

A SEGURANÇA DE SUPLEMENTOS PARA PERDA DE PESO CONTENDO GUARANÁ: UMA MINI-REVISÃO

SAFETY OF GUARANA-CONTAINING WEIGHT LOSS SUPPLEMENTS: A MINI-REVIEW

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Resumo: Centenas de preparações à base de plantas são atualmente comercializadas como suplementos para perda de peso, mas a segurança de vários destes é incerta. O suplemento que tem gerado interesse é o guaraná. Guaraná é um componente comum de diversas preparações de ervas, e é normalmente comercializado como um auxiliar à perda de peso e como um potenciador de exercício. Preocupações têm sido levantadas sobre a segurança do guaraná. Vários relatos de casos indicam possíveis riscos à saúde associados ao uso de guaraná. A literatura relata casos envolvendo o uso de suplementos com guaraná utilizado sozinho ou em combinação com outros produtos. Foram revisados os estudos clínicos e relatos de caso que descreveram eventos adversos. Foram encontrados 14 artigos com relatos de eventos adversos. Estes incluíram arritmias cardíacas, convulsões, necrose tubular aguda, insuficiência hepática e rabdomiólise. Eventos adversos ocorreram em pessoas que tomaram suplementos ou bebidas contendo guaraná, assim como em indivíduos que consomem guaraná somente em comprimidos ou bebidas. Não houve eventos adversos em um ensaio clínico com doses aparentemente baixas de cafeína no extrato de guaraná. Os profissionais de saúde devem ser mais atentos para possíveis eventos adversos em pacientes que consomem guaraná. O cuidado deve ser exercido em indivíduos que consomem este suplemento, e uma maior vigilância é necessária para monitorar adequadamente os eventos adversos associados como uso crônico.

Palavras-chave: Guaraná/eventos adversos. Perda de peso. Relatos de caso. Ensaio clínico.

Abstract: *Hundreds of herbal preparations are presently marketed as weight loss supplements, but the safety of several of these is uncertain. One such supplement which has generated interest is guarana. Guarana is a common component of several herbal mixtures, and is commonly marketed as a weight loss aid, and as an exercise enhancer. Concerns have been raised about the safety of guarana-containing supplements, and several case reports indicating possible health hazards linked to the use of guarana are documented in the literature. Literature case reports involving the use of supplements involving guarana, either alone or in combination with other products was reviewed and the reported adverse events were documented. Reports of adverse events from clinical trials involving the use of guarana-containing supplements as weight loss aids were also reviewed. 14 articles with reports of adverse events were identified both from case reports and*

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clinical trials. These included cardiac arrhythmias, seizures, acute tubular necrosis, hepatic failure and rhabdomyolysis. Adverse events occurred in persons taking combination supplements or drinks containing guarana, as well as in individuals consuming guarana-only pills or drinks. There were no adverse events in a clinical trial with seemingly low doses of caffeine in the guarana extract. Physicians should be more vigilant in watching for possible adverse events in patients consuming guarana. Caution should be exercised in individuals consuming this supplement, and greater surveillance is needed to adequately monitor for adverse events associated with its chronic use.

Key words: Guarana/ Adverse events. Weight loss. Case reports. Clinical trials as topic.

INTRODUCTION

The increase in prevalence of overweight and obesity has resulted in the popularity of weight loss supplements. Hundreds of these supplements are currently marketed, but the safety of several is uncertain. One such supplement which has generated interest is guarana.

Guarana, also referred to as guaranine, *Paullinia spp.* is a plant which is native to the Amazon basin¹, and is commonly used by inhabitants of this region for improving awareness and energy². Guarana contains mainly caffeine, with smaller amounts of theophylline and theobromine³. It is thought to promote weight loss by increasing metabolism⁴, as well as suppressing appetite⁵. Guarana is commonly available as an over-the-counter pill, and is also a component of a variety of energy drinks⁶.

There has been an increasing concern regarding the safety of guarana as a weight loss supplement⁷. Results of an in-vitro study have shown that the cytotoxic activity of guarana could be harmful to human health⁸, though this has been disputed by the observations from other studies⁹⁻¹⁰. However, clinical signs of toxicity from ingestion of herbal mixtures containing guarana have been reported in animals, with the symptoms appearing within eight hours of oral intake¹¹.

A clinical toxicology study report concluded that consumption of an herbal mixture containing guarana was not associated with any serious adverse reactions (25 ml twice daily)¹². However, the study duration was 28 days, and data regarding its safety on the medium- and long-term are lacking. The objective of this mini-review was to examine the evidence from case reports and weight loss clinical trials reporting adverse events associated with the use of guarana products.

