Received: 9 June 2021 | Revised: 22 September 2021 | Accepted: 23 September 2021

DOI: 10.1111/1541-4337.12862

COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Comprehensive REVIEWS in Food Science and Food Safety WILEY

Effects of the consumption of guarana on human health: A narrative review

Elizabeth A. F. S. Torres[1] | **Ana Clara da C. Pinaffi-Langley**[1] | **Marcela de Souza Figueira**[1] | **Karina Silva Cordeiro**[1] | **Leonardo Dias Negrão**[1] | **Maiara Jurema Soares**[1] | **Cintia Pereira da Silva**[1] | **Maria Carolina Zsigovics Alfino**[1] | **Geni Rodrigues Sampaio**[1] | **Adriano Costa de Camargo**[2]

[1] Department of Nutrition, School of Public Health, University of Sao Paulo, Sao Paulo, Brazil

[2] Laboratory of Antioxidants, Nutrition and Food Technology Institute, University of Chile, Santiago, Chile

Correspondence
Elizabeth A. F. S. Torres, Department of Nutrition, School of Public Health, University of Sao Paulo, Sao Paulo 01246-904, Brazil.
Email: eatorres@usp.br
Adriano Costa de Camargo, Laboratory of Antioxidants, Nutrition and Food Technology Institute, University of Chile, Santiago 7830490, Chile.
Email: adrianoesalq@gmail.com

Funding information
Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Number: 2017/20039-0

Abstract

Guarana (*Paullinia cupana*) is a plant from the Amazon region with cultural importance. Despite its early ancestral use by indigenous tribes, the first reports regarding the benefits of guarana consumption for human health were published in the 19th century. Since then, the use of guarana seed in powder and extract forms has been studied for its diverse effects on human health, such as stimulating, anti-inflammatory, antioxidant, anticancer, hypocholesterolemic, and anti-obesity effects. These effects are attributed to the high content of bioactive compounds found in guarana seeds, especially methylxanthines and flavonoids. In fact, the Brazilian Food Supplement Law has officially acknowledged guarana as a source of bioactive compounds. The number and diversity of studies focused on guarana and human health are increasing; thus, organizing and describing the available evidence on guarana and its applications is necessary to provide a framework for future studies. In this narrative review, we have organized the available information regarding guarana and its potential effects on human health. Guarana produces unique fruits with great potential for human health applications. However, the available evidence lacks human studies and mechanistic investigations. Future studies should be designed considering its applicability to human health, including intake levels and toxicity studies.

KEYWORDS
phenolics, plant extract, plants, polyphenols, public health

1 | INTRODUCTION

The origin of guarana (*Paullinia cupana* var. *sorbilis*) is profoundly intertwined with the cultural identity of the indigenous population of the Amazon region. The curious-looking fruit resembles a human eye (Figure 1), a characteristic that features prominently in the legend of its origin: the sowing of the eyes of an indigenous child that died tragically (Nazaré & Figueirêdo, 1982). This legend demonstrates that the importance of guarana reaches far beyond its status as food. Rather, the fruit carries important significance to the indigenous population and must be regarded as a cultural patrimony.

The consumption of guarana was first described by Jesuit missionaries in the 17th century. They noted that indigenous people of the Amazon consumed it daily for

FIGURE 1 Ripe guarana fruit resembling a human eye (AnitaFortis, CC BY-SA 3.0 https://creativecommons.org/licenses/by-sa/3.0, via Wikimedia Commons)

energy and medicinal purposes, such as treatment for headache, diarrhea, fever, and cramps. They also believed that the daily consumption of guarana offered protection against malaria and parasite diseases. Remarkably, these missionaries noted that the fruit was as valuable to the tribes as gold was to the European colonizers (Henman, 1982; Smith & Atroch, 2010). During the colonial period, the consumption and commerce of guarana intensified; it was advertised as a tonic, stimulant, and aphrodisiac. In the beginning of the 20th century, guarana was introduced as a flavoring in carbonated soft drinks and since then its name became a synonym of such drinks in Brazil (Smith & Atroch, 2010).

The first scientific reports on guarana's effect on human health originated during the 19th century. They described the use of guarana seed powder to treat headaches, diarrhea, and urinary diseases, comparing its effects with those of coffee and tea. Previously in the same century, German botanist Theodore von Martius identified and isolated caffeine from the composition of guarana (Breitbach et al., 2013; Schimpl et al., 2013). Accordingly, many scientific studies using guarana have focused on health effects associated with caffeine, such as cognitive and stimulant effects (Silva, Soares-Freitas, Sampaio, et al., 2019). Other studies have indicated that guarana's benefits to human health originate from a complex synergistic effect among its various components rather than caffeine alone (Haskell et al., 2007; Kennedy et al., 2004; Ruchel et al., 2016). In the last decade, guarana has attracted the interest of pharmaceutical industries due to its effects on diverse aspects of human health, including cancer, cardiovascular diseases, and diabetes (Silva et al., 2018).

Because of the increasing amount and diversity of studies focused on guarana and human health, organizing and describing the available evidence is necessary to guide the design of future studies. Herein, we aimed to retrieve and compile the available information regarding guarana and its effects on human health. We also aimed to describe possible applications of the fruit in emerging areas of human health to provide a framework for future studies. For this narrative review, we searched Google Scholar, PubMed, SciELO, Science Direct, Embase, and Scopus databases for articles on guarana in English, Spanish, and Brazilian Portuguese without period restrictions. The search terms used included "guarana," "*Paullinia cupana*," and "guarana extract," among other terms specific to human health and disease.

2 | CHEMICAL COMPOSITION

The chemical composition of guarana varies according to genotype, cultivar, location, and climate conditions. Brazil is the only country that produces guarana commercially; however, low productivity related to high genetic variability represents an obstacle to the use of its full potential. Nina et al. (2021) investigated the phytochemical diversity of several guarana genotypes cultivated in the Western Amazon region and identified considerable variability in metabolite content among them. Based on variations in caffeine, catechin, and epicatechin content, they classified the genotypes as three different chemotype groups: energetic & antioxidant, energetic, and antioxidant guarana. Similarly, da Silva et al. (2017) differentiated guarana seeds from different geographical regions based on variations in their flavonoid content. This indicates that guarana seeds originated from different cultivars and regions have distinct proportions of bioactive compounds. Thus, guarana extracts containing mostly "energetic" guarana genotypes may display great stimulating effects but diminished antioxidant effects, while those containing mostly "antioxidant" genotypes may display the opposite, demonstrating how this variability may play a role in the application of guarana in human health.

Among the diverse chemical composition of guarana, plant secondary metabolites considered bioactive compounds hold special interest for the effects of guarana in human health. Angelo et al. (2008) identified several expressed sequence tags in guarana related to the biosynthesis of important metabolites, including 94 expressed sequence tags related to purine alkaloid metabolism and 129 expressed sequence tags related to flavonoid metabolism. Among these, the authors identified markers related to the expression of essential enzymes for the biosynthesis of catechin and its isomer, epicatechin, such

TABLE 1 Main bioactive compounds found in guarana seed

Compound name	Mean mg/100 g of guarana seed	Standard error mg/100 g of guarana seed	N	Minimum mg/100 g of guarana seed	Maximum mg/100 g of guarana seed	Reference
Methylxanthines						
Caffeine	2797	623	7	850	5130	Machado et al. (2018); Santana et al. (2019); Santana and Macedo (2019); Sousa et al. (2010); Yonekura et al. (2016)
Theobromine	20	4	7	6	39	Machado et al. (2018); Santana et al. (2019); Santana and Macedo (2019); Sousa et al. (2010); Yonekura et al. (2016)
Theophylline	50	18	6	10	130	Machado et al. (2018); Santana et al. (2019); Santana and Macedo (2019); Sousa et al. (2010)
Monomeric flavan-3-ols						
Catechin	2056	573	12	460	7600	da Silva et al. (2017); Machado et al. (2018); Mendes et al. (2019); Santana et al. (2019); Yonekura et al. (2016)
Epicatechin gallate	13	5	4	4	26	Santana et al. (2019); Santana and Macedo (2019)
Epicatechin	1340	334	12	370	4400	da Silva et al. (2017); Machado et al. (2018); Mendes et al. (2019); Santana et al. (2019); Yonekura et al. (2016)
Proanthocyanidins						
Procyanidin B1	374	3	3	370	380	Machado et al. (2018); Mendes et al. (2019)
Procyanidin B2	314	80	4	100	490	Machado et al. (2018); Mendes et al. (2019); Sousa et al. (2010)
Procyanidin A2	60	–	1	–	–	Sousa et al. (2010)

as dihydroflavanol 4-reductase and anthocyanidin synthase. In fact, flavanols represented by catechin and epicatechin are the major bioactive compounds found in guarana seeds along with caffeine.

Guarana contains a high amount of caffeine. While popular caffeine sources such as espresso coffee (U.S. Department of Agriculture, 2020a), black tea (U.S. Department of Agriculture, 2020b), and 85% chocolate (Mudenuti et al., 2018) have approximately 0.21%, 0.02%, and 2.34% of caffeine content, respectively, guarana has up to 5.3% of caffeine in its composition. Similarly, guarana has a high flavan-3-ol content, with catechin and epicatechin representing up to 3% and 2% of its composition, respectively. Other common sources of flavan-3-ol such as cocoa powder (epicatechin: 0.20%, catechin: 0.06%), green tea (epicatechin: 0.02%, catechin: 0.09%), and cacao bean (epicatechin: 0.10%, catechin: 0.09%) have 10−100 times less catechin and epicatechin than guarana (Bhagwat & Haytowitz, 2015). Table 1 shows the main bioactive compounds content of guarana seed.

In addition to monomeric flavan-3-ols, guarana contains proanthocyanidins, which are oligomers (dimers, trimers, and tetramers) of flavan-3-ol. The most representative are proanthocyanidin B1 and B2, but recent studies have demonstrated that guarana contains proanthocyanidins with varying degrees of polymerization (Figure 2 and Table 2) (da Costa da Silva et al., 2017; Pinaffi et al., 2020). Furthermore, the residue obtained during the production of guarana extracts contains insoluble-bound polyphenols with potential biological activity, representing an overlooked fraction of guarana (da Costa Pinaffi et al., 2020).

Besides the characterization of polyphenols and methylxanthines, several studies have investigated other aspects of guarana seed composition. Dalonso and Petkowicz (2014) characterized the polysaccharides of guarana seeds and showed that different starch fractions had distinct amylose and amylopectin content. Avato et al. (2003) reported that guarana seed oil contained

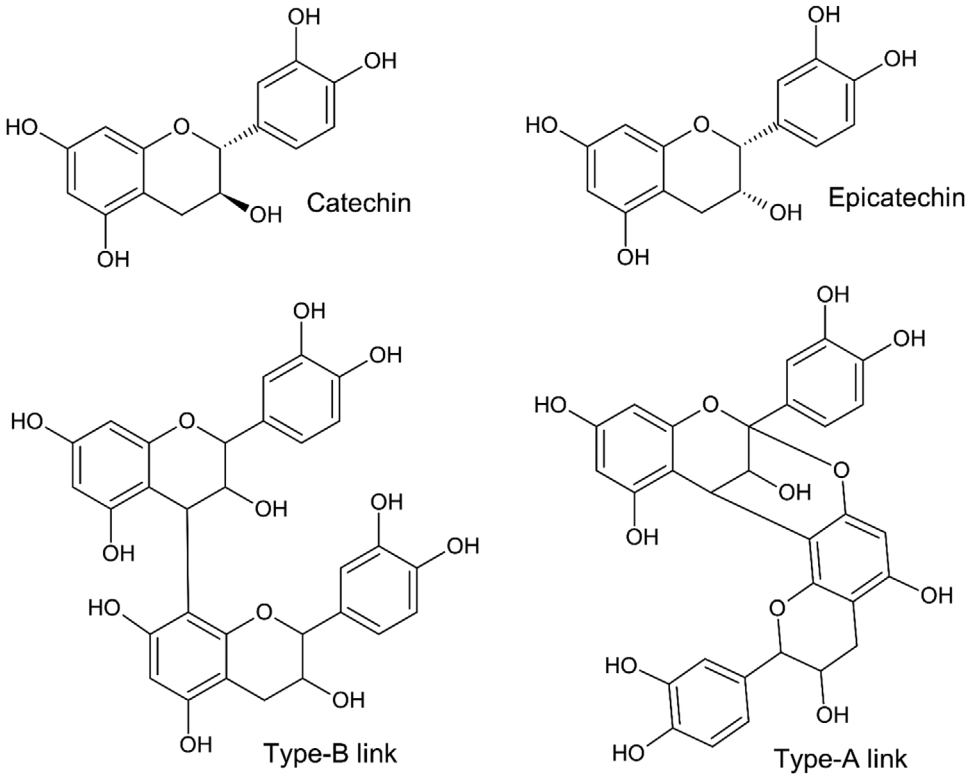

FIGURE 2 Chemical structures of catechin and epicatechin, and simplified representation of proanthocyanidins type-A and type-B linkage

3% of cyanolipids and 28% of acylglycerols. Additionally, other studies have quantified and described the mineral composition of guarana seeds, including important trace elements such as Mn, Fe, and Zn (Adolfo et al., 2020; de Gois et al., 2016; Santos et al., 2019).

Besides agricultural and environmental factors—such as season, soil quality, and harvest time—processing methods can also affect guarana's composition. Briefly, the production of guarana seed powder involves three main processing steps: fermentation, roasting, and grinding. After harvest, the guarana fruit undergoes fermentation to facilitate pulp and shell removal. The seeds are then roasted to achieve specific moisture contents depending on the final product (from 5% to 12% moisture content) (SEBRAE, 2016). Finally, the seeds are ground to obtain guarana powder.

Among these processing steps, roasting has the most direct impact on guarana's bioactive composition. Ushirobira et al. (2004) reported that sun-dried seeds lost a considerable amount of polyphenols and methylxanthines compared with the reference sample (seeds dried in a clay pot for 2 h). Conversely, seeds roasted for 2.5–4 h in a metallic pot had greater polyphenol concentrations than the reference sample while maintaining comparable methylxanthine contents. This illustrates that differences in processing (from traditional to industrial methods) may translate into differences in the bioactivity of guarana seed powder. Furthermore, Veiga et al. (2014) analyzed the content of polycyclic aromatic hydrocarbons in roasted seeds. They surmised that the average guarana seed powder intake represented a level of exposure within the limits established by the European legislation.

3 | EFFECTS ON HUMAN HEALTH

3.1 | Bioavailability

Upon consumption, bioactive compounds must be absorbed into the systemic circulation and reach tissues and cells in a sufficiently high concentration to be deemed bioavailable and exert physiological effects at a systemic level. While caffeine is widely bioavailable (Blanchard & Sawers, 1983), polyphenols have low bioavailability owing to low absorption and rapid elimination. Flavan-3-ols are mostly absorbed in the small intestine and undergo extensive metabolization (Shahidi et al., 2019), reaching plasma concentrations in the 10^{-9} M range (Halliwell et al., 2005). Nonetheless, polyphenols that are not absorbed and accumulate in the gastrointestinal phase (e.g., insoluble-bound polyphenols that accumulate in the colon) can still exert direct or indirect physiological effects.

TABLE 2 Monomeric and oligomeric flavan-3-ol structures found in guarana

Compound	Molecular mass	Elemental composition
	g•mol^{-1}	
Monomers		
Catechin	290.3	$C_{15}H_{14}O_6$
Epicatechin	290.3	$C_{15}H_{14}O_6$
Dimers		
Type-A afzelechin dimer	544.5	$C_{30}H_{24}O_{10}$
Type-A flavan-3-ol dimer	560.5	$C_{30}H_{26}O_{11}$
Procyanidin A2	576.5	$C_{30}H_{24}O_{12}$
Type-A procyanidin dimer	576.5	$C_{30}H_{24}O_{12}$
Procyanidin B2	578.5	$C_{30}H_{26}O_{12}$
Type-B procyanidin dimer	578.5	$C_{30}H_{26}O_{12}$
Trimers		
Type-A afzelechin trimer	814.7	$C_{45}H_{34}O_{15}$
Type-A flavan-3-ol trimer	830.7	$C_{45}H_{34}O_{16}$
Type-A flavan-3-ol trimer	846.7	$C_{45}H_{34}O_{17}$
Type-A procyanidin trimer	864.8	$C_{45}H_{36}O_{18}$
Type-B procyanidin trimer	866.8	$C_{45}H_{38}O_{18}$
Tetramers		
Type-B afzelechin tetramer	1091.0	$C_{60}H_{50}O_{20}$
Type-B flavan-3-ol tetramer	1107.0	$C_{60}H_{50}O_{21}$
Type-B flavan-3-ol tetramer	1123.0	$C_{60}H_{50}O_{22}$
Type-A flavan-3-ol tetramer	1119.0	$C_{60}H_{46}O_{22}$
Type-A flavan-3-ol tetramer	1135.0	$C_{60}H_{46}O_{23}$
Type-A procyanidin tetramer	1153.0	$C_{60}H_{48}O_{24}$
Type-B procyanidin tetramer	1155.0	$C_{60}H_{50}O_{24}$

Source: da Costa Pinaffi et al. (2020) and da Silva et al. (2017).

