson and Thompson, 1998; Smith and Atroch, 2007). Despite these alleged effects, the stimulant property is still the "label" identifying the main physiological activity of guarana not only in Brazil but also in other countries.

7. Pharmacological activity

It is interesting to mention that in 1982 Henman suggested what he called as "The Guaraná Project: a modest proposal". The aim was to improve guarana as an economic crop in Amazon. Among three aspects listed as important, the second was an investigation of the pharmacology of guarana use and the claims made for it as a medicinal plant. He emphasized the need for detailed chemical studies already realizing that other substances present in guarana seeds might be responsible for physiological effects caused by this plant. The other two aspects were to get knowledge on the genetic diversity of *Paullinia* and to unite all possible information on guarana as a crop and medicinal plant to bring a social benefit for the Amazonian population. Since then a number of studies were carried out with guarana, but most still working on its stimulant property and with the powder or water/alcoholic extracts. Little was made attempting to isolate and test new guarana substances. Table 5 summarizes studies on the pharmacological activities of guarana. Below we briefly highlight some of these studies.

With a slightly bitter, astringent and acidic taste, guarana powder dissolved in water is considered by the indigenous people to be an elixir that promotes long life. Based on the traditional use, Cadet de Gassicourt (1817) in Paris first described guarana as a medicine, indicating it to be a stomach tonic, aphrodisiac and antipyretic for specific use in the treatment of dysentery and diarrhoea. Because of the stimulant property of caffeine on the central nervous system, guarana has been widely used in the pharmaceutical market. It has also been included in the pharmacopoeias of Brazil, Mexico, the United States and several European countries (Nazaré and Figueiredo, 1982; Anvisa-Brazil, 2010).

In addition to the stimulating action of caffeine on the central nervous system, other effects have been attributed to guarana, such as improved alertness, reaction time, speed of information processing, memory, mood and performance in physical exercises as well as thermogenic effects associated with weight loss and gastric acid secretion (Sigma-Aldrich, 2010). Guarana has been shown to be a promising option for the treatment of mental and physical fatigue related to cancer because its use lacks significant side effects and it is low in cost compared with traditional drug therapy (Campos et al., 2011a).

Guarana has also been attributed with inducing a weak diuretic effect that might be related to the presence of theobromine, which has a known diuretic effect. Theophylline also has a stimulant property similar to caffeine, but to a lesser extent, and is characterised as a bronchodilator (Alves and Bragagnolo, 2002; Heckman et al., 2010). However, both compounds are found in

Table 5
Pharmacological activities of guarana. ? indicates unavailable information.

Pharmacological activity	Type of extract	Other components administrated	*in vivo/in vitro*	Model	Administration (*in vivo*)	Control used	Dose range tested	Active concentration	Outcome	Observation	Reference
Antiaggregatory activity	Aqueous extract and fractions separated by TLC	?*	*in vivo*	Decreased platelet aggregation and platelet thromboxane formation from [14C]-arachidonic acid in rabbit	Intravenous injection (1 ml) or nasogastric tube (20 ml)	Control: no treatment	100 mg/ml	100 mg/ml	Decreased platelet aggregation (1) 37,27% and (2) 31% of control values. Platelet thromboxane formation from [14C]-arachidonic acid (1) 78,7% and (2) 50% of control values	Only one concentration tested	Bydlowski et al. (1991)
Anti-fatigue effect	Suspension	?	*in vivo*	Assessment of anti-fatigue effect: forced swimming test	Oral—The animals ingested as sole source of liquid	Water/Tween-80 0.1% Caffeine 0.1 mg/ml Ginseng (*Panax ginseng*) 5.0 mg/ml	0.3 and 3.0 mg/ml	0.3 mg/ml	It was observed that the animals treated with two doses of guarana presented greater swimming time in 15 out of the 16 measured, as compared to the control group. However, only in two of the measurements the differences were statistically significant (days 100 and 200). On the other hand, the animals treated either with caffeine or with ginseng did not show this effect		Espinola et al. (1997)
Tonic action	Water extract	?	*in vivo*	Increased the blood glucose level and decreased the liver glycogen contents on exercise in normal and epinephrine-induced glycogenolytic mice	Oral	Control: no treatment	20, 100 and 500 mg/kg	100 and 500 mg/kg i	100 and 500 mg/kg increase the blood glucose level. 500 mg/kg decreased glycogen contents. Not affect the blood glucose in epinephrine-induced glycogenolytic and exercise mice		Miura et al. (1998)
Antioxidant activity	50% aqueous alcoholic extract	?	*in vitro*	Inhibition of spontaneous lipoper-oxidation of homogenates from the brains of rats	?	Water/Tween-80 0.1%. Caffeine 0.1 mg/ml. Ginseng (*Panax ginseng*) 5.0 mg/ml	0.8, 1.6, 3.3 and 6.6 mg/ml of final concentration mid-reaction	1.2 mg/ml	An increasing inhibition of spontaneous lipoperoxidation can be observed which is proportional to the concentrations, inhibition of 50% of the process being calculated at 1.2 mg/ml.		Mattei et al. (1998)
Antioxidant activity	Ethanol extract	?	*in vitro*	Reduction the lipid peroxidation	?	?	0.5, 1.0, 2.0 μg/ml	2 μg/ml	The malonyldialdehyde test (MDA test) showed that the reduction of cellular damage was 65.2%		Basile et al. (2005)
Antioxidant activity	Distilled water, methanol, 35% acetone and 60% ethanol (room	?	*in vitro*	Inhibition of oxidation of an aqueous system of	?	?	?	?	In the linoleic emulsion system, oxidation of *b*-carotene was effectively inhibited by all extracts		Majhenic et al. (2007)