METHODS

Published articles and abstracts were identified by searching Pubmed, Medline and Google Scholar. The MeSH terms used included: "guarana" AND extracts, "guarana" AND adverse effects, "guaranine" AND adverse effects, "paullinia" AND adverse effects, "xenadrine" AND adverse effects, "guarana" AND obesity, "guaranine" AND obesity, "paullinia" AND obesity, "xenadrine" AND obesity, "guarana" AND weight loss, "guaranine" AND weight loss, "paullinia" AND weight loss, "xenadrine" AND weight loss, "guarana" AND ergogenic, "guarana" AND caffeine, "guarana" AND exercise, "guarana" AND safety, "guarana" AND toxicity, "guarana" and clinical trials, "guarana AND theophylline, "guarana AND theobromine. The bibliographies of identified articles were also searched. Case reports or series of adverse events involving the use of guarana-containing supplements for weight loss or to enhance energy expenditure were included in this review. Such reports had to indicate that the observed adverse event(s) occurred in humans, and may have likely been caused by the consumption of guarana-containing products. Adverse event reports of clinical trials involving the use of guarana-containing supplements for weight loss were also included. Case reports or clinical trials involving the use of guarana for purposes aside weight loss or energy expenditure enhancement were excluded.

RESULTS

We screened 186 abstracts, of which 172 were excluded. Reasons for exclusion included in-vitro studies, adverse event reports in animal studies, and case reports of adverse events in humans taking guarana for reasons other than weight reduction or energy enhancement. Thus 15 articles were identified and included in this review. The main adverse events observed in their reports are shown in Table 1.

Case reports of adverse events

Ten articles with case reports suggesting a possible association between consumption of guarana-containing weight loss supplements and adverse events were identified. In these reports, guarana was used either as a weight loss aid, or to enhance exercise performance.

Moaddeb et al¹³ (2011) reported a case of hypertensive urgency in a 34-year-old female patient who took Xenadrine EFX[®] for weight loss. The patient's blood pressure was controlled after stoppage of the supplement, with adjunct anti-hypertensive therapy. The authors concluded that physicians should monitor for potential cardiovascular adverse events in patients taking Xenadrine[®].

Cannon et al¹⁴ (2001) reported a fatal case of cardiac arrhythmia in a 25-year-old woman who consumed an energy drink containing guarana. The authors stressed the need for physicians to be more familiar with the toxic profile of such supplements.

Baghkani and Jafari¹⁵ (2002) reported a case of premature ventricular contraction in a 51-year-old woman who consumed two herbal supplements containing large amounts of guarana extracts for over four weeks. The patient had no prior history of cardiovascular disease. Her palpitations subsided 10 days after stoppage of the supplements. The authors concluded that healthcare professionals should be aware of potential adverse events and toxicities associated with the use of guarana extracts.

Vágási et al¹⁶ (2007) reported a case of acute renal and hepatic failure in a 30-year-old female who took Guarana products over a considerable period of time. Wani et al¹⁶ (2006) also reported acute renal failure in a 24-year-old man who ingested Arsenal X[®] (a guarana-containing product) for a two-week duration. In both cases, the authors noted that severe risks may be associated with the use of such nutraceuticals.

Mansi and Huang¹⁷ (2004) reported a case of rhabdomyolysis in a middle-aged woman who had a history of consumption of herbal combination containing guarana, with the onset of symptoms within three hours after the intake of the supplement. The authors suggested that physicians measure creatine kinase enzymes in patients taking such herbal mixtures.

Dodadio et al¹⁸ (2000) reported a case of myoglobinuria in a 29-year-old male who ingested herbal mixture containing guarana, Ginkgo biloba and kava. The onset of symptoms (muscle pain and passage of dark urine) was a few hours after ingestion of the herbal mixture. The authors highlighted the dangers of the use of such herbal supplements.

Cerebral infarction in a 33-year-old man who consumed an herbal medicine containing both Ma Huang extract and guarana was reported by du Boisgueheneuc et al¹⁹ (2001). The authors stated that they could not find any other cause for the stroke, aside the use of the herbal mixture.

Kockler et al²⁰ (2001) reported a case of seizure in a 22-year-old man who took Hydroxycut[®] (a mixture of garcinia extracts and guarana) for a two-week duration. Iyadurai et al²¹ (2007) also reported a case series involving four patients who experienced multiple seizure episodes while consuming guarana-containing drinks; with the seizures being abated once they stopped consuming the drinks. Both groups of authors concluded that consumption of the guarana-containing drinks could have provoked the seizures.

Adverse event reports from weight loss clinical trials

Four randomized clinical trials (RCT) evaluating the effectiveness of guarana as a weight loss supplement, with documented reports on adverse events associated with its use were also identified.

