

Benefits and Effectiveness of Using *Paullinia cupana*: A Review Article

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Abstract Guarana is native to the Amazonian region of Brazil and, widely used in liquid preparations due to its stimulating effect, along with other therapeutic properties. Its chemical components, methylxanthines and condensed tannins, exhibiting a marked biological activity, may be found in commercially available powdered guarana brands at varying levels, possibly due to their provenance and drying processes. However, the chemical standardization of its extract maintains the same quantified content of active substances on each and every lot of extract produced, thus assuring their quality and therapeutic efficacy. Consumption of guarana by the population should be controlled, since there is controversy as to its dosage and association with allopathic drugs, the interactions of which may result in increasing the therapeutic effect, reducing efficacy or even bringing about adverse reactions. However, the use of guarana in adequate concentrations may contribute to achieve therapeutic properties with less toxicity on account of it being some natural antioxidants source and considered one of the most important new substances directly used as effective medicinal agents.

Keywords: *Paullinia cupana*, guaraná, sapindaceae, Amazônia

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1. Introduction

Paullinia cupana Kunth originates from the Amazon Basin, belongs to family Sapindaceae and is consumed on a global scale [1]. Historical data reveal that guaraná was already known by the Maués, Andiráns and Marabitanas tribes of Amazonia, before the arrival of the Europeans, due to its stimulating [2], antidepressant [3] and diuretic [4] activities.

Large amounts of methylxanthines, including caffeine, theophylline and theobromine, in addition to saponins, polyphenols, and especially condensed tannins, are responsible for the benefits brought on to the population on account of being chemical substances bearing bioactive properties [5].

Therefore, the biologic activities of guarana possess therapeutic indications, to be investigated in the prevention treatment of diseases, with promising perspectives for producing novel phyto drugs.

2. Chemical Characteristics

Guarana seeds (Figure 1), source: Rebelo/INPA-Brazil, contain a high concentration of bioactive components,

described in 1669, when their daily use by the indigenous peoples of the Amazon region, was observed.



Figure 1. Guaraná fruit

Among the main chemical constituents of guarana, methylxanthines, I- Caffeine (1,3,7-trimethylxanthine), II- Theophylline (1,3-dimethylxanthine) and III- Theobromine (3,7-dimethylxanthine) (Figure 2 & Figure 3) [90] and condensed tannins, are composed of interconnected monomeric units, the main ones of which being

proanthocyanidin: catechin and epicatechin (flavan-3-ol), due to their antioxidant effect in the protection of atherosclerotic cardiovascular diseases and the process of carcinogenesis [6,7,8,9]. Phytochemical composition includes: xanthine: caffeine (1,3,7-trimethylxanthine) (2 to 7.5%), theobromine (0.02 to 0.03%) and theophylline (0.25%). In the essential oil, cyclic sesquiterpenes and cyclic monoterpenes were identified. Minerals were also identified: calcium (0.1%), phosphorus (0.3%), potassium (0.3%), magnesium (0.08%), iron (4.3 mg); flavonoids: catechol and epicatechol; tannins (8.5 to 25%) [2,9-15].

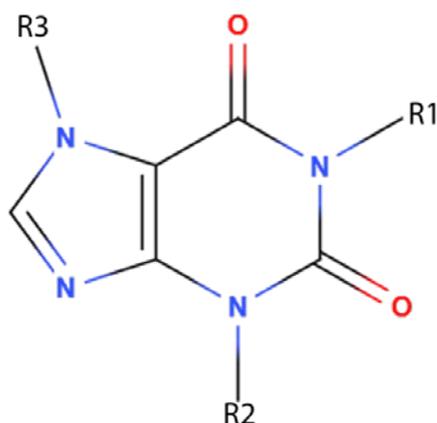


Figure 2. Guaraná-methylxanthines

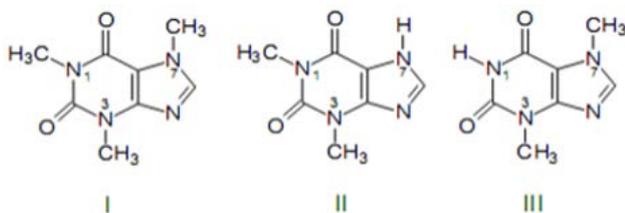


Figure 3. Methylxanthines

3. Biological Activity

Several studies on the medicinal properties of guarana seeds have been carried out, especially in the last three decades, demonstrating the potential of the biological activities concentrated in guarana with its exceptional content of methylxanthines and proanthocyanidins [11]. Thus, the isolated substances have already been analyzed according to the studies described below (Table 1).