Several studies demonstrated that the gastrointestinal tract itself can be a key action site of pro-oxidant compounds (e.g., sulfite myoglobin, heme proteins, copper and iron ions, aldehydes, mycotoxins, polycyclic aromatic hydrocarbons, nonsteroidal anti-inflammatory drugs, among others) (Fuentes et al., 2021; Halliwell et al., 2000; Sampaio et al., 2021). According to Mendes et al. (2019), a significant concentration of flavan-3-ols (catechin, 95%; epicatechin, 66%; procyanidin B1, 84%; and procyanidin B2, 50%) from guarana seed powder reached the small intestine after in vitro digestion. Therefore, guarana flavanols may counteract excessive oxidative stress at the gastrointestinal level. Furthermore, polyphenols that accumulate in the colon can exert physiological effects through the action of metabolites formed upon colonic fermentation (Gonzales-Sarrias et al., 2017; Mudenuti et al., 2021). Mendes et al. (2019) reported that a very low proportion of guarana flavan-3-ols (2.7–4.7%) reached the colon after in vitro digestion. Accordingly, da Costa Pinaffi et al. (2020) reported that insoluble-bound polyphenols represent a small percentage of the total phenolic content of guarana powder.

Few studies have addressed the bioavailability of bioactive compounds from guarana. Yonekura et al. (2016) observed plasma concentrations of catechin, epicatechin, and their methylated metabolites ranging between 0.38 and 0.64 nmol/ml in human volunteers 1 h after the ingestion of guarana powder (3 g containing 90 mg of catechin and 60 mg of epicatechin). These very low concentrations were sufficient to exert measurable physiological effects on oxidative stress parameters, demonstrating the bioavailability and bio-efficacy of polyphenols from guarana. In an in vitro study, guarana flavan-3-ols that underwent simulated gastrointestinal digestion were not detected after Caco-2 cell permeation (da Silva, 2016). However, the authors reported the presence of unidentified compounds in the basolateral cell compartment. Moreover, the relatively low sensitivity of the detection method may have affected the detection of absorbed compounds.

Before being bioavailable, bioactive compounds must also be bioaccessible. In other words, dietary bioactive compounds must release from the food matrix, be solubilized, and resist degradation. Considering that guarana powder is commonly consumed in association with other foods, Mendes et al. (2019) evaluated the effect of macronutrients on the bioaccessibility and bioavailability of flavan-3-ols from guarana after simulated digestion using Caco-2 cells. They reported that milk protein had a negative impact on flavan-3-ol bioaccessibility, whereas vegetable lipids exerted a positive effect. Conversely, the addition of macronutrients did not affect caffeine bioaccesibility. Regarding bioavailability, the authors detected digested flavan-3-ols after Caco-2 cell permeation and did not observe any effects related to the presence of other macronutrients.

Despite the indication that polyphenols from guarana are sufficiently bioavailable to exert physiological effects in humans, further studies investigating the relationship between dosage and plasma concentration as well as studies determining the presence of diverse metabolites (such as methylated, glucuronidated, and sulfated flavan-3-ol derivatives as well as microbial metabolites of procyanidins such as valerolactone derivatives) in systemic circulation and/or organs and tissues are needed to fully elucidate the bioavailability of bioactive compounds from guarana.

3.2 | Toxicity

Bioactive compounds present in the composition of functional foods and herbal medicines can be foreign to the human body. Therefore, the products of their

biotransformation may lead to adverse events or toxic effects, highlighting the importance of studies on the toxicity of these compounds (Lapa et al., 2010).

Regarding guarana, in vivo studies using aqueous guarana extract in association with other plants have reported that these formulations have low toxicity and are safe in low dosages, even with prolonged consumption (de Mello et al., 2010; De Oliveira Campos et al., 2011; Espinola et al., 1997; Mattei et al., 1998; Oliveira et al., 2005). In an in vitro study, Santa Maria et al. (1998) demonstrated that an aqueous extract containing 10 mg/ml of guarana was not toxic to Chinese hamster ovary cells and bacterial cells. In another study, Antonelli-Ushirobira et al. (2010) observed possible toxicity in the liver of male rats that received 150−300 mg/kg of guarana for 90 days. Teixeira et al. (2021) investigated the safety of a supplement comprising guarana, selenium, and L-carnitine for human consumption. They observed that the administration of this supplement (concentration range: 0.04−2.1 mg/ml) did not induce mortality during leukocyte culture; instead, it downregulated *CASP3* and *CASP8*, reducing cell apoptosis. Moreover, the authors observed no toxic effects on red earthworms, concluding that this guarana-containing supplement may be safe for humans.

Guarana flavanols—the main chemical component in guarana seeds aside from caffeine—have been seldom investigated regarding their involvement in pharmacokinetics and pharmacodynamic interactions. Ventura et al. (2018) reported that the concurrent administration of lamotrigine (10 mg/kg), an antiepileptic drug, and guarana (821 mg/kg) negatively affected the rate of drug systemic exposure in rats. Therefore, pharmacological and toxicological studies are necessary to determine safe dosages and modes of administration. Nonetheless, the aforementioned studies indicate that guarana has low toxicologic potential.

3.3 | Antioxidant properties

Antioxidants are substances that scavenge free radicals and deactivate pro-oxidant metal ions owing to their ability to donate electrons to oxidized species (i.e., acting as a reducing agent) as well as to chelate transition metal ions (Oroian & Escriche, 2015). Antioxidant compounds also decrease the generation of free radicals through the inhibition of enzymes involved in reactive oxygen species production (Fu et al., 2011). Furthermore, they may play a role in the inhibition of lipid peroxidation (Durak et al., 2014).

Antioxidants are divided into two categories: enzymatic and non-enzymatic. Non-enzymatic antioxidants are organic molecules or mineral elements originated from endogenous (e.g., metabolic processes) or exogenous (e.g., diet) sources. Among several important dietary sources, such as berries, spices, and legumes (Carlsen et al., 2010), some studies have focused on the antioxidant activity of guarana due to its high content of bioactive compounds, demonstrating its antioxidant effects in vitro and in vivo (Mattei et al., 1998) (Figure 3).

The bioactive compounds found in guarana include methylxanthines, tannins, saponins, catechins, and proanthocyanidins, as well as residual concentrations of other compounds that are also associated with health benefits (Cadona et al., 2016).

According to Portella et al. (2013), guarana demonstrated high antioxidant activity in vitro—mainly at concentrations of 1 and 5 μg/ml—suppressing the production of conjugated dienes and thiobarbituric acid reactive substances, eliminating tryptophan, and showing high total reactive antioxidant potential. Similarly, guarana in different concentrations reduced luminol oxidation induced by peroxyl radical, with concentrations between 0.5 and 10 μg/ml displaying very strong inhibitory activities. Furthermore, Mattei et al. (1998) reported that guarana displayed antioxidant effects and inhibited lipid peroxidation in vitro even at low concentrations (1.2 μg/ml).

A study by Yonekura et al. (2016) showed that the consumption of 3 g of guarana powder (90 mg of catechin and 60 mg of epicatechin) by healthy individuals increased plasma oxygen radical absorbance capacity, indicating a reduction in damage caused by peroxyl radicals, while reducing ex vivo oxidation of LDL cholesterol (LDL-c) (Yonekura et al., 2016). Moreover, guarana catechins were bioavailable and reduced oxidative stress markers in these individuals through direct antioxidant action and increased regulation of antioxidant/detoxifying enzymes (e.g., superoxide dismutase, catalase, and glutathione peroxidase). Yonekura et al. (2016) also reported that the daily intake of guarana powder had acute and cumulative effects on the activity of glutathione peroxidase and catalase, which are phase II antioxidant enzymes that reduce peroxides to water molecules. In contrast, antioxidant status markers, such as reduction in LDL-c oxidation ex vivo and in lymphocytes DNA damage induced by hydrogen peroxide, only improved temporarily.

Boasquívis et al. (2018) showed that the protective effects of guarana extract (5, 10, or 50 mg/ml) are associated with its antioxidant activity and proteostasis modulation. Using a *C. elegans* model, they demonstrated that guarana increased life span and proteasome activity, reduced intracellular reactive oxygen species and accumulation of autophagosomes, and increased the expression of superoxide dismutase-3 and chaperonin HSP-16.2, suggesting that guarana may have therapeutic potential in age-related diseases. Similarly, Peixoto et al. (2017) studied the effect of guarana seed extract (100, 200, or 300 μg/ml) in

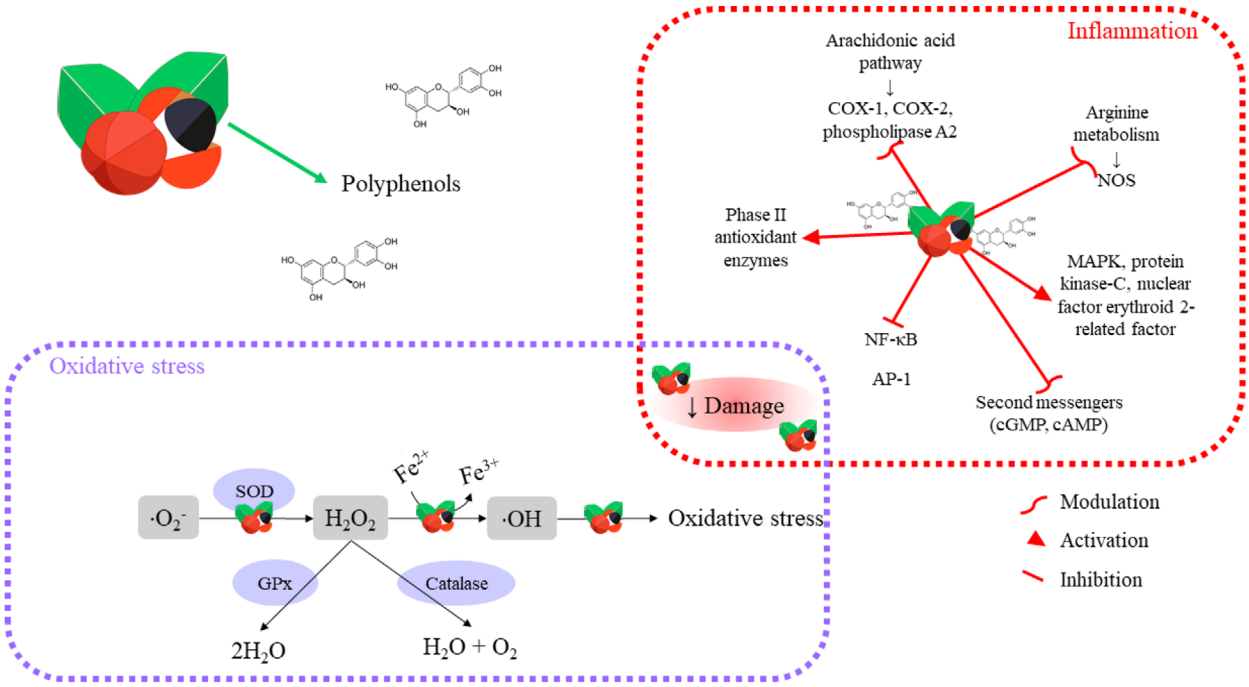

FIGURE 3 Bioactive compounds found in guarana are involved in several biological mechanisms. In oxidative stress, polyphenols from guarana can affect the formation of reactive oxygen species by modulating enzymes involved in their generation, chelating transition metal ions, and directly scavenging radical species. In inflammation, polyphenols from guarana may affect several different aspects of the inflammation process. SOD, superoxide dismutase; GPx, glutathione peroxidase; COX, cyclooxygenase; NOS, nitric oxide synthase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; AP-1; activator protein 1; cGMP, cyclic guanosine monophosphate; cAMP; cyclic adenosine monophosphate

a *C. elegans* model, reporting an increase in resistance to oxidative stress and life span, as well as a reduction in aging markers such as muscle function decline and polyQ40 aggregation.

Bulku et al. (2010) evaluated the safety of a dietary supplement containing guarana, sage, and oolong tea extracts (192 or 1344 mg/kg of supplement daily for 4 months) and investigated changes in antioxidant enzymes of the liver, kidneys, and heart; serum chemistry profile; and organ histopathology using an animal model with Fischer 344 rats. They observed an increase in total glutathione and glutathione peroxidase concentrations, as well as an increase in superoxide dismutase activity in the liver, kidney, and heart. Concomitantly, the levels of oxidative stress in the organs of rats that received the supplement were lower than those in the organs of rats in the control group. Similarly, Kleber Silveira et al. (2018) observed a decrease in the activity of antioxidant enzymes (catalase, sodium dismutase, and glutathione peroxidase) in the liver, kidney, and colon of Wistar rats that received 21 mg/kg of guarana seed powder without an increase in the expression of oxidative damage markers. Therefore, guarana seed powder improves redox status in vivo.

Acrolein is a toxic organic compound associated with oxidative damage in the brain and other organs, such as the liver. Individuals are exposed to acrolein in tobacco smoke, heated animal fat, vehicle exhaust, and certain foods (e.g., roasted coffee) (Agency for Toxic Substances and Disease Registry, 2007). Bittencourt et al. (2020) used a Wistar rat model to evaluate the protective effect of guarana extract against acrolein exposure. Animals treated with 150–350 mg/kg/day of guarana extract exposed to acrolein (2.5 mg/kg/day) displayed no hepatic or central nervous system damage, indicating that guarana can protect against acrolein-induced oxidative damage.

More recently, Machado et al. (2021) demonstrated that guarana extracts with and without methylxanthines displayed antioxidant activity measured by their ability to scavenge 2,2-diphenyl-1-picrylhydrazyl radicals (i.e., DPPH assay). In particular, the extract free of methylxanthines but rich in tannins had a half maximal inhibitory concentration of 5.88 μg/ml, demonstrating the antioxidant potential of guarana-derived tannins.

Furthermore, the use of natural antioxidants in the food industry has been receiving increased interest due to the notion that natural food ingredients are safer than synthetic ones (Yanishlieva & Marinova, 2001). Food manufacturers use antioxidants to stabilize food lipids, preventing product quality deterioration (Shahidi & Zhong, 2015). A study by Pateiro et al. (2018) revealed that

guarana seeds are very effective against color deterioration and lipid and protein oxidation in pork burgers, demonstrating the potential of guarana as a natural antioxidant in the food industry (Yanishlieva & Marinova, 2001). Findings from a study by de Carvalho et al. (2019) supported the use of guarana seed extract as a natural antioxidant in lamb patties. Apart from exhibiting antioxidant properties, the authors highlighted that the addition of guarana seed extract to the patties did not affect their sensorial properties.

Therefore, guarana has important and varied antioxidant properties that have potential to be explored in different areas of human health and in the procurement of natural food additives. Further studies are necessary to elucidate its mechanisms of action and confirm its antioxidant effects in humans.

3.4 | Anti-inflammatory properties

Inflammation is an intrinsic process of the body's immune defense. When inflammatory processes are sustained for a long period of time, inflammation becomes chronic. Several diseases are associated with chronic inflammation, including noncommunicable chronic diseases such as cardiovascular diseases, diabetes, cancer, and obesity. Collectively, these chronic diseases represented 74% of all deaths globally in 2019 (World Health Organization, 2020a).

Chronic inflammation is defined by the infiltration of macrophages, dendritic cells, and lymphocytes in tissues, which stimulates the production of inflammatory cytokines such as interleukin (IL)—including IL-1β, IL-6, and IL-8—tumor necrosis factor (TNF)-α, and interferon-γ, growth factors, and enzymes (Pahwa et al., 2021; Zhang & Tsao, 2016). Several risk factors are associated with an increased production of pro-inflammatory molecules and mediators, including age, smoking, stress, and dietary habits. Lifestyle interventions are effective in improving chronic inflammation, such as increasing the consumption of fruits, vegetables, and legumes while decreasing the consumption of saturated and trans fats and simple sugars. This effect is attributed to bioactive compounds ubiquitously found in these plant-based foods and their ability to modulate inflammatory processes (Pahwa et al., 2021).

Guarana has demonstrated potential anti-inflammatory properties. Ruchel et al. (2016) investigated the effects of guarana on hypercholesterolemia, a metabolic dysfunction characterized by high levels of blood LDL-c and associated with the development of inflammatory lesions. The administration of 50 mg/kg/day of guarana powder to hypercholesterolemic rats was associated with lower adenosine deaminase activity compared with those who received a normal diet, indicating that guarana contributed to minimizing the inflammatory process caused by the hypercholesterolemic diet.

