Guaraná (Paullinia cupana, Sapindaceae) is found exclusively in the Amazon region. The fruit resembles the human eye, which exemplifies the cultural significance of guaraná to the indigenous population. Historical use records of guaraná date back to the 17th century. Guaraná was consumed daily for energy and medicinal purposes including treatment for headache, diarrhea, fever, and cramps. Traditional medicine also describes protective benefits against malaria and parasitic diseases. During the colonial period, guaraná was used as a tonic, stimulant, and aphrodisiac. It gained considerable popularity during the 20th century as a soft drink and has since become synonymous with such drinks in Brazil. More recently, animal, cell, and human studies have reported its use to treat headaches, diarrhea, and urinary diseases. Guaraná has been shown to have beneficial effects on cognitive function, cancer, cardiovascular disease, and diabetes. The purpose of this narrative review was to compile available information regarding guaraná and its effects on human health. Additionally, this review aimed to describe possible applications in emerging areas of human health and provide a framework for future studies.

A keyword search was performed using Google Scholar, PubMed, SciELO, Science Direct, Embase, and Scopus databases. Articles in English, Spanish, and Brazilian Portuguese were included. No other study design information was included. A flow diagram was not included.

The chemical composition of guaraná varies due to genotype, cultivar, location, and climate. Based on this variability, the genotypes are classified into three chemotypes: energetic, antioxidant, and both energetic and antioxidant. Depending on the region, guaraná extracts contain distinctly different proportions of bioactive compounds. This, along with low yields, presents an obstacle to the use of guaraná to its full potential as an herbal medicine. Additionally, processing methods also affect guaraná’s composition. Studies showed that sun-dried seeds using a clay pot for two hours lost considerable amounts of polyphenols and methylxanthines compared with a reference sample,
whereas roasting in a metallic pot for 2.5 to 4 hours showed greater polyphenol concentrations than the reference sample.

The most abundant bioactive compounds are caffeine and flavonoids catechin and epicatechin. Guaraná contains more caffeine than coffee (Coffea spp., Rubiaceae), black tea (Camellia sinensis, Theaceae), and cacao (Theobroma cacao, Malvaceae) in the form of chocolate. Guaraná also contains a higher percentage of flavan-3-ol than cocoa powder, cacao bean, and green tea. Guaraná contains important trace minerals including manganese (Mn), iron (Fe), and zinc (Zn). Caffeine is most bioavailable, whereas polyphenols were shown to have relatively low but sufficient bioavailability.

The antioxidant properties of guaraná have been demonstrated through in vitro, in vivo, and animal studies. In a human trial completed with healthy participants, supplementation of 3 g of guaraná powder reduced damage caused by peroxyl radicals while reducing ex vivo oxidation of low-density lipoprotein cholesterol (LDL-c). The study showed that bioavailable catechins reduced oxidative stress markers through direct antioxidant activity and increased antioxidant and detoxifying enzymes. The study showed that daily intake had acute and cumulative effects that reduced peroxides in water molecules. However, antioxidant status markers only improved temporarily. Another study found that guaraná seeds are effective against food color deterioration and lipid and protein oxidation in pork burgers. Further studies are needed to determine the mechanisms of action and confirm antioxidant effects in humans.

Guaraná has demonstrated anti-inflammatory properties as observed in animal models. No human studies were reported. The authors noted that further studies on humans are necessary to confirm the anti-inflammatory effects and applicability in human health.

Guaraná powder has been shown to have anti-obesity and cardioprotective effects. Studies have demonstrated anti-obesity effects in animal models as well as overweight or obese participants. A 15-day intervention with a daily intake of 3 g of guaraná seed powder (90 mg (+)-catechin and 60 mg (-)-epicatechin) demonstrated improvement in LDL-c oxidation levels. Another in vivo study with healthy older adults showed that regular consumption of guaraná lowered LDL-c levels at doses of 1 and 5 µg/mL. A study conducted on older adults of the Amazon region of Maués, Brazil found a significant association between habitual guaraná consumption (≥ twice a week) and lower oxidative protein product levels in both men and women and lower LDL-c levels in women. Animal studies have shown potential for the use of guaraná in weight management, in that guaraná prevented weight gain and increased energetic metabolism.

