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The effects of Guarana (Paullinia cupana) supplementation on the cognitive performance of young healthy adults – a Systematic Review.

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Abstract

OBJECTIVES: Guarana (Paullinia cupana) from the Sapindaceae family, native to the Amazon basin, is a natural stimulant herb that can be found in popular energy drinks, pharmaceutical shops or local herb shops. With the use of natural health products increasing, guarana has gained a fair amount of popularity in the past years. In this systematic review, we examined the effects of guarana supplementation on cognitive performance. A secondary objective was to compare guarana with caffeine on cognitive performance.

METHODS: Searches were made in PubMed using the terms 'Guarana' or 'Paullinia cupana'. Filters focused on Controlled Clinical trials. Inclusion criteria were met by studies using interventions with guarana, while focusing on guarana's effects on cognition. Participants needed to be young, healthy adults. Studies not published in English or Greek were excluded. The last date of our search was March 7, 2019.

RESULTS: A total of 29 studies were identified and screened. After screening, 17 studies were excluded. The remaining 12 studies were found eligible for data extraction. After reading the full text of the 12 studies, 3 studies were excluded. In the end, 9 studies were found eligible for our systematic review (n = 369 participants). In these studies, guarana showed to improve reaction time and accuracy of performance at cognitive tasks. No significant differences were found when comparing guarana with caffeine.

CONCLUSION: Guarana seems to improve reaction time and accuracy of performance at tasks, but no significant effects were found when compared with caffeine. High quality randomized controlled clinical trials with a low risk of bias are needed to further study the herb.

Keywords

Guarana, Paullinia Cupana, Caffeine, Cognition, Nootropics, Herbal Medicine, Systematic Review

INTRODUCTION

Cognition and Cognitive Enhancing Substances

Cognition is 'the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses' (*Oxford Dictionary*). Cognitive skills are perception, memory, language, attention, executive functions, psychomotor functions, information processing, applying knowledge and changing preferences (Froestl W, Muhs A, Pfeifer A, 2014).

Most cognitive enhancing substances, in general, are stimulants of the nervous system. Stimulants are known to increase physical and mental performance. They may interfere with the central nervous system or the peripheral nervous system. In the peripheral nervous system, stimulants increase the action of the sympathetic nervous system via stimulation of the hormone adrenaline. In the central nervous system, most stimulants interfere with the neurotransmitters norepinephrine, dopamine, glutamate or serotonin, increasing the activity of their circuits (Rang et al., 2012).

Substances that are used to improve cognitive function in healthy individuals are named nootropics (Frati et al., 2015). Nootropics act as direct or indirect agonists of dopamine receptor D1, adrenoceptor A2 or both types of receptors in the prefrontal cortex (Spencer, Devilbiss and Berridge, 2015), as vasodilators increasing blood flow to the brain, or by increasing glutaminergic neurotransmission (Noor Azuin Suliman et al., 2016). The most common nootropics are amphetamines (Wood et al., 2014) methylphenidate (Wood et al., 2014) eugeroics (modafinil, armodafinil) (Bagot, Kaminer, 2014) nicotine (Heishman, Kleykamp and Singleton, 2010) and caffeine (Wood et al., 2014).

Numerous cognitive tests are available for the assessment of cognition. However, with the completion of this systematic review, we have encountered great heterogeneity of cognitive tests across studies. In order to perform a meta-analysis of the outcome results, such heterogeneity must be eliminated. Thus, we propose the CDR computerized assessment system (Keith A. Wesnes, 2000) for the evaluation of the effects of guarana on cognition accompanied by the Serial of 3s and Serial of 7s tasks. The CDR battery has been found sensitive for the assessment of the cognitive effects of herbal extracts and can be used to both mentally impaired and healthy participants (Kennedy, 2004). The tests included in the CDR battery system are immediate/delayed word recall, word recognition, picture recognition, simple reaction time, digit vigilance, choice reaction time, numeric working memory and spatial working memory. The measurements of the single tests of the battery are combined into five cognitive outcome factors: 'Speed of Attention' factor, 'Speed of Memory' factor, 'Accuracy of Attention' factor, 'Secondary Memory' factor and 'Working Memory' factor. The battery may be accompanied with other cognitive tests, such as the Serial of 7s or Serial of 3s. The Serial of 7s test was proposed in 1942 Hayman and has been used for decades for the evaluation of memory and concentration by neurologists and psychiatrists. The simplicity of the test and its diachronic use make it a great supplementary cognitive test next to the CDR battery.

