Proceeding

Supplementary Issue: Spring Conferences of Sports Science. Costa Blanca Sports Science Events, 19-20 June 2020. Alicante, Spain.

Guarana and physical performance: A myth or reality?

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ABSTRACT

Guarana (*Paullinia cupana*) is a rainforest vine that was domesticated in the Amazon for its caffeine-rich fruits. Each fruit contains from one to three seeds which, properly dried, give rise to a brown paste with a bitter taste. The Food and Drug Administration generally recognizes guarana as safe, although there are no established dosages and it is unclear how much guarana is in each drink, because many companies do not list a milligram amount. The increasing number of energy drink with caffeine-related clearly shows that there seems to be a real risk for adverse health effects such as arrhythmias. However, under moderate use and without combining other stimulants or alcohol, the risk for such side effects seem negligible. Anyway, there is an overwhelming lack of evidence to substantiate claims that guarana contribute to the enhancement of physical or cognitive performance. Additional well-designed, randomized, placebo-controlled studies are needed in order to assess claims made for this product and further elucidate potential adverse effects.
Keywords: Athletes; Guarana; Nutrition; Oxidative stress; Physical performance.

Cite this article as:
D'Angelo, S. & Ascione, A. (2020). Guarana and physical performance: A myth or reality?. *Journal of Human Sport and Exercise, 15*(3proc), S539-S551. doi:https://doi.org/10.14198/jhse.2020.15.Proc3.07

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Supplementary Issue: Spring Conferences of Sports Science. Costa Blanca Sports Science Events, 19-20 June 2020. Alicante, Spain.
JOURNAL OF HUMAN SPORT & EXERCISE ISSN 1988-5202

doi:10.14198/jhse.2020.15.Proc3.07

INTRODUCTION

Nutrition can play a crucial role in optimizing training sessions as well as with recovery and metabolic adaptation. Athletes believe that nutritional supplements can enhance performance and recovery by reducing muscle damage, immune dysfunction, fatigue, and oxidative stress (D'Angelo 2019; D'Angelo & Cusano, 2020; Meccariello et al, 2020). Oxidative stress has observed during aging, in some pathological conditions (Ingrosso et al, 1995; Ingrosso et al., 1996; Galletti at al., 2007; D'Angelo et al, 2012; D'Angelo et al, 2013), and a series of studies have revealed that it can also develop during contractile activity (Simioli et al., 2018; D'Angelo & Rosa, 2020a).

Recent research attention has focused on the effects of bioactive compounds, indicated as nutraceutical (D'Angelo et al, 2019a; D'Angelo & Tafuri, 2020). One example is the phytochemicals, as polyphenols (D'Angelo, 2020), bioactive molecules characterized by the presence of multiples of phenol structural units. In fact, in recent decades, special attention has been paid to the anti-oxidative (D'Angelo et al, 2009; Zappia et al, 2010; D'Angelo & Sammartino, 2015; del Monaco et al, 2015; Motti et al, 2018; Vuoso et al, 2020) or anti-proliferative role (D'Angelo et al, 2019b; D'Angelo et al, 2017; Martino et al, 2019; Boccellino et al, 2020) of these phytochemicals introduced by diet, with evidence supporting the contribution of polyphenols not only in the prevention of numerous diseases, but also in the modification of sports performance (D'Angelo & Rosa, 2020b; Smith & Atroch, 2010).

Therefore, the use of phytochemicals could ameliorate or aid to maintain a high performance and avoid adverse consequences on the outcome of sporting events. Accordingly, currently there is a growing interest for phytochemicals. An example is the guarana (GUA).

GUARANÀ'S HISTORY

The GUA plant has a well-established history that started before the conquest of America. Roasted seed extracts have been used as medicinal beverages since pre-Colombian times It has been domesticated in inter-fluvial forests between the lower Tapajós River and the lower Madeira River in the Brazilian Amazon (Smith & Atroch, 2007). The Maués Indians in Brazil discovered and named the guarana fruit (Kuri, 2008). 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 (Angelo 2008). To prepare the traditional guarana´ beverage, the hard cylinder is grated with the bony tongue of the pirarucu (*Arapaima gigas*), one of the largest fish in the Amazon, or a small piece of flat rough stone, such as sandstone (Smith & Atroch, 2007).