4. Bioactive Compound Contents

In the scientific literature, the data on the concentration of guarana powder are conflicting, depending on the region of planting and techniques used for its cultivation and drying processes. Studies have verified different levels of caffeine in marketed powdered Guarana brands, being outside the pharmacopoeia quality specifications. The caffeine content in the samples presented a great variability, in the range of 9.52 to 36.71 mg / g of powder. Due to this variation, the consumers of this product are liable to ingest uncontrolled doses, which may cause a health damage [44]. This demonstrates the need to

implement quantitative techniques in the physical-chemical quality control of plant raw materials, in addition to the need to qualify suppliers by emphasizing the control in acquisition, storage and handling [45].

Under this context, studies will provide better definitions, showing guarana to bear a higher caffeine content than that of coffee seeds (7.59 mg caffeine / gram of guarana powder), verified in the studies [44], in threefold higher quantity, with a mean caffeine concentration of 20.68 mg / g (caffeine / gram of powder), and this difference can reach up to fourfold [46].

Technological alternatives are necessary in order to consume guarana since it tastes bitter and irritates the gastrointestinal tract. Short-term medicinal effects are commonly considered to result from caffeine and associated alkaloids high content as well as considerable amounts of tannins [4,47]. Thus, future research may show that various saponins also play an important role in pharmacology of the drug, particularly with regard to its long-term influence as a general and prophylactic toner.

Studies have noted that five minutes after consumption, caffeine can be detected throughout the human body, reaching its peak action after 30 minutes and lasting from four to six hours. Excessive consumption of caffeine-rich foods can cause unpleasant symptoms such as irritability, headaches, insomnia, diarrhea and tachycardia. Guarana should not be consumed by individuals, with a history of heart disease, hypertension, sensitive to caffeine use, and with gastrointestinal disorders (irritable bowel syndrome, colitis, diarrhea, gastritis). Eating more than 400mg per day can lead to so-called "caffeinism" the most common symptoms of which have shown to be anxiety, restlessness, irritability, tremors, appetite loss, muscle tension, insomnia, and heart palpitations. The safe dose of guarana powder has not been defined as of yet [44,48,49,50].

Conversely, effects can be described as increased alertness and reduced fatigue associated with improved performance of activities [3,18,27,44,51].

Studies have shown guarana concentration to be of critical importance for the cytotoxic activity of the compounds present in guarana. Low guarana concentrations have been shown to be harmless, whereas higher ones could be cytotoxic [33,52,53].

As to phenols, they are not considered to be toxic in normal amounts and conditions, except for polymeric phenols called tannins, which have the ability to complex and precipitate proteins from aqueous solutions [54]. When oxidized, tannins turn into quinones, which form covalent bonds with some functional groups of the proteins, mainly the cysteine and lysine ϵ -amino sulfide groups [55].

More specifically, tannins are high molecular weight compounds, containing enough phenolic hydroxyl groups, to allow the formation of stable cross-links with proteins [56]. They are present in a larger quantity in the foods normally consumed, in the composition of the dietary fiber fraction of different foods and may be considered indigestible or partially digestible [54,56,57,58,59].

Experimental evidence confirms previous observations that polyphenolic compounds significantly inhibit iron absorption, but the negative effect of tannin on iron absorption can be effectively prevented by simultaneous administration of ascorbic acid [60,61].