Another study using an HFF-1 cell model demonstrated that the use of low-level laser therapy combined with guarana extract administration (1, 3, 5, 10, or 30 μg/ml) downregulated the expression of pro-inflammatory proteins and upregulated the expression of interleukin-10, demonstrating its anti-inflammatory effects and indicating that the use of guarana may improve the efficacy of this type of treatment (Maldaner et al., 2020).

Finally, a recent study using a methylxanthine-free and tannin-rich guarana extract reported that the administration of 90 μg/ml of extract to THP-1 cells activated by lipopolysaccharides inhibited TNF-α production by almost 84% while presenting no toxicity to these cells (Machado et al., 2021). Nonetheless, further studies on humans are necessary to elucidate and confirm the anti-inflammatory effects of guarana and its applicability in human health.

3.5 | Cardiovascular health and obesity

A study (Taddei et al., 2020) analyzing data from over 1100 population-based studies estimated that 3.7—4.2 million deaths worldwide in 2017 could be attributed to hyperlipidemia and the cardiovascular risk that it represents. Hyperlipidemia is a lipid metabolism dysfunction defined by high levels of serum LDL-c, total cholesterol, and triglycerides in affected individuals. This disorder represents a major risk factor for atherosclerosis, ischemic heart disease, and obesity. Conversely, obesity is defined as a metabolic disorder associated with adverse effects related to cardiovascular diseases (e.g., stroke), type 2 diabetes, cancer, gallbladder diseases, osteoarthritis, pulmonary diseases, and sleep apnea (Alonso-Castro et al., 2019; Bortolin et al., 2019; Ruchel et al., 2019). In less than 45 years, the worldwide obesity prevalence has increased three-fold; almost 700 million adults were obese in 2016 and 40 million children (5 years old or younger) were overweight or obese in 2019 (World Health Organization, 2020b).

Over the past years, the use of herbal products for weight loss has become a common practice. Among these, guarana seed powder is a popular nonprescription dietary herb supplement. Consumption of guarana powder has shown anti-obesity and cardioprotective effects, as well as hypolipemiant, anti-inflammatory, hypotensive, and antioxidant properties. These health benefits may prevent the development of chronic diseases caused by lipid profile changes. Several studies applying different experimental models have demonstrated these effects in animals and overweight or obese subjects using guarana alone or in combination with other medicinal plants (Alonso-Castro et al., 2019; Bortolin et al., 2019; Ruchel et al., 2019).

Several studies have demonstrated the positive effects of guarana consumption on heart disease over the past two decades. Ruchel et al. (2019) evaluated the effect of guarana powder in the purine metabolism and inflammatory profile in lymphocytes and serum of rats with Poloxamer-407-induced hyperlipidemia. They reported that guarana (12.5, 25, and 50 mg/kg/day) and caffeine (0.2 mg/kg/day) prevented a hyperlipidemia-induced increase in INF-c levels, halting the inflammatory process caused by lipotoxicity and promoting an anti-inflammatory response. These findings may be attributed to methylxanthines and flavanols present in guarana, which have well defined lipolytic effects.

In an adult male Wistar rat model, guarana powder (12.5, 25, and 50 mg/kg/day) consumption reduced total cholesterol and LDL-c levels similar to that of simvastatin, partially reduced hyperlipidemia-induced liver damage, prevented changes in acetylcholinesterase activity, and improved memory impairment related to hyperlipidemia (Ruchel et al., 2019). Furthermore, guarana powder contributed to inflammatory process reduction by decreasing ATP levels and increasing extracellular adenosine, as well as decreasing total cholesterol and LDL-c to basal levels (Ruchel et al., 2016).

Studies conducted with human subjects have also demonstrated the benefits of guarana consumption in lipid metabolism, oxidative stress, LDL-c oxidation, and metabolic disorders. When healthy overweight individuals completed a 15-day intervention with a daily intake of 3 g of guarana seed powder containing 90 mg of (+)-catechin and 60 mg of (−)-epicatechin, Yonekura et al. (2016) observed an improvement in LDL-c oxidation levels.

Portella et al. (2013) investigated the potential effects of guarana consumption in healthy older adults who habitually ingested guarana on serum oxidation and in vitro LDL-c oxidation. Isolated LDL-c samples were exposed to five different guarana concentrations (0.05, 0.1, 0.5, 1, and 5 μg/ml); after treatment, they demonstrated lower LDL-c oxidation, especially at concentrations of 1 and 5 μg/ml. The effect of guarana on LDL-c oxidation may partially explain its protective effects on cardiometabolic diseases.

Krewer et al. (2011) described the potential beneficial effects of habitual guarana consumption (≥2 times/week), including a lower prevalence of hypertension, obesity, and metabolic syndrome, as well as lower cholesterol (total and LDL-c) and advanced oxidation protein product levels. The aforementioned observational study evaluated the associations between metabolic disorders (obesity, hypertension, type 2 diabetes, and dyslipidemia), anthropometric parameters, biochemical biomarkers of lipid, glucose, and oxidative metabolism, and the habitual ingestion of guarana by older adults of the Amazon region of Maués, Brazil. They identified a significant association between habitual guarana consumption and lower advanced oxidative protein product levels in both men and women and lower cholesterol and LDL-c levels in women.

The effects of guarana consumption on LDL-c and serum oxidation are associated with its bioactive compounds, such as catechins and methylxanthines. However, the underlying mechanisms of action remain unclear. Polyphenols from guarana may incorporate into LDL-c, rendering the serum of individuals less susceptible to oxidation (Krewer et al., 2011; Portella et al., 2013). Nonetheless, guarana powder may be a promising supplement for patients with hyperlipidemia.

Anti-obesity mechanisms of plant extracts and isolated phytochemicals have been widely explored. These mechanisms include appetite reduction, modulation of lipid absorption and metabolism, thermogenesis, and changes in the gut microbiota. In particular, studies have indicated that gut microbiota composition may be associated with the development of obesity and obesity-associated disorders (Bortolin et al., 2019).

Animal and cellular models were conducted to assess the effectiveness of guarana seed powder in weight loss, metabolic and inflammatory parameters, lipid metabolism, obesity-related diseases, and adipogenesis, as well as its possible mechanisms of action. Bortolin et al. (2019) reported that guarana seed powder supplementation (0.5% [w/w] of total diet) in male Wistar rats for 18 weeks prevented weight gain, insulin resistance acquisition, and adipokine dysregulation while inducing brown adipose tissue expansion. Moreover, an 8-week guarana supplementation (1 g/kg) in mice led to an increase in energetic metabolism (energy expenditure) and stimulated mitochondrial biogenesis, contributing to weight and adipose tissue accumulation control, even when associated with a high-fat diet (Lima et al., 2018).

Guarana treatment (1 g of guarana powder/kg of weight) in Swiss female mice and their offspring in different phases of life ameliorated the effect of maternal obesity through weight reduction and/or weight gain prevention, adipose tissue depot reduction, increased energy expenditure, and increased gene expression and concentration levels of cytokine and inflammatory markers, such as leptin, IL-6, TNF-α, and MCP-1 (Lima et al., 2019).

To examine the effects of guarana on tissue lipid metabolism, Lima et al. (2005) supplemented sedentary and trained male adult Wistar rats with different doses of guarana extract (0.130 g/kg and 0.325 g/kg) for 14 days. The highest dose of guarana supplementation decreased total food intake and induced changes in lipid metabolism.

Guarana has anti-adipogenic potential due to its ability to modulate miRNAs and genes related to this process in a 3T3L1 cell model (150 μg/ml). Guarana prevented triacylglycerol accumulation in a dose-dependent

manner and promoted the up-regulation of anti-adipogenic genes (*Wnt10b*, *Wnt3a*, *Wnt1*, *Gata3*, and *Dlk1*) and down-regulation of pro-adipogenic genes (*Cebpα*, *Pparγ*, and *Creb1*) (Lima et al., 2017).

Most studies with human subjects that investigated the effects of guarana on weight loss and other anti-obesity effects used guarana in combination with other substances. Alkhatib et al. (2015) believe that the thermogenic effect of multi-ingredient mixtures—such as those containing caffeine, guarana, ephedrine, capsaicin, and green tea extracts—act synergistically to increase fatty acid oxidation, energy expenditure, resting metabolic rate, hemodynamics, and sympathetic function.

Harrold et al. (2013) and Andersen and Fogh (2001) conducted studies with a patented mixed herbal preparation containing 112 mg of yerba maté (leaves of *Ilex paraguayensis*), 95 mg of guarana (seeds of *Paullinia cupana*), and 36 mg of damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) to verify the impact of its consumption on appetite and food intake, as well as on gastric emptying, 10- and 45-day weight loss, and 12-month weight maintenance of healthy normo-weight and overweight volunteers. Those who consumed the herbal preparation experienced significant reductions in food intake, energy intake, hunger, and desire to eat. Furthermore, the consumption of the herbal preparation in capsule form significantly delayed gastric emptying, reduced the time to perceived gastric fullness, and induced significant weight loss over 10 and 45 days in overweight patients. Over the 12 months of follow-up, the volunteers maintained a constant weight, suggesting that this herbal preparation may be used in weight maintenance strategies.

Other human studies also evaluated the effects of supplements containing guarana in combination with other compounds (green tea extract, black tea, extracts of bitter orange, ginger extract, rutin, caffeine, cayenne pepper, Ma Huang, vitamin C, etc.) on weight loss and other anti-obesity effects. Alkhatib et al. (2015) reported that the consumption of a commercially available supplement containing, among other ingredients, guarana seed extract increased fatty acid oxidation during exercise and satiety while decreasing the rate of perceived exertion. Opala et al. (2006) reported a significant change in body composition improvement index and decrease in body fat measured with the 4-skinfold method. Bérubé-Parent et al. (2005) reported an increase in 24-h energy expenditure, while Roberts et al. (2005) reported an increase in metabolic rate. Finally, Boozer et al. (2001) reported weight and body fat loss; waist and hip circumference reduction; and triglyceride, alanine aminotransferase, and aspartate aminotransferase levels decrease. These authors used guarana as a source of methylxanthines and attributed its effects to guarana's high caffeine content.

In an in vitro study, Silva, Thomazini, Holkem et al. (2019) demonstrated the anti-obesity potential of guarana seed powder through its high capacity to inhibit lipase activity, which was comparable to that of orlistat. These results suggest that guarana seed powder may be an alternative to anti-obesity drugs.

Although guarana displays a potential for application in cardiovascular health and weight management, future studies should focus on guarana alone to elucidate its mechanisms of action. In addition, further human studies are needed to confirm the effects of guarana consumption observed in animal models.

3.6 | Diabetes

According to data from the International Diabetes Federation, the global diabetes prevalence in 2019 was 9.3% (463 million people); this number is expected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al., 2019). Diabetes prevention and control require management of blood glucose levels, which can be achieved through diet modification strategies (Roglic & World Health Organization, 2016).

Studies have shown that some dietary polyphenols exhibit anti-diabetic properties (Hanhineva et al., 2010; Kim et al., 2016). Recently, studies have indicated an association between consumption of polyphenols and a decrease in the risk of developing type 2 diabetes. Rienks et al. (2018) conducted a systematic review to summarize the evidence regarding polyphenol exposure in association with type 2 diabetes incidence.

After analyzing 28 meta-analyses, an association between polyphenol intake and reduced risk of type 2 diabetes was observed for total polyphenols (hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.34−0.93), total flavonoids (HR: 0.88; 95% CI: 0.81−0.96), flavan-3-ols (HR: 0.89; 95% CI: 0.81−0.99), and catechins (HR: 0.86; 95% CI: 0.75−0.97) intake. Regarding single compounds, the dietary intake of catechin was significantly inversely associated with type 2 diabetes incidence (Rienks et al., 2018).

As mentioned in Section 2, guarana is a source of polyphenols such as catechin, epicatechin, and proanthocyanidins (Schimpl et al., 2013; Yonekura et al., 2016). Dietary polyphenols may inhibit α-amylase and α-glucosidase, inhibit glucose absorption in the intestine by sodium-dependent glucose transporter 1, stimulate insulin secretion, and reduce hepatic glucose output. Polyphenols may also enhance insulin-dependent glucose uptake, activate 5′ adenosine monophosphate-activated protein kinase, modify the microbiome, and display anti-inflammatory effects (Kim et al., 2016). However, to the

best of our knowledge, only two studies about the role of polyphenols from guarana on glucose metabolism have been published to date.

Silva et al. (2018) evaluated the potential inhibitory activity of guarana extracts after in vitro digestion on α-amylase and α-glucosidase. They demonstrated that polyphenols from guarana inhibited α-glucosidase and α-amylase activities. In this case, these effects were attributed to soluble polyphenols such as catechin and its isomer epicatechin, and procyanidins B1 and B2. Subsequently, da Costa Pinaffi et al. (2020) investigated the contribution of insoluble phenolic compounds occurring in guarana powder, such as dimeric and oligomeric proanthocyanidins, in α-glucosidase inhibition. They further demonstrated that both soluble and insoluble-bound polyphenols of guarana inhibited α-glucosidase activity in a dose-dependent manner in vitro. Moreover, the concentration of phenolic compounds released from the insoluble-bound fraction required to inhibit 50% of α-glucosidase activity was 5.8-fold lower than that of the soluble counterpart.

The inhibitory activity of phenolic extracts and individual polyphenols is highly dependent on phenolic composition and the molecular structure of these compounds. Thus, to increase the inhibitory efficiency of phenolic extracts, the main active compounds and/or fractions involved in this process must be identified (Sun & Miao, 2020). The mechanism of action of polyphenols from guarana is not fully understood yet.

Raimundo et al. (2020) investigated the impact of polyphenol consumption on diabetes biomarkers (blood glucose, glycated hemoglobin, insulin, pro-insulin, insulin resistance, IAPP/amylin, pro-IAPP/pro-amylin, glucagon, and C-peptide). They indicated that dietary polyphenols may have a beneficial effect on blood glucose levels of individuals with diabetes and those at risk of developing the disease. The effects of phenolic subgroups (e.g., mixture of isoflavones, flavanols, and resveratrol) on blood glucose levels did not differ significantly. Furthermore, the decrease in hyperglycemia was significantly more pronounced in individuals with diabetes receiving antidiabetic medication compared with those not receiving medication. This result suggests a potential synergistic effect between polyphenol supplementation and diabetes treatment medication, opening new venues for exploring the use of polyphenol-rich diets as co-adjuvants in diabetes management strategies (Raimundo et al., 2020).

Starch digestion can be hindered in vivo by dietary polyphenols, potentially due to their inhibitory activities against α-amylase and α-glucosidase in the small intestine. In addition, alleviation of postprandial hyperglycemia by polyphenols may result from both inhibited starch digestion and influenced glucose transport (Sun & Miao, 2020). Thus, future studies on guarana and diabetes should evaluate the effects of polyphenols on glucose transport through the expression of glucose transporters—including SGLT1, GLUT2, and GLUT4—in tissue cells.

3.7 | Cancer

The International Agency for Research on Cancer estimates that 19.3 million new cancer cases and 10.0 million cancer-related death occurred worldwide in 2020. In another 20 years, this burden is projected to increase by almost 50% (Sung et al., 2021). Cancer comprises several diseases originated from abnormal genetic expression. Considered a noncommunicable disease, it may affect any human body cell or tissue at any age, although it is more common in adults and older people. Cancer displays distinctive characteristics that reflect intrinsic aspects of cells and tumors, such as dysregulated cell proliferation, faulty cell death mechanisms, and distant metastasis (Rivenbark & Coleman, 2014). Cancer can be treated using surgical procedures, chemotherapy, and/or radiotherapy based on its clinical stage and type (Martins et al., 2017). Many treatments cause adverse reactions and side effects—such as fatigue, anorexia/cachexia, and sleep disturbances—as a consequence of damaging normal cells along with the targeted cancer cells (Harorani et al., 2020). In this scenario, the use of guarana in adjuvant therapy or in the management of side effects has attracted the interest of the scientific community.

In vitro and in vivo studies have indicated potential pharmacological applications of guarana extract in human health and cancer, demonstrating its chemo-preventative, antitumor, antimutagenic, and anticarcinogenic effects (Fukumasu, Avanzo, Heidor, et al., 2006; Fukumasu et al., 2011). These effects are strongly associated with the main bioactive compounds of guarana, namely polyphenols and caffeine, that can directly or indirectly modulate the expression of genes involved in carcinogenesis and in cancer cell growth inhibition (Cadona et al., 2017; Dabulici et al., 2020; Fukumasu, da Silva, Avanzo, et al., 2006).