The fruits of GUA are orange-red capsules that contain black seeds, partially covered by white arils (Figure 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. The contrasting colours of the partially open fruit creates the appearance of eye- balls, thus, giving credence to the legend about the origin of the domestication of GUA. This myth, which is attributed to the Maués Indians, has it that a malevolent god attracted a beloved male child of the village into the jungle and killed him out of jealousy. The people of the village found the child dead, lying in the forest. A benevolent God consoles the village with a present in the form of guarana. The right eye was planted in the village, and it sprouted and produced fruits that resembled a child's eye (Leila Larisa Medeiros Marques, 2019). GUA is in popular use for a variety of therapeutic purposes, including as a

tonic, a stimulant of the nervous system (in cases of physical or intellectual stress), even as an antidiarrheic, diuretic and antineuralgic agent (Mattei 1998).

Figure 1. Guarana fruits. Orange fruits with red capsules containing black seeds partially covered by white arils.

WHAT IS GUARANA?

Guarana (*Paullinia cupana Mart. var. sorbilis Mart. Sapindaceae*) is a plant native to the Amazon region known for its stimulant and medicinal properties and used for centuries by indigenous communities of the Amazon (named after the Guarani people). 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 (Figure 1). (Schimpl et al., 2013). Each fruit contains from one to three seeds that, properly dried, ground, kneaded and mixed with cassava flour, give rise to a brown paste with a bitter astringent flavour and particularly rich in caffein (CAF) (from 2.5 to 8%): the CAF content of guarana seeds is 2 to 5 times higher than that of Arabica coffee seeds. GUA pasta can be marketed as such, in the form of cylindrical rolls 10-30 cm long, or used for the production of tonic and refreshing drinks to which gives an aroma particularly appreciated by South American children. Guarana seeds also contain traces of theobromine and theophylline, other alkaloids in the xanthine group (Figure 2). The evolutionary 'purpose' of the xanthines is unclear, but they may help protect the plants from attack by insect pests, herbivores and pathogens (Krewer et al., 2011).

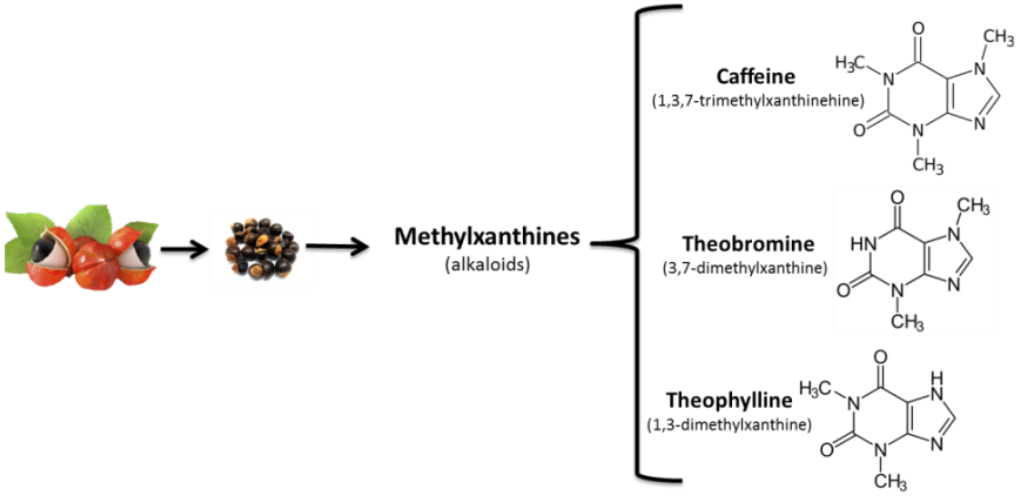

Figure 2. The methyl-xanthine present in guarana seeds.