	temperature - TR and boiling temperature - TB)			b-carotene and linoleic acid					of guarana seed. The highest inhibitions of b-carotene oxidation were shown by methanol guarana seed extracts 87.8% (TR) and 85.9% (TB), respectively, while the lowest inhibition of *b*-carotene oxidation was shown by water guarana seed extract, 70.9% (TR) and 67.8% (TB), respectively. The temperature of the extraction did not have a significant effect on the inhibition of *b*-carotene oxidation.		
Antioxidant activity	Aqueous (AqE) and crude (EBPC) extracts and semi-purified (EPA and EPB) fractions (Patent No. PI 0006638-9, Brazil)	?	*in vitro*	Measurement of the antioxidant activity by reduction of the DPPH radical	?	Ascorbic acid (2 mM) relative antioxidant capacity (RAC)=1.00	2.0 to 20.0 μg/ml	RAC in relation to ascorbic acid AqE: 0.46 ± 0.01 EBPC: 0.69 ± 0.03 EPA: 0.75 ± 0.01 EPB: 0.36 ± 0.02	EPA fraction showed the highest content of total polyphenols, reflecting the antioxidant analysis, with a low IC50 and a higher RAC in relation to the other extracts		Yamaguti-Sasaki et al. (2007)
Antioxidant activity	Methanolic extract and pectic fraction	?	*in vivo*	Antioxidant activities determined by the hydroxyl radical-scavenging activity	?	Butyl hydroxyanisole and ascorbic acid	0.1, 1.0, 5.0 and 10 mg/ml	Methanolic extract: 10 mg/mlPectic fraction: 10 mg/ml	Methanolic extract exhibited a strong capacity for scavenging DPPH radicals (90.9%) and the polysaccharide showed a DPPH_-scavenging activity of 68.4%.		Dalonso and Petkowicz (2012a)
Weight loss and delayed gastric emptying	Powder in capsules	*Ilex paraguariensis* and *Turnera diffusa* var. *aphrodisiaca.*	*in vivo*	Delayed gastric emptying and weight loss over 10 days and 45 days and weight maintenance over 12 months	Oral	Placebo: capsules with lactose contents	Guarana: 95 mg, *Ilex. paraguariensis:* 112 mg *Turnera diffusa*: 35 mg	Guarana: 95 mg, *Ilex paraguariensis:* 112 mg and *T. diffusa*: 35 mg	53% increase of gastric emptying times (GET). 10 days: body weight reductions were 0.8 ± 0.05 kg 45 days: 5.1 ± 0.5 kg 12 months: weight maintenance of the group (73 kg at the beginning and 72.5 kg at the end).	Only one concentration tested	Andersen and Fogh (2001)
Weight loss	Powder in capsules	Ma Huang and Guarana as the main active ingredients	*in vivo*	Overweight humans the short-term safety and efficacy for weight loss of an herbal supplement containing Ma-Huang/Guarana	Oral—6 tablets/day, 8 weeks	Placebo: tablet containing carboxymethyl-cellulose, micronized silica and alfalfa	Guarana 40 mg Ma Huang 12 mg	Guarana 40 mg Ma Huang 12 mg	Active treatment produced significantly ($p < 0.006$) greater loss of weight (−4.0 ± 3.4 kg) and fat (2.1 ± 3.0% fat) over the 8-week treatment period than did placebo (−0.8 ± 2.4 kg and −0.2 ± 2.3% fat). Active treatment also produced greater reductions in hip circumference and serum triglyceride levels. Eight of the 35	Only one concentration tested	Boozer et al. (2001)