Boozer et al²² (2001) conducted an eight-week RCT evaluating the efficacy of guarana-containing supplements for weight loss. The daily caffeine dosage of the subjects taking guarana was 282-330 mg. Two of the volunteers in the guarana group developed hypertension, five reported palpitations, and another reported irritability. These adverse events were serious enough to cause withdrawal of the participants. Dry mouth, insomnia and headache were also reported as adverse events. The authors concluded that the safety of the herbal supplement on the long-term warrants further investigation.

In a cross-over RCT, Haller et al²³ (2005) evaluated the metabolic and hemodynamic effects of guarana-containing supplement (Xenadrine RFA[®]). The dose of caffeine in the guarana extract was 800 mg; the placebo and Xenadrine[®] tablets were taken five hours apart. The authors reported that consumption of the supplement caused increases in heart rate, blood pressure and post-prandial glucose concentration, and significantly decreased serum potassium concentrations. They concluded that taking such supplements could have detrimental consequences in individuals with hypertension as well as atherosclerosis.

In a 12-week RCT evaluating the efficacy of a guarana-containing botanical extract as a weight loss supplement (0.5 to 3.7 cups of caffeine daily), Opala et al²⁴ (2006) did not report any serious adverse events associated with the use of guarana.

Armstrong et al²⁵ (2001) in a six-week RCT evaluated the efficacy of a guarana-containing thermogenic weight loss supplement (Xenadrine RFA-1) in 20 obese adults. The daily dosage of the guarana extract was 1820 mg, equivalent to 400 mg caffeine. Though they did not measure adverse events directly, increased heart rate and anxiety were reported in two subjects; the increase in heart rate was severe enough to result in a withdrawal in one of these subjects. The authors urged closer attention to monitoring of adverse events associated with the consumption of Xenadrine RFA-1.

DISCUSSION

The observations from case reports and clinical trials indicate that guarana intake is associated with adverse events which occurred in major organs and systems. While some of these events occurred in patients or volunteers consuming products containing other herbal medicines in addition to guarana, others occurred in individuals taking guarana-only supplements. It should also be noted that in the RCT that reported no adverse events with guarana consumption, the daily dosage of caffeine, though not specified, appears to be lower than the amounts of caffeine available in commercially-available guarana products.

As earlier noted, guarana contains high amounts of caffeine, and caffeine consumption is associated with an increased stimulation of the autonomic nervous system. High intake of caffeine (> 500mg daily) causes caffeinism, a condition which is characterized by numerous symptoms including restlessness, anxiety, agitation, palpitations and diarrhea²⁶. It therefore seems plausible that the adverse events observed in case series as well as clinical trials were due to the effect of guarana consumption.

Guarana contains small amounts of theophylline, which together with caffeine act as methylxanthines. Research reports have suggested that this methylxanthine combination can reduce seizure thresholds²⁷. Furthermore, theophylline alone is known to possess cardiotoxic potential, via inhibition of phosphodiesterases²⁸. Though not much research has been conducted on the third guarana component, theobromine, its pharmacology and toxicology properties are thought to be similar to those of caffeine²⁹⁻³¹. It is unclear if the manufacturers of guarana pills take this into account in the labelling of their products.

Aside its observed effects on major organs and systems, there is controversy regarding the effects of guarana on cellular tissues. Investigators have demonstrated that guarana could have genotoxic and mutagenic effects in prokaryotic organisms via oxygen reactive species³². Contrary to this however, a more recent study has shown that guarana could have cytoprotective effects by preventing the cytotoxic effects of rotenone³³. Though the findings from these cell culture studies are inconclusive, the paucity of data on the long-term safety of guarana suggests that development of cancers due to its ingestion for long periods cannot be ruled out in humans.

CONCLUSION

The totality of available evidence suggests that consumption of supplements containing guarana may be associated with harmful health effects. Caution should be exercised in individuals consuming this supplement, and greater surveillance is needed to adequately monitor for adverse events associated with its use.

Funding

None

Conflict of interest

None

Frame 1- Possible adverse events associated with the use of guarana-containing supplements

Organ/System	Adverse event(s)
Cardiovascular	Arrhythmias, hypertension, tachycardia, palpitation
Respiratory	Tachypnea
Nervous	Seizures, cerebral infarction, headache
Psychological/Psychiatric	Irritability, insomnia
Liver	Hepatic failure
Gastrointestinal	Worsening of diarrhea
Renal/Urinary	Acute tubular necrosis
Metabolic	Hyperglycemia, hypokalemia
Musculoskeletal	Myoglobinuria, rhabdomyolysis

Source: developed by the authors

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