CULTIVATION

There are approximately 195 species of *Paullinia* distributed in the American tropics and subtropics. Of these, at least nine species are described as native to Brazil, including *Paullinia cupana* (H.B.K., *Sapindaceae*). GUA plants are commercially cultivated exclusively in Brazil to supply the national carbonated soft-drink industry and natural product stores around the world. (Angelo P.C.2008). There has been increased interest in the GUA plant for its medicinal and stimulant properties by the food, pharmaceutical and cosmetic industries. Consequently, over the last decade, there has been a significant increase in the area of plantations. GUA is widely used in the food industry in the form of syrups, extracts, and distillates, primarily as a flavouring agent and as a source of CAF by soft drink manufacturers. The greatest economic value of guarana is currently in the manufacture of beverages. The American Beverage Company alone uses 70% of the GUA seeds produced annually. The remaining production (30%) is destined for the phytochemical industry and exportation, mainly to Japan and the United States (Suframa, 2003). In 1972 the Law 5823, termed the Law of Juices, was enacted. This law established quantitative limits of GUA at 0.2–2 g l−1 soda and 1–10 g l−1 syrup. 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.

CHEMICAL COMPOSITION

Caffeine (1,3,7-trimethylxanthine) is an alkaloid that can be found in coffee beans, tea leaves, cocoa beans and other plants. CAF is a methylxanthine, a methylated derivative of xanthine; it has a structure similar to nucleosides and other xanthines that can be found in several natural sources (Cano-Marquina et al., 2013). Xanthines constitute a group of alkaloids commonly used for their stimulant and bronchodilator actions. CAF has a half-life of approximately 4–6 h. The physiological actions of CAF concentration found in human drinkers include several primary and secondary effects described in selective pharmacological experiments. However, some of them do not reproduce, or are counterbalanced by actions at other targets, when CAF is directly administered to humans. The main detected effects of CAF in humans affect the cardiovascular system and the central nervous system, together with modifications in the metabolism of carbohydrates or in inflammatory mechanisms. Other actions of CAF include activation of the metabolic rate and diuresis.

In addition to CAF, other purinic alkaloids were found in smaller proportions (below 0.3%) in guarana plants, including theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) (Figure 2). The xanthic bases of guarana, however, do not explain all of this therapeutic action of GUA.

The seeds are rich in compounds such as saponins, proteins, fatty acids; other alkaloids in the xanthine group, and trace elements, such as manganese, rubidium, nickel and strontium; high molecular weight polysaccharides, as pectin and a group of polysaccharides called hemicelluloses, such as xylans. The seeds also contain high concentration of tannins, polyphenols, such as catechins, epicatechins and proanthocyanins (Angelo et al., 2008), responsible for the antioxidant power of these extracts, probably. Saponins and tannins are substances that have proven antioxidant action. Therefore, it is possible that part of the revitalizing effects of guarana may be due to possible antioxidant action (Mattei 1998). The tannin in present in guarana 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. Additionally, small variations have been identified in the monomers constituting these fruit's tannins. GUA

seeds also contain acylglycerol and cyanolipids, a class of lipids found in some families, for example, *Sapindaceae* and *Boraginaceae*.

The effects of ingestion of GUA are similar to those of CAF and the concentration of CAF can vary widely in the preparation of GUA. However, the duration of action may be considerably different due to possible interactions between the CAF and saponins and tannins in GUA.

GUA methyl-xanthines have been extensively studied over the years; conversely, investigations have been scarce for many other classes of compounds, with possibly interesting pharmacological effects. In fact, although tannins have been isolated from GUA, there is still much to be explored about this class of substances. The effect of GUA is not yet known. Whether it is of additive or synergistic effect when combined with CAF is not clear (Bittencourt et al., 2014).