Mice treated with aqueous guarana extract (2 mg/g) had reduced DNA damage in hepatic cells, demonstrating an anticarcinogenic effect (Fukumasu, Avanzo, Heidor, et al., 2006). Similarly, young mice treated with 0.1, 1, or 2 mg of guarana/g of body weight exhibited a dose-dependent lower incidence of macroscopic hepatic lesions, as well as a lower PCNA expression, compared with those who did not receive guarana (Fukumasu, da Silva, Avanzo, et al., 2006). In a mice metastasis model, the cancer cells of animals treated with 2 mg of guarana/g of body weight displayed reduced proliferation and increased apoptosis, resulting in a reduction in tumor size (Fukumasu et al., 2008).

Furthermore, mice with Ehrlich ascites carcinoma who received guarana (100, 1000, or 2000 mg/kg) lived longer and exhibited a reduction in ascites without any side or toxic effects, demonstrating antiproliferative properties attributed to a reduction in cyclin D1 expression and cell cycle interruption (Fukumasu et al., 2011).

Some of guarana's therapeutic effects have been attributed to its caffeine content, suggesting that the combination of caffeine and anticancer drugs may represent an efficient strategy for cancer treatment. Caffeine inhibits anticancer drugs intracellular efflux, halts cell cycle progression, induces cancer cell apoptosis, promotes anticancer immune response, and reduces angiogenesis and metastasis. Specifically, caffeine modulates apoptosis in a dose-dependent manner through the depletion of glutathione and reactive oxygen species, increase in the expression of proapoptotic agents (c-Fos c-Myc), decrease in the expression of anti-apoptotic agents (Bcl-2, c-N-Ras), and inhibition of the PI3K/Akt/mTOR/p70S6K pathway (Tej & Nayak, 2018).

In cancer, many metabolic pathways are dysregulated, intracellular levels of reactive oxygen species are exacerbated, and the expression of genes related to survival, proliferation, and cell death is increased, resulting in aggressive diseases. Guarana in varied concentrations (0.1–100 mg/ml) can affect these cancer-related alterations, halting tumor growth through the reduction in the expression of MAPK (p-p39, p-HSP27), mTORC1 (p-S6K), and mTORC2 (p-AKT) proteins in cell models. For instance, the expression of mTORC1 was inhibited in breast (MCF-7) and colorectal cancer cells (HT-29) after a 72-h treatment with 100 μg/ml of guarana extract. This effect is similar to that of oxaliplatin, an important drug for colorectal cancer treatment. Moreover, when the drug and guarana extract are administered concomitantly, the anticancer effect is potentialized. In contrast, in the same concentrations, guarana does not promote impactful cellular alterations in normal cells (PBMC, HFF-1) (Cadona et al., 2016, 2017).

The reduction in cell viability and proliferation in breast cancer related to the use of drugs such as cyclophosphamide, doxorubicin, 5-fluoracil, paclitaxel, vinorelbine, gemcitabine, and methotrexate is a similar effect to that observed with the use of low concentrations of guarana (1, 5, and 10 μg/ml) in MCF-7 cells (Hertz et al., 2015). Therefore, guarana may have important applications in cancer treatment considering its selective and dose- and time-dependent effects. Furthermore, the development of alternative therapies that incur less cytotoxic effects on healthy cells is important to lower the incidence of adverse effects in cancer patients, ultimately improving their quality of life (Cadona et al., 2017; Machado et al., 2015). Further in vivo studies and clinical trials are necessary to elucidate and confirm the anticancer effects of guarana in humans.

The use of caffeinated oral supplements (e.g., pills, capsules, and dry and liquid extracts) for side effects management in cancer patients has demonstrated improvement in symptoms and therapy adverse events, quality of life, physical and emotional wellbeing, survival, and mortality. Despite the varied quality of evidence, some findings support that guarana consumption may alleviate fatigue in patients with breast cancer (Leggett et al., 2015).

Cancer-related fatigue is a common side effect of chemoradiotherapy, presenting as a persistent and subjective physical, emotional, and/or cognitive exhaustion and negatively affecting the patient's general state and quality of life. Moreover, this fatigue is associated with other symptoms such as depression, lethargy, pain, and sleep disturbances. The stimulating properties of guarana have led to its evaluation as a potential treatment for cancer side effects.

A clinical study that administered 75 mg/day of guarana to breast cancer patients undergoing radiotherapy did not observe improvements in post-treatment depression and fatigue (Miranda et al., 2009). In contrast, in another clinical study, De Oliveira Campos et al. (2011) administered 50 mg of guarana twice daily for 21 days after the first cycle of chemotherapy to breast cancer patients with progressive fatigue. In this randomized study, patients were evaluated at three time points (days 1, 21, and 49) and the findings indicated that guarana may represent a non-toxic, cheap, and efficient alternative treatment for acute fatigue, sleep disturbances, anxiety, and depression, effects mostly attributed to its stimulating effects.

Marcon et al. (2011) developed a guarana extract that demonstrated great anti-inflammatory potential in vivo, reducing the levels of IL-6 and TNF-α in mice. However, the administration of this extract (37.5 mg twice daily) in a clinical trial to patients with different solid tumors undergoing chemotherapy resulted in questionable antifatigue effects (Del Giglio et al., 2013). In a subsequent clinical study, they utilized a lower dose of guarana extract (7.5 and 12.5 mg) with improved effects. The presence of magnesium silicate in the excipient may have interfered in these results; thus, new studies utilizing an excipient free of magnesium silicate are necessary to confirm the antifatigue effects of this purified guarana extract (Sette et al., 2018).

Another clinical study administered 50 mg of guarana extract twice daily to patients with head and neck carcinoma undergoing chemoradiotherapy and presenting with persistent fatigue. They investigated general aspects of quality of life, pain, food intake, deglutition, cough, and weight loss, observing no beneficial effect for this population (Martins et al., 2017). The use of guarana as a nonpharmaceutical alternative therapy for cancer-related fatigue

seems positive, but of short duration. Fatigue has a complex and non-uniform physiopathology, which may complicate its treatment (De Waele & Van Belle, 2010).

Anorexia/cachexia represents another common adverse effect in cancer patients. In a clinical study, Palma et al. (2016) observed that patients with advanced cancer (primary neoplasm in the lung, breast, urinary tract, and gynecologic and gastrointestinal systems) who received 50 mg of dry guarana extract twice daily for 4 weeks displayed improved appetite, reduced drowsiness, and stable weight. The gonadotoxic effects of cancer treatments may cause hot flashes in patients with breast cancer, negatively impacting their quality of life. In another clinical study, the oral administration of 50 mg of dry guarana extracts twice daily for 6 weeks resulted in a significant reduction in the intensity of hot flashes without any toxic effects (Oliveira et al., 2013).

Few studies have investigated the use of guarana in cancer therapy or prevention. Most studies have focused on the use of guarana to treat symptoms of the disease and side effects of chemo- and radiotherapy, especially in women with breast cancer. Although many studies have reported positive health effects regarding the use of isolated and purified bioactive compounds, the investigation of these compounds in their food matrixes is important because they may represent an easily accessible alternative to conventional therapies. Furthermore, future studies should focus on different populations and types of cancer considering that physio-pathological mechanisms vary according to the cell or tissue affected, as well as on elucidating the pathways and biomarkers that are modified upon guarana administration.

3.8 | Cognitive function

Cognition comprises the capacity of learning, maintaining healthy executive functions, storing and processing information (memory), and using this properly stored information, as well as processes such as processing speed, attention, and concentration (Pan et al., 2019); language; decision-making (World Health Organization, 2020c); and problem-solving. Several conditions, of which many are associated with aging, negatively affect these processes, compromising the cognition (Morley et al., 2015). The aging process naturally involves varied degrees of cognitive decline, which can result in mild cognitive impairment and dementia (Morley, 2018). While mild cognitive impairment is part of the normal cognitive changes that occur in dementia (Sanford, 2017), cognitive dysfunction is a symptomatic domain identified in many mental disorders such as major depressive disorder, which contributes significantly to occupational and functional disability (Pan et al., 2019). Furthermore, functional cognitive disorders are a group of overlapping conditions in which cognitive symptoms are present but are inconsistently experienced and unrelated to systemic or brain diseases (McWhirter et al., 2020); they are neurodegenerative in nature rather than subjective or functional (Hamilton et al., 2020). Approximately 25% of patients who visit memory clinics receive diagnoses that may indicate the presence of functional cognitive disorders (McWhirter et al., 2020), with a prevalence of 3%–19% among those older than 65 years old (Gauthier et al., 2006).

The first human studies on cognition using guarana were conducted with 500 mg of guarana capsules twice daily in young and older individuals. Although the intervention had no significant impact in cognitive performance (Galduróz & Carlini, 1994), it improved visual spatial organization (Galduróz & Carlini, 1996). The effects of guarana consumption on the cognitive function of young individuals may be masked by their already good cognitive health (Galduróz & Carlini, 1994) or lessened by the lack of long-term consumption.

In animal model studies, adult Wistar rats consumed 2–60 mg/kg/day of guarana for approximately 30 days. The animals demonstrated an improved cognitive performance (Otobone et al., 2005) and memory (Ruchel et al., 2019), and the chronic supplementation presented low toxicity (Otobone et al., 2005). Furthermore, Wistar rats that consumed 21 mg/kg/day of guarana extract for 180 days had an increase in glutathione peroxidase levels and a reduction in oxidative stress-related damage in the hippocampus (Mingori et al., 2017). Thus, the consumption of guarana may have protective effects for the brain and promote improvement in cognition.

In human studies, encapsulated guarana powder doses of 75 mg/day acutely improved attention, memory, and speed of performance (Kennedy et al., 2004); doses of 35–75 mg/day for 5 days resulted in improved cognitive performance; and a dose of 300 mg/day for the same period improved alertness, albeit with a lesser effect on cognition than that observed with lower doses (Kennedy et al., 2004). Doses greater than 300 mg/day showed no significant effect (Silvestrini et al., 2013). Conversely, the consumption of guarana alone and in a drink with vitamins and ginseng before and after exercise resulted in improved cognitive performance with a dose of 37.5 mg/day (Pomportes et al., 2017), and improved information processing with a dose of 300 mg/day (Pomportes et al., 2019).

The consumption of guarana associated with other dietary supplements, such as creatinine, also demonstrated positive effects on cognition. Furthermore, 1500 mg of guarana powder before physical exercise showed an improvement in cognition, mainly related to decision-making (Pomportes et al., 2015), while 222.2 mg of guarana

powder in combination with a complex of multivitamins and minerals improved cognitive performance (Kennedy et al., 2008; Veasey et al., 2015; White et al., 2017), memory, attention (Scholey et al., 2013), and mental fatigue (Kennedy et al., 2008). The use of multivitamins and minerals with or without guarana powder improves brain activity and cognitive performance in adults (McWhirter et al., 2020; Morley, 2018). However, the cognitive improvement related to decision-making and reaction time (processing speed/response) was observed after the addition of 300 mg of guarana to the multivitamins and minerals (Pomportes et al., 2015).

The effects of guarana powder are greater than those of caffeine alone. The presence of other bioactive compounds, such as tannins (Galduróz & Carlini, 1994, 1996), theobromine, and catechins (Mingori et al., 2017; Ruchel et al., 2017), may contribute to this improvement despite the composition of guarana containing high levels of caffeine (Otobone et al., 2005; Pomportes et al., 2015). Therefore, improvements in cognitive performance are a result of improvements in memory, attention, decision-making, and processing speed/response originating from complex synergistic effects between the distinct bioactive compounds present in guarana. Further human studies should focus on cognitive impairment.

3.9 | Depression

According to the Pan American Health Organization, depression is a mental disorder characterized by persistent sadness and a loss of interest in activities that are normally pleasurable (Pan American Health Organization, 2017). This common disorder can affect any individual, compromises their ability to function in several aspects (ability to work, sleep, study, eat, among others), and is related to biological, genetic, psychological, and environmental factors. More than 300 million people experience depression and approximately 800 thousand people die by suicide each year worldwide, with depression as one of the main causes of such deaths (Pan American Health Organization, n.d.).

Only a few studies have focused on the effects of guarana consumption on depression. These studies have used animal models and doses of 25.5–200 mg/kg/day, observing effects similar to antidepressants after tests to induce depressive behaviors, such as tail suspension and forced swimming. These effects included reduction in immobility (Campos et al., 2005; Otobone et al., 2007), inhibition of norepinephrine, serotonin, and dopamine reuptake, and increase in the release of these neurotransmitters (Campos et al., 2004), contributing positively to depression and depressive symptoms.

Clinical studies on the relationship between guarana and depression focused on individuals with tumors and/or undergoing chemotherapy. These individuals presented depressive symptoms but were not clinically depressed. These studies used doses between 50.0 and 100 mg/day without significant changes in depressive symptoms (da Costa De Oliveira Campos et al., 2011; Del Giglio et al., 2013; Miranda et al., 2008, 2009). Nonetheless, it is important to emphasize that the individuals who participated in these studies were not depressed nor had biochemical markers related to depression analyzed. Therefore, studies involving clinically depressed individuals and the analysis of important biomarkers are needed.

Individuals with depression have high- or low-grade chronic inflammation (Osimo et al., 2019). Polyphenols, especially flavonoids, are associated with a reduction in depressive symptoms (Godos et al., 2018) and inflammation (Mingori et al., 2017; Trebatická & ɯuračková, 2015). Flavan-3-ols (e.g., catechin and epicatechin) and proanthocyanidins contribute to mental health by reducing monoamine oxidase activity, attenuating inflammation, and increasing brain-derived neurotrophic factor expression (Khalatbary & Khademi, 2020; Naoi et al., 2019; Stringer et al., 2015; Xu et al., 2010). Thus, polyphenols play a beneficial role in depression through their anti-inflammatory potential.

As aforementioned, animal studies on depression using guarana have shown potential beneficial effects. In addition, studies with flavanols and proanthocyanidins, which represent the main polyphenols present in guarana, have associated their consumption with positive effects on depression. Therefore, future human studies must focus on the effects of guarana on depressive symptoms, risk of depression, possible biochemical markers (inflammatory markers such as cytokines; monoamines such as serotonin and dopamine; and neuroprotective agents such as brain-derived neurotrophic factor), and as adjuvant therapy in depression treatment (e.g., medication dose reduction and condition improvement duration).