Table 1. Biological activity verified in the seed of *P. cupana*

Chemical substance	Verified biological activity	According to data from
Guarana extract	Therapeutic benefits in gastric disorders on rats pre-treated with guarana (50 and 100 mg / kg powder) showed a significant reduction in the ethanol-induced gastric lesions severity, similar to that of caffeine (20 and 30 mg / kg powder). This can be accounted for by the effect of increased blood flow in the gastrointestinal mucosa.	[16,17]
	Improvement of cognitive behavior. The effect of chronic treatment on cognitive behavior was studied in rats submitted to the Morris labyrinthine test, and a beneficial effect on cognition, weight evolution and survival was observed, showing low toxicity for lyophilized crude extracts at 30 mg / kg).	[3]
	Anxiolytic, antidepressant and motor stimulant effects. The freeze-dried crude extract (CB), 30 mg / kg (caffeine 10 mg / kg) following acute and chronic oral administration in rats, produced an effect similar to that of antidepressant after long-term administration.	[18]
	Improvement of depression. It has been shown that chronic treatment with semi-purified extract in rats 8 mg / kg) produced panicolytic and anxiolytic effects, and that dopaminergic and serotonergic neurotransmission systems are involved in this effect promoted by the aqueous fraction.	[19, 20]
	Dental plaque shield. <i>In vitro</i> evaluation against <i>Streptococcus mutans</i> showed the effect on the prevention of bacterial plaque prevention.	[5]
	Preventive chemo effect on hepatocarcinogenesis and reduced diethylnitrosamine-induced DNA damage in mice for 14 day with guarana powder (2.0 mg / g diluted in 0.2 mL of filtered water), exhibiting a reduction of 68.6% in the tumor loading area.	[21]
	Ergogenic and increased reasoning ability. 30 mg / kg was chronically administered, increasing the physical capacity of mice subjected to stressful situations, such as forced swimming. The animals had the same average life span, indicating the guarana's low toxicity.	[2]
	Antibacterial and antioxidant activity. An antimicrobial assay proved the ethanol extract to be active against Gram-negative and Gram-positive bacteria (16 to 64 µg / mL). Antioxidant assay results demonstrated guarana ethanol extract to considerably reduced lipid peroxidation with 65.2% cell damage reduction using a guarana extract at a concentration of 2 µg / mL <i>in vitro</i> .	[12]
	Pulmonary chemopreventive effect. Studies evaluated the effects of guarana (2.0 mg <i>P. cupana</i> / g body weight) diluted in 0.2 mL of filtered water and administered <i>in vivo</i> per oral consumption. The treatment decreased proliferation and increased apoptosis of tumor cells, thus reducing the tumor loading area, assigning caffeine to play a key role in controlling the metastasis process and the anticancer effects of catechins (tannins).	[21]
	Weight loss. Study with healthy overweight adult patients consuming capsules containing 95 mg of guarana resulted in delayed gastric emptying, reduced gastric fullness time, and significant weight loss by 45 days.	[22]
Methylxanthines	Hypolipidic effect. It verified the effect of supplementation on lipid metabolism in rats supplemented with daily doses of 325 g / kg body weight with lyophilized hydroalcoholic guarana extract.	[23]
	Diuretic action. Use to treat edema associated with congestive heart failure. The diuretic effect occurs by antagonizing adenosine receptors A1 and A2a.	[24]
Caffeine (1,3,7-trimethylxanthine)	Thermogenic effect. Even a low dose of caffeine (100 mg) in humans has the potential of inducing a thermogenic effect at rest. It is unknown whether this is due to the increasing fat or carbohydrate oxidation, or both	[25]
	Anorexigenic and stimulant properties. A randomized, double-blind, placebo-controlled trial effectively promoted weight loss and fat reduction of overweight men and women with 240 mg / day of caffeine over the 8-week treatment period.	[26]
	Psychoactive effects. A double-blind, randomized, placebo-controlled, parallel-group study on young adults evaluated the acute effects of a vitamin / mineral / guarana supplement (containing 40 mg of caffeine). The results demonstrated that the enhancing properties of guarana cognition provide evidence that its addition to a multi-vitamin-mineral supplement may improve cognitive performance and reduce mental fatigue associated with frequent mental effort.	[27]
	Antidepressant. Guarana extract was evaluated in comparison to caffeine, in the behavior of rats in forced swimming and in open field tests. At concentrations of (25 and 50 mg / kg, powder) and caffeine (10 and 20 mg / kg, powder) it significantly reduced the duration of immobility in the forced swimming test, suggesting a similar effect to that of antidepressant in mice. However, a high dose of guarana (100 mg / kg) and caffeine (30 mg / kg) significantly increased locomotor activity in the open field test. Results suggest caffeine to be involved in the antidepressant activity of guarana.	[28]
	Cardioprotective, thermogenic, hypolipid, and nontoxic. Studies with rats daily supplemented with 150 mg of caffeine (dose equivalent to that of humans) for 12 months produced no adverse cardiovascular effects, caused significant weight loss in mice, and induced no vital target organ toxicity or biochemical abnormalities, suggesting an increase in the basal metabolic rate, by bringing about increased energy expenditure at the expense of fat	[29]
	Vasoconstrictor. Migraine, tonic, energetic, and aphrodisiac treatment. The authors noted that the Sateré-Maués Indians originally used guarana for centuries to obtain medicinal effects. Meta-analysis, suggests that caffeine, due to its vasoconstrictive effect resulting from the blockade of adenosine receptors, may be useful in relieving headache through the ingestion of 100 mg of caffeine.	[4,30,31]