Table 5 (*continued*)

Pharmacological activity	Type of extract	Other components administrated	*in vivo/in vitro*	Model	Administration (*in vivo*)	Control used	Dose range tested	Active concentration	Outcome	Observation	Reference
									actively treated subjects (23%) and none of the 32 placebo-treated control subjects withdrew from the protocol because of potential treatment-related effects		
Weight loss	Powders in capsules	Green tea	*in vivo*	Increase in energy expenditure, substrate oxidation and blood pressure	Oral	Placebo: inert filler of cellulose	200 mg caffeine of guaraná and a variable dose of EGCG (90, 200, 300 or 400 mg) of green tea three times daily	200 mg caffeine/ 90 mg EGCG × 3	Energy expenditure increased by about 750 kJ. No effect observed for lipid oxidation. Systolic and diastolic blood pressure increased by about 7 and 5 mmHg, respectively, compared with placebo. The same results are shown in every doses		Bérubé-Parent et al. (2005)
Weight loss	Powder in capsules (Zotrim™)	*Ilex paraguayensis* and *Turnera diffusa* var. *aphrodisiaca*	*in vivo*	Decrease of self-reported weight, waist circumference and hip circumference	Oral	Placebo: capsules with lactose contents	Guarana: 95 mg, *Ilex paraguariensis:* 112 mg, *Turnera diffusa*: 35 mg. 2 tablets per day for the first week and 3 tablets for the rest of the study	Guarana: 95 mg, *Ilex paraguariensis:* 112 mg, *Turnera diffusa*: 35 mg. 2 tablets per day for the first week and 3 tablets for the rest of the study	Self-reported weight, waist circumference and hip circumference reduced significantly, while 22% of subjects experienced a clinically significant weight loss. The anthropometric changes were in line with other commercial diet and exercise programmes. Reported between-meal hunger, and consumption of snacks reduced across the six weeks. Reported satiety after meals increased and subjects claimed to be more in control of snacking, emotional eating and portion sizes	Only one concentration tested	Ruxton et al. (2007)
Ergogenic and "fat burning" effects	Aqueous extract (GE) and decaffeinated guarana extract (DG)	?	*in vivo*	Aspects of lipid metabolism in sedentary (C) and trained rats (T): body weight, food and water intake; muscle fat content, oleate incorporation, glycogen content, and carnitine palmitoyltransferase I (CPT I) activity and mRNA expression;	Oral	Sedentary and trained rats not supplementa-tion	0.130 (G1) and 0.325 (G2) mg/ kg	0.130 mg/kg	Muscle oleate incorporation was decreased in rats receiving decaffeinated guarana in relation to G1 and G2; as was CPT I mRNA expression in the gastrocnemius. Whole extract supplementation, but not DG induced reduced plasma lactate concentration in trained rats. G1 showed higher		Lima et al. (2005)