Guarana

Guarana (Paullinia cupana) is a plant that is very common in Latin America and is widely used in Brazil. the plant's seeds are about the size of coffee beans. Guarana beans contain about double the concentration of caffeine found in coffee beans (3.6–5.8% caffeine, compared to 1–2% found in coffee beans) (WebMD 2017).

The caffeine found in guarana, is named 'guaranine'. Guaranine is a synonym of caffeine (Liguori, Hughes, Grass, 1997). Guarana plants contain guaranine, as a defense mechanism against herbivore animals (Nathanson JA, 1984). Other than guaranine, guarana contains theophylline and theobromine (Espinola et al., 1997), as well as tannins, catechins, epicatechins (Haskell et al., 2006), which may contribute to a different behavioural effect from caffeine (Duchan, Patel, 2010).

Guarana has been used for centuries in North America and the Amazon (Henman, 1982; as cited by Haskell et al., 2006) as a stimulant and a nootropic. Native tribes have used the herb as an aphrodisiac, as an energy and endurance booster and as a wakefulness agent. In modern days, guarana is used for it's cognitive and physical enhancing properties. It is brewed in tea, eaten raw or supplemented in capsules. Also, it has become a very popular ingredient of mainstream energy drinks (van den Eynde et al., 2008). It is usually found at low concentrations in energy drinks and is thought to enhance the stimulating properties of caffeine.

Studies made on guarana show that the herb improves decision-making performance (Pomportes et al., 2014), temporal performance (Pomportes et al., 2017), task performance (Kennedy et al., 2004), working memory and attentional processing (Scholey et al., 2013). Promising effects in some cognitive domains were found by Haskell et al. (2007), Kennedy et al. (2004), Scholey et al. (2013) and Nehlig (2010).

We decided to perform this systematic review on guarana because of the increasing popularity of the herb. Guarana has been used for centuries in Latin America. In the modern age, the introduction of energy drinks and the trend of society towards Natural Health Products (NHPs), has boosted the worldwide market of guarana (Future Market Insights, 2016). A herb that was once used by indigenous tribes in the Amazon has now found it's way into local herb shops, popular energy drinks and pharmaceutical shops. In this review, we examine the effects of guarana (Paullinia cupana) on cognition. A secondary objective is to compare guarana with caffeine on cognitive performance. Such a comparison aims to evaluate the role of different compounds found in guarana and their possible synergy with guaranine.

METHODS

Type of Study

The study was a systematic review. Searches were made in PubMed. Search terms were 'Guarana' or 'Paullinia cupana'. The PubMed filter was customized to 'Controlled Clinical Trial'. The search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA criteria; Moher D et al., 2009). The last date of our search was March 7, 2019.

Study Selection

We selected studies using the following inclusion criteria:
a) The study must use an intervention containing guarana.
b) The study must examine the effects of the guarana intervention on cognition.
c) The population must be young adults. Young adults were defined as those who were younger than 45 years old. This