4 | FINAL REMARKS

Selected clinical studies on guarana are organized in Table 3. No adverse events were reported during the interventions conducted by Yonekura et al. (2016) and Silvestrini et al. (2013). Moreover, no grade 3 or 4 toxicities were reported by Palma et al. (2016), while Sette et al. (2018) reported that 3.5% of patients who received guarana extract experienced grade 3–4 insomnia and 9–14% reported grades 1–2 anxiety, tachycardia, mucositis, and gastric pain. Similarly, Oliveira et al. (2013) reported that the

TABLE 3 Selected clinical studies on guarana published in the past 10 years

Study design	Intervention	Main findings	Reference
Interventional study	Adult athletes received a single-dose drink containing 300 mg of guarana	Improvement in effort perception and information processing	Pomportes et al. (2019)
Interventional study	Women with breast cancer received 7.5 or 12.5 mg of guarana extract twice daily for 3 weeks	Improvement in treatment-related fatigue	Sette et al. (2018)
Interventional study	Adults received a single-dose drink containing 37.5 mg of guarana	Improvement in cognitive performance	Pomportes et al. (2017)
Interventional study	Adults received a single-dose multivitamin containing 222.2 mg of guarana powder	Improvement in cognitive performance	White et al. (2017)
Interventional study	Adults with advanced cancer received 50 mg of guarana extract twice daily for 4 weeks	Improvement in appetite and weight maintenance	Palma et al. (2016)
Interventional study	Clinically healthy individuals received 3 g of guarana seed powder for 15 days	Reduction in oxidative stress markers	Yonekura et al. (2016)
Interventional study	Healthy active participants received a multi-ingredient product containing 100 mg of guarana seed extract for 2 weeks	Acute effect on exercise-related fat loss improvement	Alkhatib et al. (2015)
Interventional study	Adult athletes received a single-dose supplement containing 1.5 g of guarana	Improvement in cognitive performance related to decision-making	Pomportes et al. (2015)
Interventional study	Adult men received a single-dose multivitamin containing 222.2 mg of guarana powder	Improvement in cognitive performance	Veasey et al. (2015)
Interventional study	Adults with solid tumors received 37.5 mg of guarana twice daily for 42 days	No significant effect on depressive symptoms	Del Giglio et al. (2013)
Interventional study	Normo- to overweight women consumed an herb extract formulation containing 95 mg of guarana 15 min before breakfast and lunch	Acute effect on caloric intake and meal duration	Harrold et al. (2013)
Interventional study	Breast cancer survivors received 50 mg of guarana extract twice daily for 6 weeks	Improvement in the severity of hot flashes	Oliveira et al. (2013)
Observational study	N/A	Healthy older adults who consumed guarana routinely had lower levels of LDL oxidation	Portella et al. (2013)
Interventional study	Adults received a single-dose multivitamin containing 222.2 mg of guarana powder	Improvement in cognitive performance, contentment self-assessment, attention, and memory	Scholey et al. (2013)
Interventional study	Adults received 360 mg of guarana thrice daily for 5 days	No significant effect on cognitive function	Silvestrini et al. (2013)
Interventional study	Women with breast cancer received 50 mg of guarana twice daily for 21 days	Improvement in treatment-related fatigue	De Oliveira Campos et al. (2011)
Observational study	N/A	Older adults who consumed guarana routinely had lower risk for obesity, hypertension, and metabolic syndrome	Krewer et al. (2011)

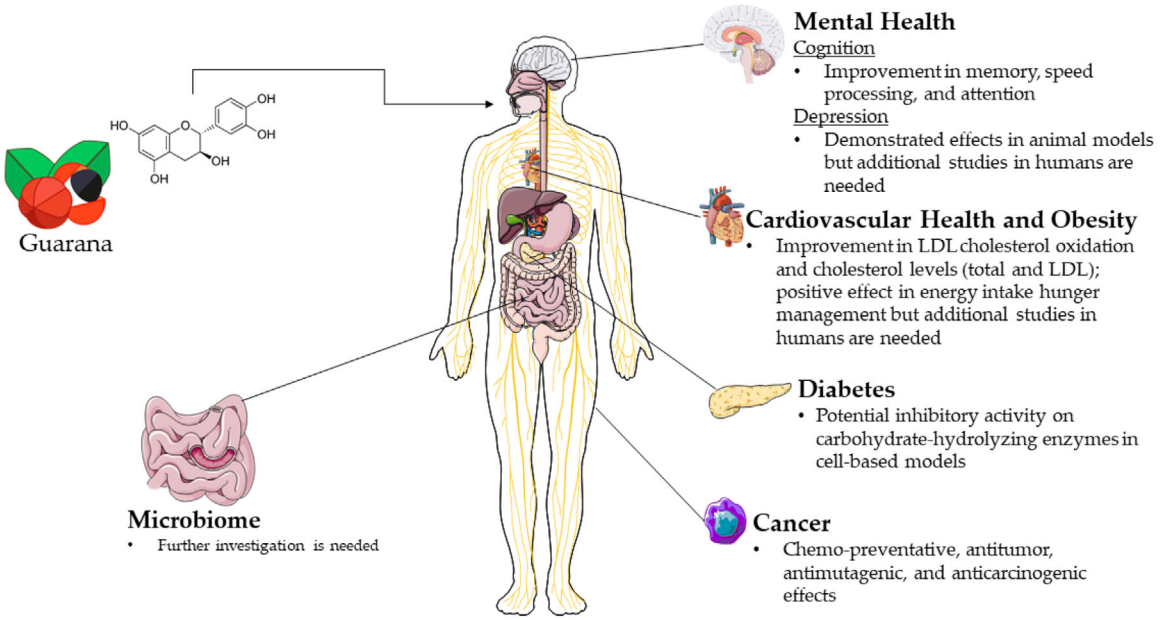

FIGURE 4 Illustration summarizing the diverse applications of guarana on human health

most common adverse events experienced by patients who received guarana extract were insomnia, nausea, headache, sweating, anxiety, and constipation; nonetheless, these adverse events were mild and did not result in early discontinuation. Del Giglio et al. (2013) observed that the adverse events (including insomnia, dizziness, and anxiety) occurring during their intervention were more frequent and intense than those observed during a previous study conducted by the same group (De Oliveira Campos et al., 2011), which they attributed to a higher guarana dosage. Finally, the PlantLIBRA project analyzed the adverse effects associated with the consumption of plant food supplements. Consumers self-reported experiencing insomnia, tachycardia, dizziness, constipation, and diarrhea after consuming supplements containing guarana (Colombo et al., 2020). As described, the most common adverse events reported by intervention studies are related to those associated with overconsumption of caffeine (U.S. Food and Drug Administration, 2018). Therefore, designing studies considering these aspects would result in more realistic and applicable findings, as well as possibly fewer or less intense adverse events.

This study summarizes the diverse applications of guarana on human health (Figure 4). For a long time, studies focused on guarana health effects associated with its caffeine content. In fact, caffeine is a stimulant affecting the central nervous system and cognition parameters such as long-term memory (de Mejia & Ramirez-Mares, 2014). Accordingly, cognitive and stimulatory effects associated with guarana consumption are widely attributed to its caffeine content. Haskell et al. (2007) demonstrated that guarana supplementation (37.5 and 75 mg of guarana containing 4.5 and 9 mg of caffeine, respectively) acutely improved cognitive and mood parameters in healthy volunteers. Interestingly, the authors pointed out that the caffeine content of these doses was below the psychoactive threshold for caffeine, rendering it unlikely that caffeine alone was responsible for the effects observed in the study. More recently, Schuster and Mitchell (2019) reported that interactions between polyphenols and caffeine in foods such as coffee, chocolate, and teas positively affect the cognitive effects of caffeine while decreasing its negative neuropsychological side effects. In the case of guarana, caffeine is commonly associated with tannins and other compounds, which may delay caffeine absorption and result in a long-lasting, continuous stimulatory effect (Schimpl et al., 2013). This and other synergistic effects may contribute to the varied health effects associated with guarana consumption.

Although more human studies are necessary to effectively translate the use of guarana in clinical practice, non-clinical studies such as in vitro, cell-based, and animal studies remain pertinent for the elucidation of specific mechanisms as well as toxicological and pharmacological aspects. Before application in clinical studies, several characteristics of the potential compound must be determined, including pharmacokinetics, absorption, metabolism, genotoxicity, mutagenicity, among others (Andrade et al., 2016). For this reason, conducting concurrent and complementary non-clinical and clinical studies is indispensable for furthering our understanding of such a complex Amazon plant.

5 | RECOMMENDATIONS AND CONCLUSION

Future efforts should be focused on designing and conducting clinical trials to confirm and elucidate several of the possible health effects reported in cell and animal models. Furthermore, guarana dosages used in animal and cell models should be defined based on quantities that would be applicable for humans. For instance, some animal models use the equivalent of 7–14 g of guarana for an average adult (70 kg). This dose would exceed the amount of caffeine that the U.S. Food and Drug Administration considers safe for a healthy adult (U.S. Food and Drug Administration, 2018).

The elucidation of mechanisms is another aspect that deserves attention. Understanding the underlying mechanisms through which guarana and its components exert effects of biological importance is important to better define and maximize its applicability. Thus, future studies should focus not only on the magnitude of effects, but also on determining what pathways, structure-activity relationships, and mechanisms are involved. Furthermore, when considering the use of guarana as adjuvant or complementary therapy for diseases such as cancer, diabetes, depression, and hyperlipidemia, future studies should investigate possible pharmacological interactions between traditional drugs and guarana components. These interactions may be beneficial, potentializing the action of an active component, or detrimental, rendering a drug less effective or causing unexpected side effects. Therefore, elucidating pharmacological interactions is paramount for safely and effectively applying guarana in the treatment of human diseases.

Regarding studies on cognition, most studies used guarana in combination with other compounds. Thus, in the future, studies should exclusively use guarana to better understand how it may affect cognition, including determining dose ranges and therapy duration for future clinical practice recommendations. In addition, although older adults represent a population of interest for studies on cognitive health, cognitive disorders affect individuals at any stage of life. Therefore, further studies should consider populations with a given cognitive disorder besides populations in a certain age range.

While findings of cellular and animal model studies using guarana indicate promising effects, those of studies with humans remain somewhat inconsistent. This is partly expected because human studies focus on distinct diseases with different etiologies and the number of studies on a specific disease remains insufficient for consolidating and translating their results into clinical practice recommendations. Moreover, methodologies vary significantly between studies (dose, intervention duration, guarana powder, or extract administration, among other aspects). Therefore, we recommend that future studies attempt to use intervention regimens comparable to those used by other studies to minimize the effects of this heterogeneity.

Studies on microbiota alterations and regulation represent an unexplored area with great potential in human health. Kleber Silveira et al. (2018) reported that a 21-day treatment with guarana seed powder (21 mg/kg) altered gut microbiota of Wistar rats without loss of diversity. Considering that guarana has insoluble-bound polyphenols, which accumulate in the colon and are metabolized by the microbiota, further studies exploring effects such as microbiota growth modulation and intestinal lumen pH alteration are warranted, including the determination of proanthocyanidin-related metabolites produced by bacterial activity (phenylacetic and phenylpropionic acids and their derivates).

In conclusion, guarana is a culturally important plant that produces fruits with great potential for human health applications. The development of more productive and less genetically variable cultivars, as well as the use of guarana seed residue (extraction byproducts) in industrial and pharmaceutical applications, will increase the intrinsic value of this plant. In the future, the name "guarana" should not represent a synonym for soft drinks but should be globally recognized along with "green tea," "cacao," and other important foods of great interest for human health.

ACKNOWLEDGMENTS

The authors acknowledge the Sao Paulo Research Foundation (FAPESP) for its financial support (2017/20039-0).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology (all authors). Data curation: A.C.C. Pinaffi-Langley, M.S. Figueira., K.S. Cordeiro, L.D. Negrão., M.J. Soares, C.P. Silva, M.C.Z. Alfino. Writing-original draft: A.C.C. Pinaffi-Langley, M.S. Figueira, K.S. Cordeiro, L.D. Negrão, M.J. Soares, C.P. Silva, M.C.Z. Alfino. writing—review and editing, A.C.C. Pinaffi-Langley, E.A.F.S. Torres, G.R. Sampaio, A.C. de Camargo, L.D. Negrão; , visualization, A.C.C. Pinaffi-Langley, L.D. Negrão.; project administration: E.A.F.S. Torres, A.C. de Camargo, G.R. Sampaio. All authors have read and agreed to the published version of the manuscript.

ORCID

Elizabeth A. F. S. Torres https://orcid.org/0000-0002-1012-1418

Ana Clara da C. Pinaffi-Langley https://orcid.org/0000-0001-6354-6658
Leonardo Dias Negrão https://orcid.org/0000-0003-4268-8045
Geni Rodrigues Sampaio https://orcid.org/0000-0002-7763-4664
Adriano Costa de Camargo https://orcid.org/0000-0001-9404-1193

REFERENCES

Adolfo, F. R., do Nascimento, P. C., Leal, G. C., Bohrer, D., Viana, C., & de Carvalho, L. M. (2020). Simultaneous determination of Fe and Ni in guarana (*Paullinia cupana* Kunth) by HR-CS GF AAS: Comparison of direct solid analysis and wet acid digestion procedures. *Journal of Food Composition and Analysis*, *88*, 103459. https://doi.org/10.1016/j.jfca.2020.103459

Agency for Toxic Substances and Disease Registry. (2007, October). ToxGuide™ for Acrolein. https://www.atsdr.cdc.gov/toxguides/toxguide-124.pdf

Alkhatib, A., Seijo, M., Larumbe, E., & Naclerio, F. (2015). Acute effectiveness of a "fat-loss" product on substrate utilization, perception of hunger, mood state and rate of perceived exertion at rest and during exercise. *Journal of the International Society of Sports Nutrition*, *12*(1), 44. https://doi.org/10.1186/s12970-015-0105-8

Alonso-Castro, A. J., Ruiz-Padilla, A. J., Ramírez-Morales, M. A., Alcocer-García, S. G., Ruiz-Noa, Y., Ibarra-Reynoso, L. D. R., Solorio-Alvarado, C. R., Zapata-Morales, J. R., Mendoza-Macías, C. L., Deveze-Álvarez, M. A., & Alba-Betancourt, C. (2019). Self-treatment with herbal products for weight-loss among overweight and obese subjects from central Mexico. *Journal of Ethnopharmacology*, *234*, 21–26. https://doi.org/10.1016/j.jep.2019.01.003

Andersen, T., & Fogh, J. (2001). Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. *Journal of Human Nutrition and Dietetics*, *14*(3), 243–250. https://doi.org/10.1046/j.1365-277X.2001.00290.x

Andrade, E. L., Bento, A. F., Cavalli, J., Oliveira, S. K., Schwanke, R. C., Siqueira, J. M., Freitas, C. S., Marcon, R., & Calixto, J. B. (2016). Non-clinical studies in the process of new drug development—Part II: Good laboratory practice, metabolism, pharmacokinetics, safety and dose translation to clinical studies. *Brazilian Journal of Medical and Biological Research*, *49*(12), e5646. https://doi.org/10.1590/1414-431X20165646

Angelo, P., Nunes-Silva, C. G., Brigido, M. M., Azevedo, J. S. N., Assuncao, E. N., Sousa, A. R. B., Patricio, F. J. B., Rego, M. M., Peixoto, J. C. C., Oliveira, W. P., Freitas, D. V., Almeida, E. R. P., Viana, A., Souza, A., Andrade, E. V., Acosta, P. O. A., Batista, J. S., Walter, M., Leomil, L. … Brazilian Amazon Consortium, G. (2008). Guarana (*Paullinia cupana* var. *sorbilis*), an anciently consumed stimulant from the Amazon rain forest: The seeded-fruit transcriptome. *Plant Cell Reports*, *27*(1), 117–124. https://doi.org/10.1007/s00299-007-0456-y

Antonelli-Ushirobira, T. M., Kaneshima, E. N., Gabriel, M., Audi, E. A., Marques, L. C., & Mello, J. C. P. P. (2010). Acute and subchronic toxicological evaluation of the semipurified extract of seeds of guarand (*Paullinia cupana*) in rodents. *Food and Chemical Toxicology*, *48*(7), 1817–1820. https://doi.org/10.1016/j.fct.2010.04.013

Avato, P., Pesante, M. A., Fanizzi, F. P., & Santos, C. A. D. (2003). Seed oil composition of *Paullinia cupana* var. *sorbilis* (Mart.) Ducke. *Lipids*, *38*(7), 773–780. https://doi.org/10.1007/s11745-003-1126-5

Bérubé-Parent, S., Pelletier, C., Doré, J., & Tremblay, A. (2005). Effects of encapsulated green tea and guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men. *British Journal of Nutrition*, *94*(3), 432–436. https://doi.org/10.1079/bjn20051502

Bhagwat, S., & Haytowitz, D. B. (2015). USDA database for the flavonoid content of selected foods.