				along with plasma lactate concentration					muscle glycogen content compared with all other groups. The results show an effect of guarana on aspects of lipid metabolism, which is abolished by decaffeination	
Antidepressant-like activity	Power in capsules (Catuma)	Catuama (5% *Paullinia cupana*, 1% Zingiber officinalis, 5% Trichilia catigua and 5% *Ptychopetalum olacoides*)	*in vitro*	Inhibition the synaptosomal uptake of noradrenaline and principally of serotonin and dopamine, in rat brain	?	?	Catuama: 10-1000 μg/ml	EC50 serotonin release: 49 (21–114) μg/ml EC50 dopamine release 17 (8–38) μg/ml	Increased, concentration-dependently, the release of serotonin in synaptosomal fractions obtained from rats and the maximal response was 116 ± 20%. Increased dopamine release, with a maximal response of 407 ± 68%	Campos et al. (2004)
Antidepressant-like activity	Power in capsules (Catuma)	Catuama (5% *Paullinia cupana*, 1% Zingiber officinalis, 5% Trichilia catigua and 5% *Ptychopetalum olacoides*)	*in vivo*	Reduction of the immobility time in two models of depression in mice, the forced swimming and the tail suspension tests	Oral	Saline (10 ml/kg po)	Catuma: 150-200 mg/kg-subchronic 300 mg/kg-acute	200 mg/kg-subchronic and 300 mg/kg-acute	The acute treatment reduced the duration of immobility in the forced swimming test (34 ± 9%) and inhibition of immobility time (45 ± 9%) according to evaluation in the tail suspension test. The subchronic treatment decreased the duration of immobility in the forced swimming test (37 ± 2%)	Campos et al. (2004)
Antidepressant-like activity	?	?	*in vivo*	Reduced the duration of immobility in the forced swimming test in mice and increased locomotor activity	Oral	Distilled water (vehicle): 10 ml/kg Caffeine: caffeine 10, 20 and 30 mg/kg	25, 50 and 100 mg/kg.	Immobility time: 25 mg/kg. Locomotion frequency: 100 mg/kg	Both guarana (25 and 50 mg/kg) and caffeine (10 and 20 mg/kg) significantly decreased the duration of immobility when compared with controls in the forced swimming test in mice. A higher dose of guarana (100 mg/kg) failed to produce such an antidepressant-like or an antistressor activity	Campos et al. (2005)
Improved cognitive performance	Dried ethanolic extract	*Panax ginseng*	*in vivo*	Improved cognitive performance (secondary memory performance,speed of performing attentional tasks, improving performance on serial subtraction mental arithmetic tasks) and effects in subjective mood in human volunteers	Oral	Placebo: 0 mg guarana and 0 mg ginseng	Guaraná: 75 mg Guaraná and *Panax ginseng:* 75 mg/200 mg	Extract of guaraná: 75 mg Guaraná and *Panax ginseng:* 75 mg/200 mg	Guarana treatment improvements were seen across attention tasks (but with some evidence of reduced accuracy), and on a sentence verification task. While also increasing the speed of attention task performance, both ginseng and the ginseng/guarana	Kennedy et al. (2004)

Table 5 (*continued*)

Pharmacological activity	Type of extract	Other components administrated	*in vivo/in vitro*	Model	Administration (*in vivo*)	Control used	Dose range tested	Active concentration	Outcome	Observation	Reference
									combination also enhanced the speed of memory task performance, with little evidence of modulated accuracy. Guarana and the combination, and to a lesser extent ginseng, also led to significant improvements in serial subtraction task performance		
Improved cognitive performance	Crude lyophilized extract (EBPC) and the semi-purified constituents (EPA and EPB)	?	*in vivo*	Increase the cognitive performance in Morris water maze test (MWMT) in rats	Gavage	0.9% NaCl containing 0.2% Tween 80	EBPC (30.0 or 60.0 mg/kg). EPA (2.0 and 4.0 mg/kg) or EPB (2.0 and 4.0 mg/kg)	EBPC: 30.0 mg/kg EPA: 2.0 mg/kg	Escape latency to find the platform was significantly reduced ($p < 0.05$) by 30.0 mg EBPC/kg dose+control when compared to control+control. 2.0 mg EPA/kg dose, but not 4.0 mgEPA/kg dose associated to control, reduced ($p < 0.05$) the escape latency in the MWMT when compared to control+control. EBPC (30.0 mg/kg), EPA (2.0 and 4.0 mg/kg) or EPB (2.0 and 4.0 mg/kg) in MWMT did not alter number of crossings in the OFT		Otobone et al. (2005)
Improved cognitive performance and mood	Standardized guaraná extract (PC-102, Pharmaton, SA) in capsules	?	*in vivo*	Behavioural effects of acute mood and cognitive throughout in cognitive research computerized test battery and bond-lader mood scales	Oral	Placebo: 0 mg guarana	37.5 mg, 75 mg, 150 mg and 300 mg	Baseline scores: 150 mg. Secondary memory factor: 37.5 mg [$t(160)=2.13$, $p=0.03$]. Bond-Lader mood scales: alert, 300 mg [$t(160)=2.37$, $p=0.042$]; Content: 37.5 mg [$t(160)=3.12$, $p=0.002$]	Improved secondary memory performance and increased alert and content mood ratings. The two lower doses produced more positive cognitive effects than the higher doses		Haskell et al. (2007)
Memory acquisition	Suspension	?	*in vivo*	Passive avoidance in mice and rats. Active avoidance in mice. Lashlev lll maze test in rats	Oral—ingested as sole source of liquid	Water/Tween-80 0.1% Caffeine 0.1 mg/ml	0.3 and 3.0 mg/ml	0.3 and 3.0 mg/ml	Both doses of guarana to mice significantly blocked the known scopolamine amnesic effect. Chronic administration of 0.3 mg/ml of guarana also was able to protect old rats from the		Espinola et al. (1997)