GUARANÀ'S PROPERTIES

The first substance of GUA was isolated in 1826 and named guaranine, a tetramethylxanthine identical to CAF. With further studies, researchers started to attribute the medicinal properties of guarana to several xanthines and the numerous tannins present in the plant. The pharmacological properties of GUA have been the main focus on some reviews. *Paullinia cupana* has been mentioned as early as 1872 for the treatment of "Sick-Headache". GUA has been associated with protection against hypertension, obesity and metabolic syndrome in elderly healthy volunteers (Krewer et al., 2011); a therapeutic role in atherosclerosis has been described (Portella et al., 2013) (Figure 3). Complementarily, the association of Yerba Mate, GUA and Damiana was associated with lower food intake in overweight woman (Harrold et al., 2013).

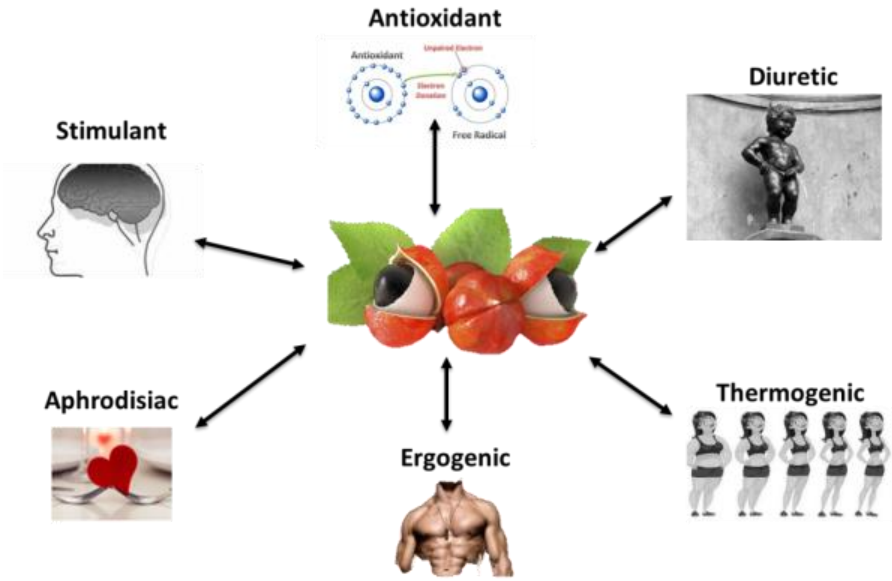

Figure 3. Presumable actions of guarana.

GUA showed anti-adipogenic potential due to its ability to modulate miRNAs and genes related to this process or an increase in energetic metabolism and stimulation of mitochondrial biogenesis, contributing to control of weight gain, even when associated with high-fat diet (Lima et al., 2017; Bonadiman et al, 2017; Andersen & Fogh, 2001). GUA was placed alongside the plants with psychoanaleptic activity (stimulants), with emphasis

on anorexigenic or weight reduction properties. Although the consumption of GUA can induce changes in lipid metabolism, these effects have been associated with the methylxanthine content of the extract.

The Amazonians have used the seeds of its fruit to increase awareness and energy. The stimulant effect of GUA is associated with high CAF content (Kolahdouzan et al., 2017).

The Food and Drug Administration generally recognizes GUA as safe, although there are no established dosages and it is unclear how much GUA is in each drink because many companies do not list a milligram amount. Therefore, it should be assumed that the amount of CAF in the products is, in reality, larger than the amount of CAF noted especially when GUA is present. The popular motivations for consuming GUA extracts as dietary supplements are: weight loss, energy boost, improvement of fitness and sexual performance, and increase of cognitive capacity. Scientific support is forthcoming for some of these motivations. Kennedy et al. (2004) reported an improvement in cognitive performance in humans, possibly due to the combination of CAF with other components of the extract (Angelo et al., 2008). Although there has been a great deal of interest in studying CAF from GUA including its benefits and harms, the most diverse pharmacological effects of guarana are associated with the tannins present in the plant seeds, which represent about 16% of the seed composition.

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. However, much of these effects may be only a strategy to increase the sales. GUA has also been indicated as a diuretic, calming aphrodisiac and tonic. 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 (Schimpl et al., 2013).