Chemical substance	Verified biological activity	According to data from
Theobromine (3,7-dimethylxanthine) Theophylline (1,3-dimethylxanthine)	The authors, in reviewing the literature, mention the bronchial protective, early aging, anti-inflammatory, and vasodilator effects.	[32]
Condensed tannins (proanthocyanin-dins: catechin and epicatechin)	Antioxidant effects. It was shown that even in low concentrations (1.2 µg / ml) <i>in vitro</i> , it also inhibited the lipid peroxidation process in rats and mice chronically treated (intraperitoneal and oral, 0.3 and 3.0 mg / ml), probably due to its tannin content. And at high doses of 1000-2000 mg / kg, it induced no significant changes in the parameters for toxicological screening.	[33]
	The authors report on the antidiarrheal effect conferred to tannins since they bear astringent properties useful for the cases of diarrheal states.	[32]
	Antioxidant, anti-inflammatory, protection against cardiovascular diseases, and increased activity of glutathione peroxidase and catalase on delaying early aging. Clinical trials with healthy overweight adult volunteers have shown the catechins present in guarana to be an important bioactive component. The consumption of 3 g of guarana powder suspended in 300 ml of water in the morning before breakfast was evaluated by means of oxidative stress markers, with the presence of catechins (30.0 g ± 0.1 / 100 g guarana) blood circulation.	[34]
	Preventive chemo effect on hepatocarcinogenesis. Some tannins are known to have protective effects against DNA damage. Findings show a reduction of 54% in the image length of the exposed animals (p < 0.05).	[35]
	Efficacy of tannic acid on inhibiting the growth of intestinal bacteria due its strong iron binding ability, affecting the growth of some intestinal bacteria that require iron for their growth. The study was carried out <i>in vitro</i> at a concentration of up to 500 µg / mL and could have an impact on human health.	[36]
	Anti-inflammatory. Preservation of cartilage and chondrocytes <i>in vitro</i> and <i>in vivo</i> . Action of the extract verified with consumption of 2.0 mg / 2 times per day in humans and of a dose of 20 mg / kg of weight in rats, administered intraperitoneally	[37-42]
	Vasodilator. These flavonoids measured a significant arterial dilatation response in humans supplemented with 1.5 mg / kg body weight of epicatechin and epicatechin over a period of 3 to 4 weeks.	[43]

However, no effect of tannins on calcium absorption was observed in rats [62]. For the authors, the explanation of the results may be due to the fact that tannins preferentially bind to the iron leaving the calcium free. With respect to calcium homeostasis, data compiled in a review indicate that caffeine is not detrimental to bone metabolism of individuals whose calcium intake is adequate to their daily metabolic needs [63].

Thus, moderate consumption of guarana (maximum 4.6mg/kg body weight/day) in healthy adults of reproductive age is not associated with adverse effects [64,65,66]. Therefore, it is important to carefully instruct the use of guarana to the population with prescription and guidelines [44,67,68,69].

5. Drug Interactions

The use of caffeine in the form of drugs, as for instance, in anti-flu drugs, and of a lot it in the composition of a variety of dietary supplements, is mainly used because of its high content [12,70,71].

Guarana potentiates the action of analgesics, antidepressant activity, and, consumed with anticoagulants can lead to inhibition of platelet aggregation, thus increasing the risk of bleeding [68].

Drug interactions are pharmacological responses, in which the effects of one or more medicinal products are altered by their concomitant administration. These interactions are both observed with synthesized chemicals (allopathic drugs), and those present in plants being used in home preparations and herbal medicines [72].

However, interactions with guarana may result in its therapeutic effect potentiation, efficacy reduction or the appearance of adverse reactions [72,73,74].

6. Use of Guarana in Allopathy

As a medicinal plant guarana holds an essential content of caffeine makes part of the pharmacopoeia of Brazil, [75] and several European countries, Mexico and the United States. "Guarana" is used in migraines as a sedative and tranquilizer, has shown to be an excellent in the convalescence of serious diseases; inestimable cardiovascular, exerting a generalized tonic action in the senile evolution. It regulates the cardiac energy, combats and prevents the passive congestions so peculiar and frequent in the aged "organs" [76]. Thus, treating the therapeutic value of this Sapindácea reveals that daily consumption has a neurostimulating effect [77]. Guarana is one of the most important and advantageous medicines of modern therapy, on account of properties. Its therapeutic value, evidenced in studies and trials, is increasing and, represents an important role of worldwide repercussion, in medicine [78]. The compendia and pharmacological catalogs clearly describe numerous and vast uses of guarana in the various formulas.