									amnesic effects of scopolamine. As stated before tannins and saponins may be responsible for such activity		
Psychoactive properties	Effervescent tablets food supplement	Vitamin and mineral	*in vivo*	Increased speed and accuracy of performing the RVIP task throughout the post-dose assessment	Oral	Effervescent tablets vitamin/ mineral/ guarana 0 mg	222.2 mg	222.2 mg	Improved task performance, in comparison to placebo, in terms of both increased speed and accuracy of performing the rapid visual informationprocessing task throughout the post-dose assessment. The increase in mental fatigue associated with extended task performance was also attenuated by the supplement	Only one concentration tested	Kennedy et al. (2008)
Anxiolytic	Semi-purified	?	*in vivo*	Evaluation of defensive behavior related to specific subtypes of anxiety disorder by elevated T-maze test (ETM)	Gavage	Positive control: paroxetine (PAR) Negative control: only the vehicle (VEH; 0.9 % NaCl plus 2 % Tween 80)	4.0, 8.0, and 16.0 mg/kg	8.0 mg/kg	PEA was therefore found to have a selective panicolytic effect on rats in the ETM test after chronic treatment (24 d). The same PEA fraction of guaraná has produced an antidepressant-like effect in the forced swimming test		Roncon et al. (2011a)
Antibacterial activities	Ethanol extract	?	*in vitro*	Antibacterial against Gram-positive bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, and Gram-negative bacteria: *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi*, *Enterobacter cloacae*, *Bacillus subtilis*	?	?	Between 16 and 128 μg/ml	from 16 μg/ml	Minimum Inhibitory Concentrations (MIC) values. *Pseudomonas aeruginos*a: 16 g/ml, *Proteus vulgaris*, *Proteus mirabilis* and *Escherichia coli*: 32 g/ml. *Salmonella typhi*, *Enterobacter cloacae* and *Staphylococcus aureusan*: 64 g/ml. *Staphylococcus epidermidiswas*: 128 g/ml. *Bacillus subtilis* and *Streptococcus faecalis* were not inhibited		Basile et al. (2005)
Antimicrobial	Distilled water, methanol, 35% acetone and 60% ethanol (room temperature—TR and boiling temperature—TB)	?	*in vitro*	Fungi: *Aspergillus niger*, *Trichoderma viride* and *Penicillium cyclopium*. Gram negative bacteria: *Escherichia coli* and *Pseudomonas*	?	Alcoholic guarana seed extract (20 g/ 100 ml 96% ethanol)	?	?	Activity against the growth of food poisoning, spoilage bacteria, such as *Escherichia coli*, *Bacillus cereus*, *Pseudomonas Fluorescens* and spoilage		Majhenic et al. (2007)

Table 5 (*continued*)