Bittencourt, L. da, S., Schnorr, C. E., Santos, D. C., Rostirolla, D. C., Moresco, K. S., Ozorio, P., Mingori, M. R., Heinfarth, L., Gelain, D. P., & Moreira, J. C. F. (2020). Chronic acrolein exposure in Wistar rats: The effects of guarana extracts. *Journal of Functional Foods*, *65*, 103733. https://doi.org/10.1016/j.jff.2019.103733

Blanchard, J., & Sawers, S. J. A. (1983). The absolute bioavailability of caffeine in man. *European Journal of Clinical Pharmacology*, *24*, 93–98. https://doi.org/10.1007/BF00613933

Boasquívis, P. F., Silva, G. M. M., Paiva, F. A., Cavalcanti, R. M., Nunez, C. V., De Paula Oliveira, R., Boasquivis, P. F., Silva, G. M. M., Paiva, F. A., Cavalcanti, R. M., Nunez, C. V., & Oliveira, R. D. (2018). Guarana (*Paullinia cupana*) extract protects caenorhabditis elegans models for alzheimer disease and huntington disease through activation of antioxidant and protein degradation pathways. *Oxidative Medicine and Cellular Longevity*, *2018*, 16. https://doi.org/10.1155/2018/9241308

Boozer, C. N., Nasser, J. A., Heymsfield, S. B., Wang, V., Chen, G., & Solomon, J. L. (2001). An herbal supplement containing Ma Huang-Guarana for weight loss: A randomized, double-blind trial. *International Journal of Obesity*, *25*(3), 316–324. https://doi.org/10.1038/sj.ijo.0801539

Bortolin, R. C., Vargas, A. R., de Miranda Ramos, V., Gasparotto, J., Chaves, P. R., Schnorr, C. E., da Boit Martinello, K., Silveira, A. K., Gomes, H. M., Rabelo, T. K., Grunwald, M. S., Ligabue-Braun, R., Gelain, D. P., & Moreira, J. C. F. (2019). Guarana supplementation attenuated obesity, insulin resistance, and adipokines dysregulation induced by a standardized human Western diet via brown adipose tissue activation. *Phytotherapy Research*, *33*(5), 1394–1403. https://doi.org/10.1002/ptr.6330

Breitbach, U. B., Niehues, M., Lopes, N. P., Faria, J. E. Q., & Brandão, M. G. L. (2013). Amazonian Brazilian medicinal plants described by C.F.P. von Martius in the 19th century. *Journal of Ethnopharmacology*, *147*(1), 180–189. https://doi.org/10.1016/j.jep.2013.02.030

Bulku, E., Zinkovsky, D., Patel, P., Javia, V., Lahoti, T., Khodos, I., Stohs, S. J., & Ray, S. D. (2010). A novel dietary supplement containing multiple phytochemicals and vitamins elevates hepatorenal and cardiac antioxidant enzymes in the absence of significant serum chemistry and genomic changes. *Oxidative Medicine and Cellular Longevity*, *3*(2), 129–144. https://doi.org/10.4161/oxim.3.2.11157

Cadona, F. C., Machado, A. K., Azzolin, V. F., Barbisan, F., Dornelles, E. B., Glanzner, W., Goncalves, P. B. D., Assmann, C. E., Ribeiro, E. E., da Cruz, I. B. M., Carla Cadoná, F., Kolinski Machado, A., Farina Azzolin, V., Barbisan, F., Bortoluzzi Dornelles, E., Glanzner, W., Bayard Dias Gonçalves, P., Elias Assmann, C., Esteves Ribeiro, E., & Beatrice Mânica da Cruz, I. (2016). Guarana caffeine-rich food increases oxaliplatin sensitivity of colorectal HT-29 cells by apoptosis pathway modulation. *Anti-Cancer Agents in Medicinal Chemistry*, *16*(8), 1055–1065. https://doi.org/10.2174/1871520616666151217121138

Cadona, F. C., Rosa, J. L., Schneider, T., Cubillos-Rojas, M., Sanchez-Tena, S., Azzolin, V. F., Assmann, C. E., Machado, A. K., Ribeiro, E. E., & da Cruz, I. B. M. (2017). Guarana, a highly caffeinated food, presents in vitro antitumor activity in colorectal and breast

cancer cell lines by inhibiting AKT/mTOR/S6K and MAPKs pathways. *Nutrition and Cancer-an International Journal*, *69*(5), 800–810. https://doi.org/10.1080/01635581.2017.1324994

Campos, A. R., Barros, A. I. S. S., Albuquerque, F. A. A. A., Leal, L. K. A. M., & Rao, V. S. N. N. (2005). Acute effects of guarana (*Paullinia cupana* Mart.) on mouse behaviour in forced swimming and open field tests. *Phytotherapy Research*, *19*(5), 441–443. https://doi.org/10.1002/ptr.1471

Campos, M. M., Fernandes, E. S., Ferreira, J., Bortolanza, L. B., Santos, A. R. S., & Calixto, J. B. (2004). Pharmacological and neurochemical evidence for antidepressant-like effects of the herbal product Catuama. *Pharmacology Biochemistry and Behavior*, *78*(4), 757–764. https://doi.org/10.1016/j.pbb.2004.05.024

Carlsen, M. H., Halvorsen, B. L., Holte, K., Bøhn, S. K., Dragland, S., Sampson, L., Willey, C., Senoo, H., Umezono, Y., Sanada, C., Barikmo, I., Berhe, N., Willett, W. C., Phillips, K. M., Jacobs, D. R., & Blomhoff, R. (2010). The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutrition Journal*, *9*(1), 3. https://doi.org/10.1186/1475-2891-9-3

Colombo, F., Di Lorenzo, C., Biella, S., Vecchio, S., Frigerio, G., & Restani, P. (2020). Adverse effects to food supplements containing botanical ingredients. *Journal of Functional Foods*, *72*, 103990. https://doi.org/10.1016/j.jff.2020.103990

da Costa Miranda, V., Cristina Trufelli, D., Bezerra de Souza Fêde, Â., Delgado Martins, F., Scatigno Saad, L., de Oliveira, V., Zampa de Campos Trindade, T., Riechelmann, R., & Del Giglio, A. (2008). Guarana (*Paullinia cupana*) for chemotherapy-related fatigue [Guaraná (*Paullinia cupana*) para fadiga induzida por quimioterapia antineoplásica]. *Einstein*, *6*(2), 195–204.

da Costa Pinaffi, A. C., Sampaio, G. R., Soares, M. J., Shahidi, F., Camargo, A. C. D.e, & Torres, E. A. F. S. (2020). Insoluble-bound polyphenols released from Guarana powder: Inhibition of alpha-glucosidase and proanthocyanidin profile. *Molecules (Basel, Switzerland)*, *25*(3), 1–17. https://doi.org/10.3390/molecules25030679

da Silva, G. S., Canuto, K. M., Ribeiro, P. R. V., de Brito, E. S., Nascimento, M. M., Zocolo, G. J., Coutinho, J. P., & de Jesus, R. M. (2017). Chemical profiling of guarana seeds (*Paullinia cupana*) from different geographical origins using UPLC-QTOF-MS combined with chemometrics. *Food Research International*, *102*(September), 700–709. https://doi.org/10.1016/j.foodres.2017.09.055

Dabulici, C. M., Sârbu, I., & Vamanu, E. (2020). The bioactive potential of functional products and bioavailability of phenolic compounds. *Foods*, *9*(7), 953. https://doi.org/10.3390/foods9070953

Dalonso, N., & Petkowicz, C. L. D. (2014). Guarana powder polysaccharides: Characterization and rheological properties of starch. *Starch-Starke*, *66* (9–10), 914–922. https://doi.org/10.1002/star.201300289

de Carvalho, F. A. L., Lorenzo, J. M., Pateiro, M., Bermúdez, R., Purriños, L., & Trindade, M. A. (2019). Effect of guarana (*Paullinia cupana*) seed and pitanga (*Eugenia uniflora* L.) leaf extracts on lamb burgers with fat replacement by chia oil emulsion during shelf life storage at 2 °C. *Food Research International*, *125*, 108554. https://doi.org/10.1016/j.foodres.2019.108554

de Gois, J. S., Almeida, T. S., de Andrade, R. M., Toaldo, I. M., Bordignon-Luiz, M. T., & Borges, D. L. G. (2016). Direct solid analysis for the determination of Mn, Ni, Rb and Sr in powdered stimulant plants using high-resolution continuum source atomic absorption spectrometry followed by chemometric classification based on elemental composition. *Polyphenol Content a. Microchemical Journal*, *124*, 283–289. https://doi.org/10.1016/j.microc.2015.08.020

de Mejia, E. G., & Ramirez-Mares, M. V. (2014). Impact of caffeine and coffee on our health. *Trends in Endocrinology & Metabolism*, *25*(10), 489–492. https://doi.org/10.1016/j.tem.2014.07.003

de Mello, J. R. B., de Mello, F. B., & Langeloh, A. (2010). Pre-clinic toxicity of a phytoterapic containing *Anemopaegma mirandum*, *Cola nitida*, *Passiflora alata*, *Paullinia cupana*, *Ptychopetalum olacoides* and thiamin chlorhydrate. *Latin American Journal of Pharmacy*, *29*(1), 57–63.

De Oliveira Campos, M. P., Riechelmann, R., Martins, L. C., Hassan, B. J., Casa, F. B. A., Giglio, A. D., Campos, M. P. D., Riechelmann, R., Martins, L. C., Hassan, B. J., Casa, F. B. A., & Del Giglio, A. (2011). Guarana (*Paullinia cupana*) improves fatigue in breast cancer patients undergoing systemic chemotherapy. *Journal of Alternative and Complementary Medicine*, *17*(6), 505–512. https://doi.org/10.1089/acm.2010.0571

De Waele, S., & Van Belle, S. (2010). Cancer-related fatigue. *Acta Clinica Belgica*, *65*(6), 378–385. https://doi.org/10.1179/acb.2010.65.6.002

Del Giglio, A. B., Cubero, D. D. I. G., Lerner, T. G., Guariento, R. T., De Azevedo, R. G. S., Paiva, H., Goldman, C., Carelli, B., Cruz, F. M., Schindler, F., Pianowski, L., De Matos, L. L., & Del Giglio, A. (2013). Purified dry extract of *Paullinia cupana* (guaraná) (PC-18) for chemotherapy-related fatigue in patients with solid tumors: An early discontinuation study. *Journal of Dietary Supplements*, *10*(4), 325–334. https://doi.org/10.3109/19390211.2013.830676

Durak, A., Gawlik-Dziki, U., & Pecio, Ł. (2014). Coffee with cinnamon—Impact of phytochemicals interactions on antioxidant and anti-inflammatory in vitro activity. *Food Chemistry*, *162*, 81–88. https://doi.org/10.1016/j.foodchem.2014.03.132

Espinola, E. B., Dias, R. F., Mattei, R., & Carlini, E. A. (1997). Pharmacological activity of Guarana (*Paullinia cupana* Mart) in laboratory animals. *Journal of Ethnopharmacology*, *55*(3), 223–229. https://doi.org/10.1016/s0378-8741(96)01506-1

Fu, L., Xu, B. T., Xu, X. R., Gan, R. Y., Zhang, Y., Xia, E. Q., & Li, H. B. (2011). Antioxidant capacities and total phenolic contents of 62 fruits. *Food Chemistry*, *129*(2), 345–350. https://doi.org/10.1016/j.foodchem.2011.04.079

Fuentes, J., de Camargo, A. C., Atala, E., Gotteland, M., Olea-Azar, C., & Speisky, H. (2021). Quercetin oxidation metabolite present in onion peel protects caco-2 cells against the oxidative stress, NF-kB activation, and loss of epithelial barrier function induced by NSAIDs. *Journal of Agricultural and Food Chemistry*, *69*(7), 2157–2167. https://doi.org/10.1021/acs.jafc.0c07085

Fukumasu, H., Avanzo, J. L., Heidor, R., Silva, T. C., Atroch, A., Moreno, F. S., & Dagli, M. L. Z. Z. (2006). Protective effects of guarana (*Paullinia cupana* Mart. var. *sorbilis*) against DEN-induced DNA damage on mouse liver. *Food and Chemical Toxicology*, *44*(6), 862–867. https://doi.org/10.1016/j.fct.2005.11.010

Fukumasu, H., Avanzo, J. L., Nagamine, M. K., Barbuto, J. A., Rao, K. V., & Dagli, M. L. Z. Z. (2008). *Paullinia cupana* Mart var. *sorbilis*, guarana, reduces cell proliferation and increases apoptosis of B16/F10 melanoma lung metastases in mice. *Brazilian Journal of Medical and Biological Research*, *41*(4), 305–310. https://doi.org/10.1590/s0100-879X2008000400008

Fukumasu, H., da Silva, T. C., Avanzo, J. L., de Lima, C. E., Mackowiak, I. I., Atroch, A., Spinosa, H. D., Moreno, F. S., & Dagli, M. L. Z. (2006). Chemopreventive effects of *Paullinia cupana* Mart var. *sorbilis*, the guarana, on mouse hepatocarcinogenesis. *Cancer Letters*, *233*(1), 158–164. https://doi.org/10.1016/j.canlet.2005.03.007

Fukumasu, H., Latorre, A. O., & Zaidan-Dagli, M. L. (2011). *Paullinia cupana* Mart. var. *sorbilis*, Guarana, increases survival of ehrlich ascites carcinoma (EAC) bearing mice by decreasing cyclin-D1 expression and inducing a G0/G1 cell cycle arrest in EAC cells. *Phytotherapy Research*, *25*(1), 11–16. https://doi.org/10.1002/ptr.3216

Galduróz, J. C., & Carlini, E. A. (1994). Acute effects of the *Paullinia cupana*, "Guaraná" on the cognition of normal volunteers. *São Paulo Medical Journal = Revista Paulista de Medicina*, *112*(3), 607–611. https://doi.org/10.1590/S1516-31801994000300007

Galduróz, J. C., & Carlini, E. A. (1996). The effects of long-term administration of guarana on the cognition of normal, elderly volunteers. *São Paulo Medical Journal = Revista Paulista de Medicina*, *114*(1), 1073–1078. https://doi.org/10.1590/S1516-31801996000100003

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J. L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M. C., Whitehouse, P., & Winblad, B. (2006). Mild cognitive impairment. *The Lancet*, *367*(9518), 1262–1270. https://doi.org/10.1016/S0140-6736(06)68542-5

Godos, J., Castellano, S., Ray, S., Grosso, G., & Galvano, F. (2018). Dietary polyphenol intake and depression: Results from the mediterranean healthy eating, lifestyle and aging (MEAL) study. *Molecules (Basel, Switzerland)*, *23*(5), 999. https://doi.org/10.3390/molecules23050999

Gonzales-Sarrias, A., Espin, J. C., & Tomas-Barberan, F. A. (2017). Non-extractable polyphenols produce gut microbiota metabolites that persist in circulation and show anti-inflammatory and free radical-scavenging effects. *Trends in Food Science & Technology*, *69*, 281–288. https://doi.org/10.1016/j.tifs.2017.07.010

Halliwell, B., Rafter, J., & Jenner, A. (2005). Health promotion by flavanoids, tocopherols, tocotrienols, and other phenols: Direct or inderect? Antioxidant or not? *The American Journal of Clinical Nutrition*, *81*(1 Suppl), 268S–276S. https://doi.org/10.1093/ajcn/81.1.268S

Halliwell, B., Zhao, K., & Whiteman, M. (2000). The gastrointestinal tract: A major site of antioxidant action? *Free Radical Research*, *33*(6), 819–830. https://doi.org/10.1080/10715760000301341

Hamilton, C. A., Matthews, F. E., Donaghy, P. C., Taylor, J. P., O'Brien, J. T., Barnett, N., Olsen, K., McKeith, I. G., & Thomas, A. J. (2020). Prospective predictors of decline v. stability in mild cognitive impairment with Lewy bodies or Alzheimer's disease. *Psychological Medicine*, 1–9. https://doi.org/10.1017/S0033291720001130

Hanhineva, K., Törrönen, R., Bondia-Pons, I., Pekkinen, J., Kolehmainen, M., Mykkänen, H., & Poutanen, K. (2010). Impact of dietary polyphenols on carbohydrate metabolism. *International Journal of Molecular Sciences*, *11*(4), 1365–1402. https://doi.org/10.3390/ijms11041365

Harorani, M., Davodabady, F., Farahani, Z., hezave, A. K., & Rafiei, F. (2020). The effect of Benson's relaxation response on sleep quality and anorexia in cancer patients undergoing chemotherapy: A randomized controlled trial. *Complementary Therapies in Medicine*, *50*, 102344. https://doi.org/10.1016/j.ctim.2020.102344

Harrold, J. A., Hughes, G. M., O'Shiel, K., Quinn, E., Boyland, E. J., Williams, N. J., & Halford, J. C. G. (2013). Acute effects of a herb extract formulation and inulin fibre on appetite, energy intake and food choice. *Appetite*, *62*, 84–90. https://doi.org/10.1016/j.appet.2012.11.018

Haskell, C. F., Kennedy, D. O., Wesnes, K. A., Milne, A. L., & Scholey, A. B. (2007). A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans. *Journal of Psychopharmacology*, *21*(1), 65–70. https://doi.org/10.1177/0269881106063815

Henman, A. R. (1982). Guaraná (*Paullinia cupana* var. *sorbilis*): Ecological and social perspectives on an economic plant of the central amazon basin. *Journal of Ethnopharmacology*, *6*(3), 311–338. https://doi.org/10.1016/0378-8741(82)90054-X

Hertz, E., Cadoná, F. C., Machado, A. K., Azzolin, V., Holmrich, S., Assmann, C., Ledur, P., Ribeiro, E. E., De Souza Filho, O. C., Mânica-Cattani, M. F., & Da Cruz, I. B. M. (2015). Effect of *Paullinia cupana* on MCF-7 breast cancer cell response to chemotherapeutic drugs. *Molecular and Clinical Oncology*, *3*(1), 37–43. https://doi.org/10.3892/mco.2014.438

Kennedy, D. O., Haskell, C. F., Robertson, B., Reay, J., Brewster-Maund, C., Luedemann, J., Maggini, S., Ruf, M., Zangara, A., & Scholey, A. B. (2008). Improved cognitive performance and mental fatigue following a multi-vitamin and mineral supplement with added guarana (*Paullinia cupana*). *Appetite*, *50*(2–3), 506–513. https://doi.org/10.1016/j.appet.2007.10.007

Kennedy, D. O., Haskell, C. F., Wesnes, K. A., & Scholey, A. B. (2004). Improved cognitive performance in human volunteers following administration of guarana (*Paullinia cupana*) extract: Comparison and interaction with Panax ginseng. *Pharmacology Biochemistry and Behavior*, *79*(3), 401–411. https://doi.org/10.1016/j.pbb.2004.07.014