It can be observed that the therapeutic knowledge of guarana is ancient, and it was observed that in the Upper Amazon, the general use of chewing small fragments of guarana paste, can prevent one from feeling thirsty, hungry, and even physically and mentally fatigued, and able to work longer hours. And that the use of the guaraná paste this way leaves a bitter taste in the mouth, which can be sweetened by the ingestion of water [79].

A specified study has found guarana to act as a physiological functions stimulant and an excellent intestinal regulator [80]. Aiming at the development of its culture and use, they report its action as an aphrodisiac to be the most important one [4,47].

Due to being a source of bioactive substances with multifaceted activity, guarana is used in therapeutics to

treat human diseases as well as to rise its effectiveness in acting as stimulants [20,32,81].

The interest in its consumption is due to its high content of caffeine and tannins [35], with antioxidant action in the promotion, prevention and recovery of health, in addition to other biological properties [82]. Thus, caffeine appears to have an effect on the control of the metastasis process [83] and the catechins associated with other derivative tannins present in guarana, such as epicatechin, ent-epicatechin and procyanidins B1, B2, B3, B4, A2 and C1 [5], have been contributing to the control of *in vivo* melanoma growth by reducing cell proliferation and increasing cell death through apoptosis, in addition to antiaging activity, and verified in this Amazonian fruit [34].

The studies on the antibacterial activity of guarana could justify some ethnopharmacological uses, such as against diarrhea and dysentery, since they demonstrate the strong activity of this plant against some pathogens of the digestive tract [12].

According to studies, the alcoholic extracts presented a higher antimicrobial activity against all the tested microorganisms than that of the aqueous extract *in vitro*, when found in three fungi transmitted by foods: *Aspergillus niger*, *Trichoderma viride* and *Penicillium cyclopium* and in three bacteria harmful to health: *Escherichia coli*, *Pseudomonas fluorescens* and *Bacillus cereus* [14]. However, the authors observed that in the aqueous extract, they presented higher amounts of caffeine and catechins, conferring greater antioxidant activity.

Due to the ongoing emergence of antibiotic-resistant strains, there is a continuing demand for new antibiotics. In many developing countries, about 80% of available medicines come from medicinal plants, and in developed countries plants are the raw material for processes that synthesize pure chemical derivatives [84].

Among the therapeutic effects of guarana, it it comes to contribute in a beneficial and effective way when included in the development of new drugs in intermediate and final pharmaceutical forms, since it minimized side effects [85], when administered correctly, and is more more cost effective since it can be obtained from natural sources and does not need to be industrialized [86,87,88].

Complexes containing caffeine and catechins (and their dimers) may be responsible for antiplatelet aggregating activity in guarana seeds and may offer health benefits by lowering the risk of thrombosis and cardiovascular disease [89].

For decades, the phenolic compounds of guarana have been of interest for studies, due to their phytochemicals bearing beneficial effects on human health, able to stabilize free radicals, increasing antioxidant activity, among other biological and pharmacological effects. Therefore, recent studies have verified that guarana catechins are bioavailable and contribute to reduce the oxidative stress of clinically healthy individuals by the direct antioxidant action of the absorbed photochemistry and the positive regulation of enzymes, thus reinforcing the published research on the benefits to human health with the use of guarana [34].

7. Summary

The therapeutic properties of guarana are attributable to more than one potentially bioactive component. These include the relatively high levels of saponins, tannins, and

caffeine contained in guarana extracts. The perspective of association with single or multiple vitamins and minerals deserves to be investigated in order to make part of new drugs. Thus, the relationship between the concentration of guarana bioactive compounds and their antioxidant capacity is associated with the therapy of diseases and beneficial effects for health. The study of the presence and concentration of these compounds in guaraná should be expanded, in order to allow a better evaluation of their effects, allowing a broader understanding that aims to contribute in several aspects regarding their use, such as: chemical composition, quality control, kind of extraction, therapeutic value, posology, pharmacological potential and association with allopathic drugs.

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Conflict of Interest

The authors declare no conflict of interest.

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