The stimulating effects of GUA are longer lasting than coffee because the CAF in GUA apparently binds with tannins. GUA powder is a product easily available in natural product stores. It is either marketed alone or in combination with other herbal drugs, creating the likelihood of additive or synergistic effects. It is also included in a variety of energy drinks. The latter are easily found in gyms and supermarkets but they contain stimulants and/or additives. The drink with the highest natural content of CAF in the world is made from toasted GUA seeds, possessing at least 5% methylxanthines, expressed as CAF. Long-term intake of the various components of these energy drinks can result in significant changes in the cardiovascular system, and even convulsions.

When GUA is added to energy drinks, it increases the amount of metabolized CAF. A series of adverse events are associated with the consumption of GUA, including irritability, heart palpitations, anxiety, disorders of the central nervous system and myoglobinuria. It is not surprising that young adults have been admitted to emergency after excessive ingestion of GUA -based energy drinks (Wassef et al., 2017). GUA can also exacerbate epileptic seizures, lowering the seizure threshold or increasing the duration of seizures. Despite these reports, when taken alone, GUA has few adverse effects and the majority of them are similar to those observed after the consumption of products containing high CAF content. The daily dose of CAF recognized as safe for adults is 400 mg. (Marques et al., 2019).

GUARANÀ AND PHYSICAL PERFORMANCE

Many substances contained in foods are also taken by athletes for ergogenic purposes, and there is little research that can scientifically prove a real benefit on sports performance deriving from the use of certain nutrients even when consumed in high doses.

In addition to the stimulating action of CAF 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. For example, GUA 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., 2011). CAF change neuronal activity as evidenced by fMRI signal changes in a network of brain areas associated with executive and attention functions during running memory processes.

An interesting result in terms of a physiological effect was obtained with purified guarana extract (containing CAF 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. 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 CAF 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 CAF, 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 (Schimpl et al., 2013).

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.

Currently, there is a growing interest for GUA, which is often attributed to CAF content depending on how the extract is prepared (Schimpl et al., 2013). In addition to CAF, guarana seeds are known to harbour a number of other possible stimulants such as flavonoids (Scholey & Haskell, 2008) or other potentially psychoactive components, including saponins and tannins (Mattei et al.,,1998), which could enhance cognitive function (Pomportes et al., 2014; Kennedy et al., 2004; Veasey et al., 2015).

In several studies as well as in sports nutrition strategy, GUA is rarely used alone but mostly associated to multivitamins mineral complex (Pomportes et al., 2014; Kennedy et al., 2008; Veasey et al., 2015).or to ginseng (Kennedy et al., 2004). We assume that, in addition to the presence of CAF, the other components of guarana seeds could potentially enhance performance via the activation of bitter taste receptors T2Rs (Soares et al., 2013) or different pathways. Some recent studies have reported that GUA ingestion could also influence cognitive abilities. More specifically, it has been reported that ingestion of GUA, could, at rest, induce an improvement in decision-making and alertness (Pomportes et al., 2014), improve memory performance (Kennedy et al., 2004) and reduce RPE after 30 min of submaximal exercise (Veasey et al., 2015).

Guarana in association with other herbal drugs, are widely used for weight loss in humans, with positive results. As a result of its methylxanthine content, the guarana extract can block adenosine and phosphodiesterase inhibitors, thereby, increasing noradrenaline activity. Considering the effects of CAF on blood pressure elevation, guarana should be avoided by hypertensive individuals. It is also strongly recommended that the combination of guarana and supplements containing ephedra should be avoided because it can increase the risk of myocardial infarction and sudden death. Also, antiarrhythmic medications, such as amiodarone, should not be consumed with guarana because such an association may decrease plasma amiodarone concentration; particularly in the heart.