Khalatbary, A. R., & Khademi, E. (2020). The green tea polyphenolic catechin epigallocatechin gallate and neuroprotection. *Nutritional Neuroscience*, *23*(4), 281–294. https://doi.org/10.1080/1028415X.2018.1500124

Kim, Y., Keogh, J. B., & Clifton, P. M. (2016). Polyphenols and glycemic control. *Nutrients*, *8*(1), 27. https://doi.org/10.3390/nu8010017

Kleber Silveira, A., Moresco, K. S., Mautone Gomes, H., da Silva Morrone, M., Kich Grun, L., Pens Gelain, D., de Mattos Pereira, L., Giongo, A., Rodrigues De Oliveira, R., & Fonseca Moreira, J. C. (2018). Guarana (*Paullinia cupana* Mart.) alters gut microbiota and modulates redox status, partially via caffeine in Wistar rats. *Phytotherapy Research*, *32*(12), 2466–2474. https://doi.org/10.1002/ptr.6185

Krewer, C. D., Ribeiro, E. E., Ribeiro, E. A. M., Moresco, R. N., da Rocha, M., Montagner, G., Machado, M. M., Viegas, K., Brito, E., & da Cruz, I. B. M. (2011). Habitual intake of Guarana and metabolic morbidities: An epidemiological study of an elderly Amazonian population. *Phytotherapy Research*, *25*(9), 1367–1374. https://doi.org/10.1002/ptr.3437

Lapa, A., Souccar, C., Lima-Landman, M., Godinho, R., & Lima, T. (2010). *Capítulo 11 - Farmacologia e toxicologia de produtos naturais*. In C. Simões, E. Schenkel, G. Gosmann, J. Mello, L. Mentz, & P. Petrovick (Eds.), Farmacognosia: Da planta ao medicamento (6th ed., pp. 247–262). UFRGS/UFSC. https://www.researchgate.net/publication/315772641_Farmacognosia_da_Planta_ao_Medicamento

Leggett, S., Koczwara, B., & Miller, M. (2015). The impact of complementary and alternative medicines on cancer symptoms, treatment side effects, quality of life, and survival in women with breast cancer-A systematic review. *Nutrition and Cancer—An International Journal*, *67*(3), 373–391. https://doi.org/10.1080/01635581.2015.1004731

Lima, N. da, S., Caria, C. R. E. P., Gambero, A., & Ribeiro, M. L. (2019). The effect of Guarana (*Paullinia cupana*) on metabolic and inflammatory parameters in adult male mice programmed by maternal obesity. *European Journal of Nutrition*, *58*(2), 765–774. https://doi.org/10.1007/s00394-018-1686-1

Lima, N. da, S., Numata, E., Mesquita, L., Dias, P., Vilegas, W., Gambero, A., & Ribeiro, M. (2017). Modulatory effects of Guarana (*Paullinia cupana*) on adipogenesis. *Nutrients*, *9*(6), 635. https://doi.org/10.3390/nu9060635

Lima, N. da, S., Teixeira, L., Gambero, A., & Ribeiro, M. L. (2018). Guarana (*Paullinia cupana*) stimulates mitochondrial biogenesis in mice fed high-fat diet. *Nutrients*, *10*(2), 12. https://doi.org/10.3390/nu10020165

Lima, W. P., Carnevali, L. C., Eder, R., Rosa, L., Bacchi, E. M., Seelaender, M. C. L. L., Costa Rosa, L. F. B. P., Bacchi, E. M., & Seelaender, M. C. L. L. (2005). Lipid metabolism in trained rats: Effect of guarana (*Paullinia cupana* Mart.) supplementation. *Clinical Nutrition*, *24*(6), 1019–1028. https://doi.org/10.1016/j.clnu.2005.08.004

Machado, A. K., Cadona, F. C., Azzolin, V. F., Dornelles, E. B., Barbisan, F., Ribeiro, E. E., Manica-Cattani, M. F., Duarte, M., Saldanha, J. R. P., & da Cruz, I. B. M. (2015). Guarana (*Paullinia cupana*) improves the proliferation and oxidative metabolism of senescent adipocyte stem cells derived from human lipoaspirates. *Food Research International*, *67*, 426–433. https://doi.org/10.1016/j.foodres.2014.11.056

Machado, K. N., de Freitas, A. A., Cunha, L. H., Faraco, A. A. G., de Pádua, R. M., Braga, F. C., Vianna-Soares, C. D., & Castilho, R. O. (2018). A rapid simultaneous determination of methylxanthines and proanthocyanidins in Brazilian guaraná (*Paullinia cupana* Kunth.). *Food Chemistry*, *239*, 180–188. https://doi.org/10.1016/j.foodchem.2017.06.089

Machado, K. N., Paula Barbosa, A., de Freitas, A. A., Alvarenga, L. F., Pádua, R. M., Faraco G. A. A., Braga, F. C., Vianna-Soares, C. D., & Castilho, R. O. (2021). TNF-α inhibition, antioxidant effects and chemical analysis of extracts and fraction from Brazilian guaraná seed powder. *Food Chemistry*, *355*, 129563. https://doi.org/10.1016/j.foodchem.2021.129563

Maldaner, D. R., Pellenz, N. L., Barbisan, F., Azzolin, V. F., Mastella, M. H., Teixeira, C. F., Duarte, T., Maia-Ribeiro, E. A., da Cruz, I. B. M., & Duarte, M. M. M. F. (2020). Interaction between low-level laser therapy and Guarana (*Paullinia cupana*) extract induces antioxidant, anti-inflammatory, and anti-apoptotic effects and promotes proliferation in dermal fibroblasts. *Journal of Cosmetic Dermatology*, *19*(3), 629–637. https://doi.org/10.1111/jocd.13055

Marcon, R., Del Giglio, A., Pianowski, L. F., & Calixto, J. B. (2011). An analysis of the role of *Paulinia cupana* (guaraná) in blood IL-1b and brain IL-6 levels as well as brain IL-6 and TNF-a mRNA expression in mice. *Journal of Clinical Oncology*, *29*(15_suppl), e21002–e21002. https://doi.org/10.1200/jco.2011.29.15_suppl.e21002

dos Santos Martins, S. P., dos, S., Ferreira, C. L., & del Giglio, A. (2017). Placebo-controlled, double-blind, randomized study of a dry Guarana extract in patients with head and neck tumors undergoing chemoradiotherapy: Effects on fatigue and quality of life. *Journal of Dietary Supplements*, *14*(1), 32–41. https://doi.org/10.1080/19390211.2016.1193081

Mattei, R., Dias, R., Espińola, E., Carlini, E., & Barros, S. B. (1998). Guarana (*Paullinia cupana*): Toxic behavioral effects in laboratory animals and antioxidant activity in vitro. *Journal of Ethnopharmacology*, *60*(2), 111–116. https://doi.org/10.1016/S0378-8741(97)00141-4

McWhirter, L., Ritchie, C., Stone, J., & Carson, A. (2020). Functional cognitive disorders: A systematic review. *The Lancet Psychiatry*, *7*(2), 191–207. https://doi.org/10.1016/S2215-0366(19)30405-5

Mendes, T. M. N., Murayama, Y., Yamaguchi, N., Sampaio, G. R., Fontes, L. C. B., Torres, E. A. F., da, S., Tamura, H., & Yonekura, L. (2019). Guaraná (*Paullinia cupana*) catechins and procyanidins: Gastrointestinal/colonic bioaccessibility, Caco-2 cell permeability and the impact of macronutrients. *Journal of Functional Foods*, *55*, 352–361. https://doi.org/10.1016/j.jff.2019.02.026

Mingori, M. R., Heimfarth, L., Ferreira, C. F., Gomes, H. M., Moresco, K. S., Delgado, J., Roncato, S., Zeidán-Chuliá, F., Gelain, D. P., & Moreira, J. C. F. (2017). Effect of *Paullinia cupana* Mart. commercial extract during the aging of middle age Wistar rats: Differential effects on the hippocampus and striatum. *Neurochemical Research*, *42*(8), 2257–2273. https://doi.org/10.1007/s11064-017-2238-4

Miranda, V. D., Trufelli, D. C., Santos, J., Campos, M. P., Nobuo, M., Miranda, M. D., Schlinder, F., Riechelmann, R., & del Giglio, A. (2009). Effectiveness of Guarana (*Paullinia cupana*) for postradiation fatigue and depression: Results of a pilot double-blind randomized study. *Journal of Alternative and Complementary Medicine*, *15*(4), 431–433. https://doi.org/10.1089/acm.2008.0324

Morley, J. E. (2018). An overview of cognitive impairment. *Clinics in Geriatric Medicine*, *34*(4), 505–513. https://doi.org/10.1016/j.cger.2018.06.003

Morley, J. E., Morris, J. C., Berg-Weger, M., Borson, S., Carpenter, B. D., del Campo, N., Dubois, B., Fargo, K., Fitten, L. J., Flaherty, J. H., Ganguli, M., Grossberg, G. T., Malmstrom, T. K., Petersen, R. D., Rodriguez, C., Saykin, A. J., Scheltens, P., Tangalos, E. G., Verghese, J. … Vellas, B. (2015). Brain health: The importance of recognizing cognitive impairment: An IAGG consensus conference. *Journal of the American Medical Directors Association*, *16*(9), 731–739. https://doi.org/10.1016/j.jamda.2015.06.017

Mudenuti, N. V. de, R., de Camargo, A. C., de Alencar, S. M., Danielski, R., Shahidi, F., Madeira, T. B., Hirooka, E. Y., Spinosa, W. A., & Grossmann, M. V. E. (2021). Phenolics and alkaloids of raw cocoa nibs and husk: The role of soluble and insoluble-bound antioxidants. *Food Bioscience*, *42*, 101085. https://doi.org/10.1016/j.fbio.2021.101085

Mudenuti, N. V. de, R., de Camargo, A. C., Shahidi, F., Madeira, T. B., Hirooka, E. Y., & Grossmann, M. V. E. (2018). Soluble and insoluble-bound fractions of phenolics and alkaloids and their antioxidant activities in raw and traditional chocolate: A comparative study. *Journal of Functional Foods*, *50*, 164–171. https://doi.org/10.1016/j.jff.2018.10.003

Naoi, M., Shamoto-Nagai, M., & Maruyama, W. (2019). Neuroprotection of multifunctional phytochemicals as novel therapeutic strategy for neurodegenerative disorders: Antiapoptotic and anti-

amyloidogenic activities by modulation of cellular signal pathways. *Future Neurology*, *14*(1), FNL9. https://doi.org/10.2217/fnl-2018-0028

Nazaré, R. F. R. D.e, & Figueirêdo, F. J. C. (1982). Contribuiçao Ao Estudo do Guaraná. https://www.embrapa.br/busca-de-publicacoes/-/publicacao/382454/contribuicao-ao-estudo-do-guarana

Nina, N. V., dos, S., Schimpl, F. C., Nascimento Filho, F. J. d., & Atroch, A. L. (2021). Phytochemistry divergence among guarana genotypes as a function of agro-industrial characters. *Crop Science*, *61*(1), 443–455. https://doi.org/10.1002/csc2.20331

Oliveira, C. H., Moraes, M. E. A., Moraes, M. O., Bezerra, F. A. F., Abib, E., & De Nucci, G. (2005). Clinical toxicology study of an herbal medicinal extract of *Paullinia cupana*, *Trichilia catigua*, *Ptychopetalum olacoides* and *Zingiber officinale* (Catuama®) in healthy volunteers. *Phytotherapy Research*, *19*(1), 54–57. https://doi.org/10.1002/ptr.1484

Oliveira, S. S., Del Giglio, A. B., Lerner, T. G., Zanellato, R. M., Tiemi, L., Reifur, L., Santi, P. X., & Del Giglio, A. (2013). *Paullinia cupana* for control of hot flashes in breast cancer patients: a pilot study. *Einstein (São Paulo, Brazil)*, *11*(4), 435–438. https://doi.org/10.1590/S1679-45082013000400005

Opala, T., Rzymski, P., Pischel, I., Wilczak, M., & Wozniak, J. (2006). Efficacy of 12 weeks supplementation of a botanical extract-based weight loss formula on body weight, body composition and blood chemistry in healthy, overweight subjects—A randomised double-blind placebo-controlled clinical trial. *European Journal of Medical Research*, *11*(8), 343–350.

Oroian, M., & Escriche, I. (2015). Antioxidants: Characterization, natural sources, extraction and analysis. *Food Research International*, *74*, 10–36. https://doi.org/10.1016/j.foodres.2015.04.018

Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: A systematic review and meta-analysis of CRP levels. *Psychological Medicine*, *49*(12), 1958–1970. https://doi.org/10.1017/S0033291719001454

Otobone, F. J., Sanches, A. C. C., Nagae, R., Martins, J. V. C., Sela, V. R., De Mello, J. C. P., & Audi, E. A. (2007). Effect of lyophilized extracts from guaraná seeds [*Paullinia cupana* var. *sorbilis* (Mart.) Ducke] on behavioral profiles in rats. *Phytotherapy Research*, *21*(6), 531–535. https://doi.org/10.1002/ptr.2089

Otobone, F. J., Sanches, A. C., Nagae, R. L., Martins, J. V. C., Obici, S., Mello, J. C. P. d., & Audi, E. A. (2005). Effect of crude extract and its semi purified constituents from guaraná seeds [*Paullinia cupana* var. *sorbilis* (Mart.) lucke] on cognitive performance in Morris water maze in rats. *Brazilian Archives of Biology and Technology*, *48*(5), 723–728. https://doi.org/10.1590/S1516-89132005000600007

Pahwa, R., Goyal, A., Bansal, P., & Jialal, I. (2021, August 11). Chronic inflammation. https://www.ncbi.nlm.nih.gov/books/NBK493173/

Palma, C. G. L., Lera, A. T., Lerner, T., De Oliveira, M. M., De Borta, T. M., Barbosa, R. P., Brito, G. M., Guazzelli, C. A., Cruz, F. J. M., & Del Giglio, A. (2016). Guarana (*Paullinia cupana*) improves anorexia in patients with advanced cancer. *Journal of Dietary Supplements*, *13*(2), 221–231. https://doi.org/10.3109/19390211.2015.1008612

Pan American Health Organization. (n.d.). Depression. https://www.paho.org/en/topics/depression

Pan American Health Organization. (2017, February 28). Depression: What you should know. https://www.paho.org/en/documents/depression-what-you-should-know

Pan, Z., Park, C., Brietzke, E., Zuckerman, H., Rong, C., Mansur, R. B., Fus, D., Subramaniapillai, M., Lee, Y., & McIntyre, R. S. (2019). Cognitive impairment in major depressive disorder. *CNS Spectrums*, *24*(1), 22–29. https://doi.org/10.1017/S1092852918001207

Pateiro, M., Vargas, F. C., Chincha, A. A. I. A., Sant'Ana, A. S., Strozzi, I., Rocchetti, G., Barba, F. J., Domínguez, R., Lucini, L., do Amaral Sobral, P. J., & Lorenzo, J. M. (2018). Guarana seed extracts as a useful strategy to extend the shelf life of pork patties: UHPLC-ESI/QTOF phenolic profile and impact on microbial inactivation, lipid and protein oxidation and antioxidant capacity. *Food Research International*, *114*, 55–63. https://doi.org/10.1016/j.foodres.2018.07.047

Peixoto, H., Roxo, M., Röhrig, T., Richling, E., Wang, X., & Wink, M. (2017). Anti-aging and antioxidant potential of *Paullinia cupana* var. *sorbilis*: Findings in caenorhabditis elegans indicate a new utilization for roasted seeds of Guarana. *Medicines*, *4*(4), 61. https://doi.org/10.3390/medicines4030061

Pomportes, L., Brisswalter, J., Casini, L., Hays, A., & Davranche, K. (2017). Cognitive performance enhancement induced by caffeine, carbohydrate and Guarana mouth rinsing during submaximal exercise. *Nutrients*, *9*(6), 17. https://doi.org/10.3390/nu9060589

Pomportes, L., Brisswalter, J., Hays, A., & Davranche, K. (2019). Effects of carbohydrate, caffeine, and guarana on cognitive performance, perceived exertion, and shooting performance in high-level athletes. *International Journal of Sports Physiology and Performance*, *14*(5), 576–582. https://doi.org/10.1123/ijspp.2017-0865

Pomportes, L., Davranche, K., Hays, A., & Brisswalter, J. (2015). Effet d'un complexe créatine–guarana sur la puissance musculaire et la performance cognitive chez des sportifs de haut niveau de performance. *Science & Sports*, *30*(4), 188–195. https://doi.org/10.1016/j.scispo.2015.04.002

Portella, R. D., Barcelos, R. P., da Rosa, E. J. F., Ribeiro, E. E., da Cruz, I. B. M., Suleiman, L., & Soares, F. A. A. (2013). Guarana (*Paullinia cupana* Kunth) effects on LDL oxidation in elderly people: An in vitro and in vivo study. *Lipids in Health and Disease*, *12*, 9. https://doi.org/10.1186/1476-511x-12-12

Raimundo, A. F., Félix, F., Andrade, R., García-Conesa, M. T., González-Sarrías, A., Gilsa-Lopes, J., do, Ó. D., Raimundo, A., Ribeiro, R., Rodriguez-Mateos, A., Santos, C. N., Schär, M., Silva, A., Cruz, I., Wang, B., Pinto, P., & Menezes, R. (2020). Combined effect of interventions with pure or enriched mixtures of (poly)phenols and anti-diabetic medication in type 2 diabetes management: A meta-analysis of randomized controlled human trials. *European Journal of Nutrition*, *59*(4), 1329–1343. https://doi.org/10.1007/s00394-020-02189-1

Rienks, J., Barbaresko, J., Oluwagbemigun, K., Schmid, M., & Nöthlings, U. (2018). Polyphenol exposure and risk of type 2 diabetes: Dose-response meta-analyses and systematic review of prospective cohort studies. *American Journal of Clinical Nutrition*, *108*(1), 49–61. https://doi.org/10.1093/ajcn/nqy083

Rivenbark, A. G., & Coleman, W. B. (2014). *Pathobiology of human disease: A dynamic encyclopedia of disease mechanisms* (pp. 349–366). Elsevier. https://doi.org/10.1016/B978-0-12-386456-7.01901-8

Roberts, A. T., Jonge-Levitan, L. d., Parker, C. C., & Greenway, F. (2005). The effect of an herbal supplement containing black

tea and caffeine on metabolic parameters in humans. *Alternative Medicine Review*, *10*(4), 321–325.