Pharmacological activity	Type of extract	Other components administrated	*in vivo/in vitro*	Model	Administration (*in vivo*)	Control used	Dose range tested	Active concentration	Outcome	Observation	Reference
				fluorescens. Gram positive bacteria: *Bacillus cereus*					fungi such as *Aspergillus niger*, *Trichoderma viride* and *Penicillium cyclopium*. The alcoholic guarana seed extracts displayed stronger antimicrobial activity against all tested microorganisms than did water extracts		
Antibacterial potential	Aqueous (AqE) and crude (EBPC) extracts and semi-purified (EPA and EPB) fractions (Patent No. PI 0006638-9, Brazil)	?	*in vitro*	Determination of the minimum inhibitory concentration (MIC) by the plate-dilution method using a sample of *Streptococcus mutans*	?	Chlorhexidine gluconate (1.2 μg/ml) Adherence inhibition (%): 82.88 ± 4.28	Extracts (mg/ml) with 750 μg/ml of tannin AqE: 4.64 EBPC 2.41 EPA: 2.50 EPB: 4.39	Adherence inhibitions of *S. mutans* AqE: 62.18%, EBPC 79.69% EPA: 52.69% EPB: 69.95%	The fractions did not affect the growth of *Streptococcus mutans*, as evaluated through determination of the minimum inhibitory concentration, with a MIC > 5000 μg/ml, the extracts affected the adherent action of *Streptococcus mutans* rather than its growth. All the samples were efficient in reducing the production of acids, with an effect comparable to the control		Yamaguti-Sasaki et al. (2007)
Protective effect against DNA damage	Aqueous	?	*in vivo*	Anti-genotoxic /cytotoxic properties of guarana in hepatocytes of mice injected with *N*-nitrosodiethylaie (DEN)	Gavage once a day	Water	2.0 mg/g BW	2.0 mg/g BW	52.54% reduction in comet image length than the DEN-only treated group when they are compared to the non-treated group	Only one concentration tested.	Fukumasu et al. (2006a)
Protection against gastric lesions	Dried extract	?	*in vivo*	Inhibition of acute gastric lesions induced by ethanol and indomethacin in rats	Oral	Tap water: 10 ml/kg. Caffeine: 20 and 30 mg/kg.	50 and 100 mg/kg	lesions induced by ethanol: 50 and 100 mg/kg lesions induced by indomethacin: 100 mg/kg	Significantly suppressed the gastric mucosal haemorrhagic erosions induced by ethanol. Against indomethacin-induced gastric mucosal damage, guarana significantly reduced the gastric lesions only at the dose of 100 mg/kg	The effect of guarana was not dose-related in this model	Campos et al. (2003)
Chemopreventive effects	Powder	?	*in vivo*	Chemopreventie in mice hepatocarcinoges injected with *N*-nitrosodiethylaie (DEN)	Oral: powder mixed with added to commercial food	Only commercial food	0.1, 1.0 or 2.0 mg/g BW	2.0 mg/g BW	50% statistically decrease ($p < 0.0325$) in the lesion incidence in comparison to control animals and a significant reduction in multiplicity ($p < 0.05$). The preneoplastic lesions number and proliferating cell nuclear		Fukumasu et al. (2006b)

									antigen expression were reduced		
Anticancer	Aqueous	?	*in vivo*	Reduced cell proliferation and apoptosis in a melanoma B16/F10 metastasis in mice	Gavage	non guaraná-treated	2.0 mg/g BW	2.0 mg/g BW	68.6% reduction in tumor burden area compared to control animals. 57.9% reduction in tumor proliferation index. and a 4.85-fold increase in apoptotic index	Only one concentration tested	Fukumasu et al. (2008)
Stimulant (cancer-related fatigue)	Powder in capsules	?	*in vivo*	Effectiveness on fatigue, sleep quality, anxiety, depression symptoms, and menopause in a group of breast cancer chemotherapy patients	Oral	Placebo capsules: cellulose	50 mg (twice daily)	50 mg (twice daily)	Guarana significantly improved the functional assessment of chronic illness therapy-fatigue (FACIT-F), functional assessment of chronic illness therapy-endocrine symptoms (FACT-ES), and brief fatigue inventoryglobal (BFI) scores compared to placebo on days 21 and 49 ($p < 0.01$). The Chalder Scale improved significantly on day 21 ($p < 0.01$) but not on day 49 (p ¼ 0.27)		Campos et al. (2011b)
Antiproliferative effect in Ehrlich Ascites Carcinoma (EAC)	Ethanol extract	?	*in vivo*	Decreased the Ehrlich Ascites Carcinoma (EAC) volume, cell number and hemorrhage treatment in bearing mice	gavage	Water	100, 1000 and 2000 mg/kg	2000 mg/kg	Reduced by 45% the mean volume of the ascites fluid (control, 8.65 ± 2.43 ml; 2000 mg/kg, 4.7 ± 3.13 ml; $p=0.0120$). Total EAC cell number decreased 54% (control $= 146.98 \times 107 \pm 36.86 \times 107$ cells; 2000 mg/kg $= 66.99 \times 107 \pm 40.30 \times 107$ cells; $p=0.0004$)		Fukumasu et al. (2011)
Effects in metabolic morbidities	Aqueous	?	*in vivo (epidemiological study)*	Associations of metabolic disorders and anthropometric and biochemical biomarkers of lipid, glucose and oxidative metabolism and the habitual ingestion of guaraná by an elderly population residing in the Amazon Riverine region	Oral	Who never drank guaraná	Variable (guarana drink ingestion two or more times a week)		The prevalence of hypertension, obesity and metabolic syndrome in the drank guarana (GI) group was lower than the prevalence found in the never drank guarana (NG) group. Lower waist circumference, on average, than the circumference found in the NG group, whereas the females in the GI group had lower cholesterol (total and LDL -c)		Krewer et al., 2011a
		?	*in vitro*		?	?					