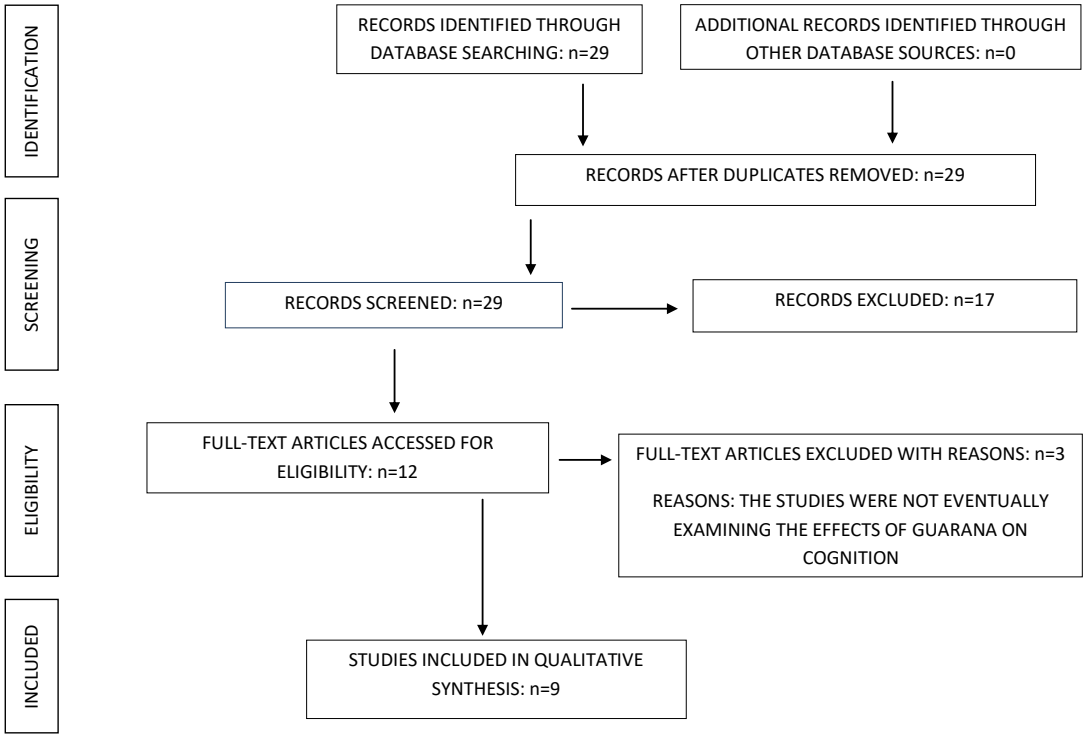

Figure 1. PRISMA Flowgraph Methods & Results of PubMed Database Search

age criterion was set to eliminate participants with possible cognitive deficiencies. Research suggests that cognitive decline may start as early as the age of 45 years (The BMJ, 2012).
d) The population must consist of healthy adults. Healthy participants were defined as those who were not systematically taking any illicit, over-the counter or medication drugs and free from psychiatric or neurological disorders.
e) Must be a controlled-clinical trial.

We excluded studies using the following criteria:
a) The studies that were not published in the English or Greek language were excluded.
b) No criteria on the date of publication were set

Risk of Bias

Of the 9 controlled clinical trials included in our review, 7 were randomized controlled clinical trials and 2 were non-randomized controlled trials. The 2 non-randomized controlled trials were assumed to have a relatively high risk of bias. The risk of bias for the 7 randomized controlled trials was assessed with the Cochrane tool for assessing risk of bias (Julian P T Higgins et al., 2011). The results are presented in figures 2 and 3.Studies using mixed guarana interventions were thought to have a relatively high risk of bias, even if the trial was conducted in a manner to eliminate bias. From the 7 randomized controlled trials included, 2 studies used guarana interventions with ginseng and vitamins, while 4 studies used guarana interventions with vitamins. The 2 studies with the guarana/ginseng interventions were thought to have a high risk of bias. Even though current research has not confirmed a nootropic effect of ginseng (Geng J et al., 2010), the herb is considered a popular nootropic in eastern societies. We did not exclude the 2 studies using guarana/ginseng interventions, but we must be cautious with the results they provide. The 4 studies using guarana interventions with multivitamins were also thought to have a potential risk of bias, but in a lesser degree. Regarding multivitamin supplements and cognitive performance (Grima NA et al., 2012) reported at their systematic review and meta-analysis, that multivitamin supplements were found to enhance immediate free recall memory but no other cognitive domains. The application of the Cochrane tool revealed that only 4 out of the 7 randomized controlled trials had a 'low risk of bias' score for at least 4 out of the 7 sections of the tool. Three of these studies used guarana interventions with multivitamins and one study used guarana intervention with ginseng and multivitamins. The latter was considered to have a potentially high risk of bias. In the end, a total of 3 studies were considered to have a relatively low risk of bias, the results of which are also presented individually.