Roglic, G., & World Health Organization. (2016). Global report on diabetes. https://www.who.int/publications/i/item/9789241565257

Ruchel, J. B., Bernardes, V. M., Braun, J. B. S., Manzoni, A. G., Passos, D. F., Castilhos, L. G., Abdalla, F. H., de Oliveira, J. S., de Andrade, C. M., Casali, E. A., da Cruz, I. B. M., & Leal, D. B. R. (2019). Lipotoxicity-associated inflammation is prevented by guarana (*Paullinia cupana*) in a model of hyperlipidemia. *Drug and Chemical Toxicology*, 1–9. https://doi.org/10.1080/01480545.2019.1624767

Ruchel, J. B., Braun, J. B. S., Adefegha, S. A., Guedes Manzoni, A., Abdalla, F. H., de Oliveira, J. S., Trelles, K., Signor, C., Lopes, S. T. A., da Silva, C. B., Castilhos, L. G., Rubin, M. A., & Leal, D. B. R. (2017). Guarana (*Paullinia cupana*) ameliorates memory impairment and modulates acetylcholinesterase activity in Poloxamer-407-induced hyperlipidemia in rat brain. *Physiology & Behavior*, *168*, 11–19. https://doi.org/10.1016/j.physbeh.2016.10.003

Ruchel, J. B., Rezer, J. F. P. P., Thorstenberg, M. L., Dos Santos, C. B., Cabral, F. L., Lopes, S. T. A. A., da Silva, C. B., MacHado, A. K., Da Cruz, I. B. M. M., Schetinger, M. R. C. C., Goncalves, J. F., Leal, D. B. R. R., Gonçalves, J. F., & Leal, D. B. R. R. (2016). Hypercholesterolemia and ecto-enzymes of purinergic system: Effects of *Paullinia cupana*. *Phytotherapy Research*, *30*(1), 49–57. https://doi.org/10.1002/ptr.5499

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., & Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *157*, 107843. https://doi.org/10.1016/j.diabres.2019.107843

Sampaio, G. R., Guizellini, G. M., da Silva, S. A., de Almeida, A. P., Pinaffi-Langley, A. C. C., Rogero, M. M., de Camargo, A. C., & Torres, E. A. F. S. (2021). Polycyclic aromatic hydrocarbons in foods: Biological effects, legislation, occurrence, analytical methods, and strategies to reduce their formation. *International Journal of Molecular Sciences*, *22*, 6010. https://doi.org/10.3390/ijms22116010

Sanford, A. M. (2017). Mild cognitive impairment. *Clinics in Geriatric Medicine*, *33*(3), 325–337. https://doi.org/10.1016/j.cger.2017.02.005

Santa Maria, A., Lopez, A., Diaz, M. M., Munoz-Mingarro, D., Pozuelo, J. M., Muñoz-Mingarro, D., & Pozuelo, J. M. (1998). Evaluation of the toxicity of guarana with in vitro bioassays. *Ecotoxicology and Environmental Safety*, *39*(3), 164–167. https://doi.org/10.1006/eesa.1997.1576

Santana, Á. L., & Macedo, G. A. (2019). Effects of hydroalcoholic and enzyme-assisted extraction processes on the recovery of catechins and methylxanthines from crude and waste seeds of guarana (*Paullinia cupana*). *Food Chemistry*, *281*, 222–230. https://doi.org/10.1016/j.foodchem.2018.12.091

Santana, Á. L., Queirós, L. D., Martínez, J., & Macedo, G. A. (2019). Pressurized liquid- and supercritical fluid extraction of crude and waste seeds of guarana (*Paullinia cupana*): Obtaining of bioactive compounds and mathematical modeling. *Food and Bioproducts Processing*, *117*, 194–202. https://doi.org/10.1016/j.fbp.2019.07.007

Santos, H. M., Coutinho, J. P., Amorim, F. A. C., Lôbo, I. P., Moreira, L. S., Nascimento, M. M., & de Jesus, R. M. (2019). Microwave-assisted digestion using diluted HNO_3 and H_2O_2 for macro and microelements determination in guarana samples by ICP OES. *Food Chemistry*, *273*, 159–165. https://doi.org/10.1016/j.foodchem.2017.12.074

Schimpl, F. C., Da Silva, J. F., Gonçalves, J. F. D. C., Mazzafera, P., Goncalves, J. F. D., & Mazzafera, P. (2013). Guarana: Revisiting a highly caffeinated plant from the Amazon. *Journal of Ethnopharmacology*, *150*(1), 14–31. https://doi.org/10.1016/j.jep.2013.08.023

Scholey, A., Bauer, I., Neale, C., Savage, K., Camfield, D., White, D., Maggini, S., Pipingas, A., Stough, C., & Hughes, M. (2013). Acute effects of different multivitamin mineral preparations with and without Guaraná on mood, cognitive performance and functional brain activation. *Nutrients*, *5*(9), 3589–3604. https://doi.org/10.3390/nu5093589

Schuster, J., & Mitchell, E. S. (2019). More than just caffeine: Psychopharmacology of methylxanthine interactions with plant-derived phytochemicals. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *89*, 263–274. https://doi.org/10.1016/j.pnpbp.2018.09.005

SEBRAE. (2016, January 7). *O cultivo e o mercado do guaraná*. https://www.sebrae.com.br/sites/PortalSebrae/artigos/o-cultivo-e-o-mercado-do-guarana,969a9e665b182410VgnVCM100000b272010aRCRD

Sette, C. V. d. M., Ribas de Alcântara, B. B., Schoueri, J. H. M., Cruz, F. M., Cubero, D. d. I. G., Pianowski, L. F., Peppone, L. J., Fonseca, F., & del Giglio, A. (2018). Purified dry *Paullinia cupana* (PC-18) extract for chemotherapy-induced fatigue: Results of two double-blind randomized clinical trials. *Journal of Dietary Supplements*, *15*(5), 673–683. https://doi.org/10.1080/19390211.2017.1384781

Shahidi, F., Vamadevan, V., Oh, W. Y., & Peng, H. (2019). Phenolic compounds in agri-food by-products, their bioavailability and health effects. *Journal of Food Bioactives*, *5*, 57–119. https://doi.org/10.31665/JFB.2019.5178

Shahidi, F., & Zhong, Y. (2015). Measurement of antioxidant activity. *Journal of Functional Foods*, *18*, 757–781. https://doi.org/10.1016/j.jff.2015.01.047

Silva, C. P., Sampaio, G. R., Freitas, R. A. M. S., & Torres, E. A. F. S. (2018). Polyphenols from guarana after in vitro digestion: Evaluation of bioacessibility and inhibition of activity of carbohydrate-hydrolyzing enzymes. *Food Chemistry*, *267*, 405–409. https://doi.org/10.1016/j.foodchem.2017.08.078

Silva, C. P., Soares-Freitas, R. A. M., Sampaio, G. R., Camargo, A. C. d., & Torres, E. A. F. S. (2019). Guarana as a source of bioactive compounds. *Journal of Food Bioactives*, *6*, 1–5. https://doi.org/10.31665/JFB.2019.6182

Silva, M. P., Thomazini, M., Holkem, A. T., Pinho, L. S., Genovese, M. I., & Fávaro-Trindade, C. S. (2019). Production and characterization of solid lipid microparticles loaded with guaraná (*Paullinia cupana*) seed extract. *Food Research International*, *123*, 144–152. https://doi.org/10.1016/j.foodres.2019.04.055

Silvestrini, G. I., Marino, F., & Cosentino, M. (2013). Effects of a commercial product containing guaraná on psychological well-being, anxiety and mood: A single-blind, placebo-controlled study in healthy subjects. *Journal of Negative Results in BioMedicine*, *12*(1), 9. https://doi.org/10.1186/1477-5751-12-9

Smith, N., & Atroch, A. L. (2010). Guarana's journey from regional tonic to aphrodisiac and global energy drink. *Evidence-Based Complementary and Alternative Medicine*, *7*(3), 279–282. https://doi.org/10.1093/ecam/nem162

Sousa, S. A., Alves, S. F., de Paula, J. A. M., Fiuza, T. S., Paula, J. R., & Bara, M. T. F. (2010). Determination of tannins and methylxanthines in powdered guarana (*Paullinia cupana* Kunth, Sapindaceae) by high performance liquid chromatography. *Revista Brasileira De Farmacognosia-Brazilian Journal of Pharmacognosy*, *20*(6), 866–870. https://doi.org/10.1590/s0102-695X2011005000001

Stringer, T. P., Guerrieri, D., Vivar, C., & Van Praag, H. (2015). Plant-derived flavanol (-)epicatechin mitigates anxiety in association with elevated hippocampal monoamine and BDNF levels, but does not influence pattern separation in mice. *Translational Psychiatry*, *5*(1), e493–e493. https://doi.org/10.1038/tp.2014.135

Sun, L., & Miao, M. (2020). Dietary polyphenols modulate starch digestion and glycaemic level: A review. *Critical Reviews in Food Science and Nutrition*, *60*(4), 541–555. https://doi.org/10.1080/10408398.2018.1544883

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Taddei, C., Zhou, B., Bixby, H., Carrillo-Larco, R. M., Danaei, G., Jackson, R. T., Farzadfar, F., Sophiea, M. K., Di Cesare, M., Iurilli, M. L. C., Martinez, A. R., Asghari, G., Dhana, K., Gulayin, P., Kakarmath, S., Santero, M., Voortman, T., Riley, L. M., Cowan, M. J., … Ezzati, M. (2020). Repositioning of the global epicentre of non-optimal cholesterol. *Nature*, *582*(7810), 73–77. https://doi.org/10.1038/s41586-020-2338-1

Teixeira, C. F., da Cruz, I., Ribeiro, E. E., Pillar, D. M., Turra, B. O., Praia, R. S., Barbisan, F., Alves, A. O., Sato, D. K., Assmann, C. E., Palma, T. V., Barcelos, R. P., Barbosa, I. M., & Azzolin, V. F. (2021). Safety indicators of a novel multi supplement based on guarana, selenium, and L-carnitine: Evidence from human and red earthworm immune cells. *Food and Chemical Toxicology*, *150*, 112066. https://doi.org/10.1016/j.fct.2021.112066

Tej, G. N. V. C., & Nayak, P. K. (2018). Mechanistic considerations in chemotherapeutic activity of caffeine. *Biomedicine and Pharmacotherapy*, *105*, 312–319. https://doi.org/10.1016/j.biopha.2018.05.144

Trebatická, J., & ųuračková, Z. (2015). Psychiatric disorders and polyphenols: Can they be helpful in therapy? *Oxidative Medicine and Cellular Longevity*, *2015*, 248529. https://doi.org/10.1155/2015/248529

U.S. Department of Agriculture. (2020a). FoodData Central—Coffee, espresso. https://fdc.nal.usda.gov/fdc-app.html#/food-details/1104140/nutrients

U.S. Department of Agriculture. (2020b). FoodData Central—Tea, hot, leaf, black. https://fdc.nal.usda.gov/fdc-app.html#/food-details/1104260/nutrients

U.S. Food and Drug Administration. (2018, December 12). Spilling the beans: How much caffeine is too much? https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much

Ushirobira, T. M. A., Yamaguti, E., Uemura, L. M., Audi, E. A., & Mello, J. C. P. (2004). Avaliacao fisico-quimica de sementes de guarana secas por diferentes metodos [Physico-chemical evaluation of guarana seeds dried by different methods]. *Revista Brasileira de Farmacogsia*, *14*(1), 15–20.

Veasey, R. C., Haskell-Ramsay, C. F., Kennedy, D. O., Wishart, K., Maggini, S., Fuchs, C. J., & Stevenson, E. J. (2015). The effects of supplementation with a vitamin and mineral complex with Guarana prior to fasted exercise on affect, exertion, cognitive performance, and substrate metabolism: A randomized controlled trial. *Nutrients*, *7*(8), 6109–6127. https://doi.org/10.3390/nu7085272

Veiga, L. L. A., Amorim, H., Moraes, J., Silva, M. C., Raices, R. S. L., & Quiterio, S. L. (2014). Quantification of polycyclic aromatic hydrocarbons in toasted guarana (*Paullinia cupana*) by high-performance liquid chromatography with a fluorescence detector. *Food Chemistry*, *152*, 612–618. https://doi.org/10.1016/j.foodchem.2013.11.154

Ventura, S., Rodrigues, M., Falcao, A., & Alves, G. (2018). Effects of *Paullinia cupana* extract on lamotrigine pharmacokinetics in rats: A herb-drug interaction on the gastrointestinal tract with potential clinical impact. *Food and Chemical Toxicology*, *115*, 170–177. https://doi.org/10.1016/j.fct.2018.03.011

White, D. J., Camfield, D. A., Maggini, S., Pipingas, A., Silberstein, R., Stough, C., & Scholey, A. (2017). The effect of a single dose of multivitamin and mineral combinations with and without guarana on functional brain activity during a continuous performance task. *Nutritional Neuroscience*, *20*(1), 8–22. https://doi.org/10.1179/1476830514y.0000000157

World Health Organization. (2020a, December 9). The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

World Health Organization. (2020b, April 1). Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

World Health Organization. (2020c, September 21). Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia

Xu, Y., Li, S., Chen, R., Li, G., Barish, P. A., You, W., Chen, L., Lin, M., Ku, B., Pan, J., & Ogle, W. O. (2010). Antidepressant-like effect of low molecular proanthocyanidin in mice: Involvement of monoaminergic system. *Pharmacology Biochemistry and Behavior*, *94*(3), 447–453. https://doi.org/10.1016/j.pbb.2009.10.007

Yanishlieva, N. V., & Marinova, E. M. (2001). Stabilisation of edible oils with natural antioxidants. *European Journal of Lipid Science and Technology*, *103*(11), 752–767. https://doi.org/10.1002/1438-9312(200111)103:11/752::AID-EJLT752/3.0.CO;2-0

Yonekura, L., Martins, C. A., Sampaio, G. R., Monteiro, M. P., Cesar, L. A. M., Mioto, B. M., Mori, C. S., Mendes, T. M. N., Ribeiro, M. L., Arcari, D. P., & Torres, E. (2016). Bioavailability of catechins from guarana (*Paullinia cupana*) and its effect on antioxidant enzymes and other oxidative stress markers in healthy human subjects. *Food & Function*, *7*(7), 2970–2978. https://doi.org/10.1039/c6fo00513f

Zhang, H., & Tsao, R. (2016). Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Current Opinion in Food Science*, *8*, 33–42. https://doi.org/10.1016/j.cofs.2016.02.002

How to cite this article: Torres, E. A. F. S., Pinaffi-Langley, A. C. C., Figueira, M. S., Cordeiro, K. S., Negrão, L. D., Soares, M. J., da Silva, C. P., Alfino, M. C. Z., Sampaio, G. R., & de Camargo, A. C. (2022). Effects of the consumption of guarana on human health: A narrative review. *Compr Rev Food Sci Food Saf*. *21*,272–295. https://doi.org/10.1111/1541-4337.12862