The studies examining weight loss in human participants generally used guaraná in combination with other ingredients. One study concluded that multi-ingredient mixtures acted synergistically to control weight through several factors. Another study showed that a capsule preparation containing 112 mg of yerba maté (Ilex paraguariensis, Aquifoliaceae), 95 mg of guaraná, and 36 mg of damiana (Turnera diffusa var. aphrodisiaca, Passifloraceae) resulted in significant reduction in food intake, energy intake, hunger, and desire to eat. Ingestion significantly reduced weight over 10- and 45-days in overweight patients. After a 12-month follow-up, patients maintained a constant weight. Other studies using different herbal combinations that included guaraná found significant changes in body composition, 24-h energy expenditure, increased metabolic rate, and changes in obesity markers.
Only two studies were identified that examined the beneficial effects of guaraná use on diabetes. Both were in vitro studies. Both studies demonstrated that polyphenols inhibited \( \alpha \)-glucosidase and \( \alpha \)-amylase activities. One reported that the activity was dose dependent.

In vitro, in vivo, and animal studies have demonstrated anti-cancer activity of guaraná suggesting that it has chemopreventive, antitumor, antimutagenic, and anticarcinogenic effects. Human studies show conflicting results. In one clinical study, 75 mg/day of guaraná was administered to patients diagnosed with breast cancer undergoing radiotherapy. No improvements were observed in post-treatment depression and fatigue. In another study, 50 mg twice daily for 21 days was administered during the first cycle of chemotherapy in patients diagnosed with breast cancer. Patients were evaluated at days 1, 21, and 49. Results of this study showed that guaraná improved acute fatigue, sleep disturbances, anxiety, and depression. The authors attributed the finding to the simulating effects of guaraná. A study on patients diagnosed with head and neck carcinoma undergoing chemotherapy showed no beneficial use of guaraná. Administration of 50 mg of dry guaraná extract twice daily for four weeks to patients with advanced cancer showed improved appetite, reduced drowsiness, and stable weight. The same dose over six weeks resulted in a significant reduction in the intensity of hot flashes (the population was not disclosed). The authors note that most studies focused on the use of guaraná to treat symptoms of the disease and side effects from cancer treatment. Very few studies investigated the use of guaraná as a cancer therapy or prevention; thus, the authors recommend that further studies are needed to substantiate anti-cancer activity of guaraná.

Guaraná may have protective qualities against cognitive decline. In human studies, guaraná powder improved attention, memory, and speed of performance with doses of 35 to 75 mg/day over five days. A dose of 300 mg/day over five days showed improved alertness. Dose amounts over 300 mg showed no significant effects. A dose of 37.5 mg/day in a drink also containing vitamins and Asian ginseng (Panax ginseng, Aralioidae) consumed before and after exercise improved cognitive performance, and with a dose of 300 mg/day improved information processing. A dose of 1500 mg of guaraná before physical exercise improved cognition related to decision-making. Several studies using different doses and combination with vitamins and minerals showed similar effects in cognitive performance, decision making, and reaction time.

Animal models have shown potential benefits of guaraná consumption in depression. However, clinical studies on patients with diagnosed tumors and/or undergoing chemotherapy showed that doses between 50 and 100 mg/day had no effect on depression. The authors emphasize that these patients were not clinically depressed. Further research is needed to determine the effect of guaraná on depression.

Animal and in vivo studies have demonstrated that guaraná has low toxicity and is safe in low doses with prolonged consumption. The most commonly reported adverse events in human studies include insomnia, anxiety, tachycardia, mucositis, and gastric pain. Other adverse events included nausea, headache, sweating, anxiety, and constipation.

The authors suggest that more human studies are necessary to "effectively translate the use of guaraná in clinical practice." However, the authors emphasize that cell and animal studies are necessary to continue to explore the mechanisms of action as well as the toxicological and pharmacological effects of guaraná. Further studies should also...
investigate possible pharmacological interactions. The authors conclude that "guaraná is a culturally important plant that produces fruits with great potential for human health applications."

The authors declare no conflict of interest.

—Samaara Robbins