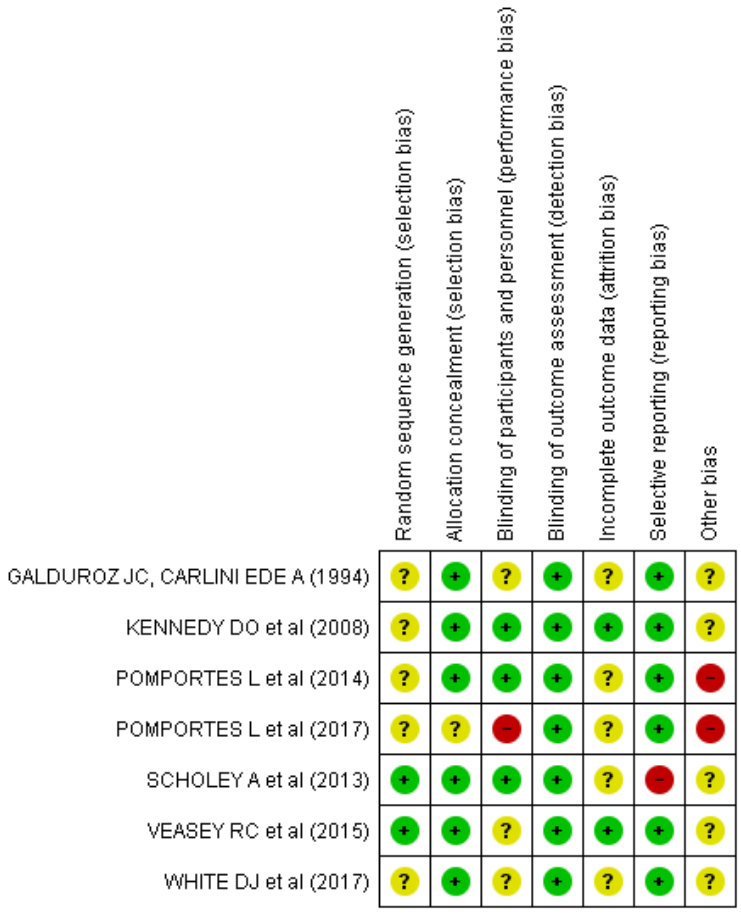

Figure 2. "Risk of Bias Summary"

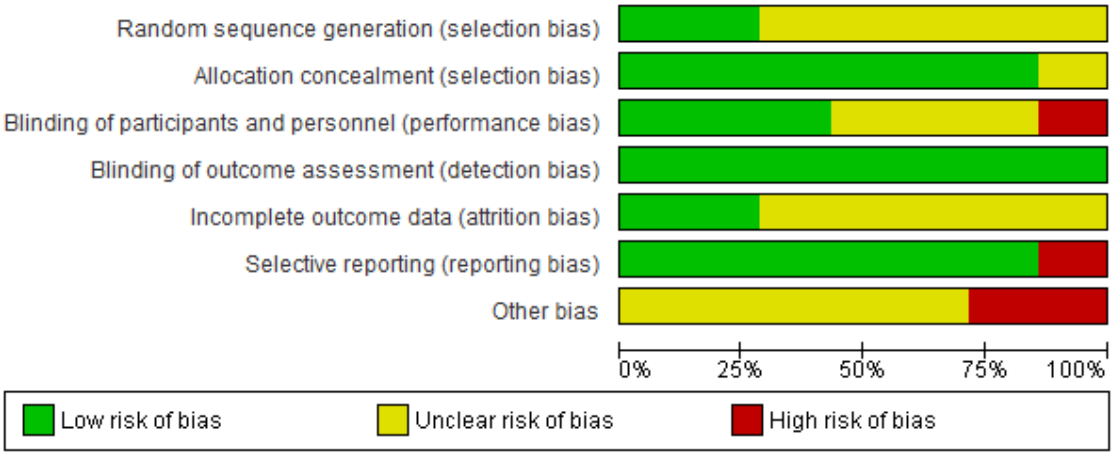

Figure 3. "Risk of Bias Graph"

RESULTS

Data extraction

One author independently extracted the data. After using the methods, a total of 29 controlled clinical trials were identified. All of the 29 trial abstracts were screened. After screening, 17 papers were excluded. These papers were excluded because they focused on guarana's effect on weight loss, metabolic parameters, blood pressure, heart rate, antiaging properties, anorexia, fatigue, physical endurance, depression, anxiety or used elderly participants.

The full-text of the remaining 12 papers was read. Three papers were excluded after full-text reading. These studies were excluded because they were eventually examining guarana's effects on mood parameters and did not use any cognitive assessing tasks. All in all, 9 papers were found eligible for our study, 7 of which were randomized controlled trials and 2 were controlled trials. Five of the studies were published between the years 2010–2017, three of the studies were published between the years 2004–2008 and one study in 1994.

Included Studies

A total of nine studies were included in our systematic review. Seven of the studies were randomized controlled trials and two were controlled trials. With the use of the Cochrane Risk of Bias tool, we concluded that more than 50% of the randomized controlled trials used, shared a high risk or an unclear risk of bias in the domains of 'random sequence generation', 'blinding of participants and personnel', 'blinding of outcome assessment' and 'incomplete outcome data'. Low risk of bias was detected for more than 50% of the studies, in the domains of 'allocation concealment' and 'selective reporting'.

The total population of the included studies consisted of 369 participants, aged 18–45 years, who were not systematically taking any illicit, over-the-counter or medication drugs and who were free from psychiatric or neurological disorders. All participants were non-smokers and abstained from caffeine and alcohol at least 10 hours from testing.Regarding the interventions, three included studies used the intervention of guarana extract at the doses of 75 mg (10% caffeine); 500 mg (2% caffeine); 37.5 mg, 75 mg, 150 mg, 300 mg all at 10% caffeine. Four included studies used the intervention of a multivitamin/mineral supplement with added guarana (222.2 mg containing 40 mg of caffeine). One included study used the combination of vitamin/mineral /guarana (300 mg) and ginseng (100 mg) and another included study used a supplement of guarana complex (37.5 mg of guarana + 12.5 mg ginseng +22.5 mg vitamin C). Comparisons were made with multivitamin supplements, caffeine extract, carbohydrates, ginseng or placebo.