Table 5 (*continued*)

Pharmacological activity	Type of extract	Other components administrated	*in vivo/in vitro*	Model	Administration (*in vivo*)	Control used	Dose range tested	Active concentration	Outcome	Observation	Reference
Cytoprotective effects	Dimethylsulfoxid extract			Protect human dopaminergic neuroblastoma SH-SY5Y cell line against rotenone-induced cytotoxicity			0.312 and 0.625 mg/ml	Increased the cell viability of SH-SY5Y cells treated with rotenone, in a dose-dependent manner. Chromatin condensation and nuclear fragmentation were significantly reduced by addition of any of both concentrations of the extract			Oliveira et al. (2011)
Aphrodisiac effect	Hydroalcohol (1:1, v/v)	?	*in vivo*	Relaxation of isolated rabbit corpus cavernosum	Bolus injections	Catuama composed by: 5% *Paullinia cupana*, 1% Zingiber *officinalis*, 5% *Trichilia catigua* and 5% *Ptychopetalum olacoides* and the hydroalcohol extracts of *Trichilia catigua*, *Zingiber officinalis* and *Ptychopetalum olacoides*	0.5–5 mg	1.5 mg	The *Paullinia cupana* extract induced maximal relaxation at a lower dose compared with other extracts. Duplicate incubations of the homogenate with the extract of *Paullinia cupana* (1 mg/ml) increased the cAMP levels by approximately 200%, whereas higher doses (10 and 100 mg/ml) caused smaller increases in the nucleotide levels (150% and 89%, respectively)		Antunes et al. (2001)

much lower amounts than caffeine in guarana and other compounds may be involved in the reported diuretic effect.

In recent years, several studies in the field of pharmacology have been focused on confirming the effects attributed to this plant and revealing the mechanism of action of its components, especially the alkaloids and tannins (Henman, 1986; Bempong and Houghton, 1992; Espinola et al., 1997; Mattei et al., 1998; Basile et al., 2005; Heard et al., 2006). Although many effects have been proven, few studies have managed to discover the active principle responsible. However, most studies attributed bioactive effects to more than one substance. For example, the stimulant property on the central nervous system is mainly attributed to guarana's alkaloids because their mechanism of action is known, although catechins may also be involved; these are present in high concentrations in guarana cotyledons (Henman, 1982; Mattei et al., 1998; Heard et al., 2006; Dalonso and Petkowicz, 2012b). Regarding catechins studies with guarana showed that they act as antioxidants by inhibiting lipid peroxidation, although antiviral, bactericidal and molluscicidal activities were also tested (Mattei et al., 1998; Santos and Mello, 2007; Yamaguti-Sasaki et al., 2007; Sousa et al., 2011). In addition to the psychoactive effects, the use of guarana for metabolic disorders has been widely studied because it possesses functional properties similar to green tea, which is also rich in catechins. Studies have shown that guarana positively affects lipid metabolism, increases basal energy and weight loss and may be useful for obesity treatments (Boozer et al., 2001; Lima et al., 2005; Opala et al., 2006; Krewer et al., 2011b).