There is great interest in the substitution of synthetic antioxidants by natural counterparts in food, encouraging a search for natural sources of antioxidants. Several studies have shown that guarana has antioxidant activities, which have been largely attributed to the polyphenols (particularly tannins). But also, the polysaccharides in guarana powder have also shown antioxidant activity *in vitro.*

Herbal drugs used in the preparation of medications for therapeutic purposes are foreign to the human body. Therefore, like any foreign substance, the products of their biotransformation may lead to reactions in the human body. For this reason, popular and even traditional use, are insufficient to validate herbal drugs as effective and safe medications. Safety should be assessed with pre-clinical and clinical pharmacological and toxicological studies.

The analysis of commercial samples shows that these medications often do not meet pharmacological specifications of quality. This is indicative of the need to implement quantitative techniques to control the physical and chemical quality of raw plant materials.

After a medicinal plant is harvested, it may lose quality in subsequent stages of processing, which makes the drying process fundamental for the quality of the final product. Guarana seeds can be dried by several distinct methods and the choice of a particular method strongly influences the quality of the product. The incorrect storage of seeds can lead to loss of material whether for physical or biological reasons. One concern about the quality of natural products is the potential for contamination by fungi, with the risk of the presence of mycotoxins. There is a need to implement analytical tests of quality control that are accurate, sensitive, and reproducible.

The ergogenic effects observed after mouth rinsing with nutritional supplements open up new perspectives in terms of performance optimization strategies. The findings suggest that, as for ingestion of nutritional supplementations, the effects on performance are highly variable between individuals (Pomportes et al., 2017).

Before using nutritional strategies with athletes during sporting events, it seems essential to determine beforehand whether the athlete is a good or bad responder. The fact that similar magnitude benefits have been observed on performance using mouth rinsing or ingestion incites to investigate thoroughly to define potential benefits and gainful usage, for example with athletes who are inclined to gastro-intestinal distress or when they need to limit energy intake (weight control)

CONCLUSIONS

Although guarana has been the focus of many scientific studies, there are still gaps to be filled. Ultimately, using the plant bioactive, either as pure compounds or as standardized extracts, requires extraction,

pharmacological screening, isolation and characterization of the biological compound, as well as toxicological and clinical evaluation. Moreover, combining bioactive from various sources creates a variety of pharmacological effects that are still far from being exhausted. It is known that the pharmacological activities of plants are due to the distinct and diverse compounds existing in their composition and their proportion can be changed depending on the way the extract is prepared. The quality control of herbal drugs is essential to ensure the pharmacological standard of quality of guarana by means of analysis required for this plant. Another crucial point is the standardization of the extract that will be used for both in vitro and in vivo tests, by identifying and quantifying the main compounds present in guarana seeds.

The increasing number of energy drink and CAF-related clearly shows that there seems to be a real risk for adverse health effects such as arrhythmias. However, under moderate use and without combining other stimulants or alcohol, the lack of a similar number of case reports makes the risk for such side effects seem negligible. It is noteworthy that a large number of serious health risks resulted were due to overconsumption of the products or their ingestion in a short period of time. Therefore, it may well be important for energy drink companies to place warnings on their products to avoid such habits. There is an overwhelming lack of evidence to substantiate claims that guarana or components of energetic drinks in general contribute to the enhancement of physical or cognitive performance. Additional well-designed, randomized, placebo-controlled studies are needed in order to assess claims made for these products and further elucidate potential adverse effects.

Little evidence suggests that CAF intake boosts performance in sports. Proper hydration and adequate rest as well as paying attention to diet and regular exercise are likely to prove more helpful. Guarana is known to help stave off hunger and it is used by people trying to lose weight. But almost all energy drinks with guarana as one of the ingredients also contain large amounts of high fructose corn syrup, a sure sign that the beverages are not particularly healthy and may lead to weight gain when taken on a regular basis. Only a few of the energy drinks containing guarana have diet versions. Guarana powder contains negligible calories but is bitter. Most people who consume guarana products outside of the traditional area of consumption are drinking highly sugared beverages. Improved eating habits and increased exercise as part of a transformed lifestyle are better bets for keeping the weight off.

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.

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