An interesting result in terms of a new physiological effect was obtained with purified guarana extract (containing caffeine and tannins), which administered orally to rats showed a panicolytic effect; thus, the extract is indicated for certain formulations for mood disorders, such as panic disorder (Roncon et al., 2011b). The positive effects of guarana extract on attention, memory and mood performance were also demonstrated in humans by Kennedy et al. (2004), using simple formulations and in combination with *Panax ginseng*. In the extracts with low caffeine content, there were no positive results; therefore, beneficial effects were attributed to the alkaloid. However, in a study by Haskell et al. (2007), cognitive performance was increased by using extracts with lower doses of caffeine, indicating that other guarana components may be involved; thus, this is a clear indication that guarana has other important substances and additional research is required, including comparisons with decaffeinated guarana, to fully understand its action.

A mixture of dried herbs containing *Ilex paraguariensis*, *Turnera diffusa* Willd. ex Schult. and guarana delayed gastric emptying, promoting increased satiety, which resulted in weight loss (Andersen and Fogh, 2001). However, this study did not consider possible physiological effects of the other two plants, as for example, the healing and protective gastric protection of *Turnera diffusa* (Taha et al., 2012) or even the fact that *Ilex paraguariensis* has also caffeine in the leaves (Saldaña et al., 1999). Other studies mixing guarana and other plants were published but without appropriate controls although providing evidence of a complementary effect in weight loss programs (Bérubé-Parent et al., 2005).

Regarding the chronic intake of guarana, Krewer et al. (2011b) assessed the association of anthropometric and metabolic disorders and the habitual intake of guarana by seniors. The authors observed a lower incidence of hypertension, obesity and metabolic syndrome in these seniors compared with those who did not take guarana.

Certain protective effects have also been demonstrated for guarana. The protective effect of guarana extract against acute ethanol-induced gastric lesions was demonstrated in rats (Campos et al., 2003). An antiproliferative effect in the treatment of Ehrlich ascites carcinoma (Fukumasu et al., 2011) and hepatocarcinogenesis in animals (Fukumasu et al., 2006b) was also observed. Additionally, aqueous guarana extract is able to inhibit platelet aggregation, which might be attributable to the procyanidins and catechins in the extract (Bydlowski et al., 1991; Subbiah, 2005).

Mattei et al. (1998) found that guarana protects against the physiological and psychological effects of stress. Because of a synergistic relationship among its components, guarana can provide benefits over time for overall health, especially for cognitive performance. Therefore, it is possible that the protective effects and benefits of guarana for human health will increase with chronic dosing (Krewer et al., 2011b).

Since Henman (1982) proposed the project "The Guaraná Project: a modest proposal" much was made regarding the physiological effects of guarana, but no enough. In addition to an increase in the number of studies to evaluate other different properties of guarana than caffeine stimulant property, there is a need for more controlled pharmacological studies as well as chemical investigations on other components of guarana. As a warning for further studies on guarana-based products a recent report showed that among five commercial products analysed (three brands of capsules and two of tablets containing guarana), all differed in terms of the presence of chemical markers of the drug both on dissolution test as well as in relation to pharmacotechnical aspects (Sousa et al., 2011). Additionally, the oxidation occurring during guarana extract production (Section 5) has to be addressed, since compounds presenting pharmacological activity, such as tannins, may be affected.

8. Conclusions

Given the information presented in this paper, it is clear that we still know very little about guarana, with special attention its bioactive components and the potential applications of guarana in the food and pharmaceutical industries. So far, caffeine has been the main reason to study guarana because the high content in the seeds. Because the demand for caffeine by different segments of food and pharmaceutical industry, and also a strongly growing market related with beauty products (Mazzafera, 2012), caffeine probably will remain as the main attractive substance and the reason to study guarana. Additionally, it is clear that more research on agronomical aspects, plant pathology, physiology and breeding are necessary to increase productivity and product quality (Atroch, 2009; Souza, 2010; Bentes and Neto, 2011). Recent transcriptomic and proteomic studies on guarana fruits are important steps for basic targeted research on the control of the metabolism of this plant, and may serve to support applied research (Ângelo et al., 2008; Souza, 2010). Significant part of the guarana production in Brazil still comes from Indians tribes in the Amazon State, and any improvement in this plant, in any aspect, may propitiates a positive economic impact in their lives.

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