The included studies used various methods to assess the effects of the intervention on cognition, and thus, heterogeneity of methods across studies was present. Two studies used the Cognitive Drug Research (CDR) computerized assessment battery and two studies used the Cognitive Demand Battery. One study used the Digit Span, the Free Recall, the Digit Symbol, the Cancellation Test and the Mosaic test, while another study used the COMPASS and standard cognitive tasks. A go/no-go task and a simple reaction time task was used from an individual study, while the Duration-Production Task with the Simon Task was used from another. The A-X CPT task and IT task with the use of fMRI was used from an included study. Finally, one of the studies which used the Cognitive Demand Battery, also used fMRI imaging of the participants after guarana supplementation.

An overview of the PICOS, the duration and the control groups for each individual study used in our review, is presented in table 1.

MAIN FINDINGS – GUARANA AND COGNITION

The main findings of our systematic review are presented in sections of different cognitive domains, which seem to be influenced by guarana supplementation. The results are presented with P values for significant results. Effect sizes were not reported across the included studies and Eta squared could not be calculated. Thus, the Cohen's D was calculated when possible by the authors of this review and was reported for each significant outcome (Jacob Cohen, 1988). Our findings on the comparison between guarana and caffeine are reported in a separate section. Results from low risk of bias studies are presented both in the main findings section and also individually.

Reaction Time

Statistically significant improvements in reaction time at tasks were reported across studies. Specifically, Kennedy DO et al. (2004) reported statistically significant improvements of reaction time for the guarana treatment group at the digit vigilance task at 4 hours ($p < 0.05$; $d = 0.47$) and at 6 hours ($p < 0.0005$; $d = 0.8$) post-dose in comparison with the placebo group. At the choice reaction time task, statistically significant improvements for the guarana treatment group in comparison with the placebo group were reported at 1 hour ($p < 0.05$; d

Table 1. PICOS, Duration and Control groups of Individual Studies Used

REFERENCE	STUDY TYPE	POPULATION	INTERVENTION	COMPARISON	OUTCOME	DURATION	CONTROL
GALDUROZ JC, CARLINI EDE A (1994)	Double Blind Randomized Controlled Trial	30 Healthy participants (mean age 28); 6 males; 24 females	500mg of guarana	12.5mg of caffeine; placebo	Guarana's effects on cognition and mood	1 familiarization visit and 2 experimental visits conducted with a 24h difference.	10 participants used caffeine; 10 participants placebo
HASKELL C.F. et al (2007)	Double-Blind, Counterbalanced, Placebo-Controlled Study	26 Healthy participants (mean age 21.38; 8 males, 18 females) 5 participants excluded	37.5mg/ 75mg/ 150mg/ 300mg/ guarana capsules	Placebo	Behavioral and Cognitive effects of Guarana supplementation	1 training session and 5 study days	Each participant was his own control
KENNEDY DO et al (2004)	Double-Blind, Counterbalanced, Placebo-Controlled Study	28 Healthy participants (mean age 21.4; 9 males, 19 females)	75mg of Guarana; 200mg of Ginseng; 75mg guarana/ 200mg ginseng	Placebo	Cognitive and Mood effects of guarana supplementation.	1 familiarization day; 4 experimental days all 7 days apart	Each participant was his own control
KENNEDY DO et al (2008)	Double-Blind, Randomized, Placebo-Controlled, Parallel Groups Study	130 Healthy participants (mean age 20.98; 60 males, 70 females) 3 participants were later excluded from the study.	Vitamin/Mineral/ Guarana (222.2mg) capsules	Placebo	The acute effects of guarana on cognition.	1 familiarization day and 14 days later, 1 experimental day	64 participants on placebo
POMPORTES L et al (2014)	Randomized, Double-Blind Crossover Design	56 Healthy participants (mean age of males 27.7; mean age of females 29.5; 32 males, 24 females)	Vitamin/Mineral/ Guarana (300mg) /Ginseng (100mg) supplement	Caffeine supplement; Placebo	Cognitive performance after guarana supplementation.	3 separate sessions with at least 48h difference.	Each participant was his own control
POMPORTES L et al (2017)	Randomized Controlled Counterbalanced Cross-over Study	24 Physically active participants (mean age 26; 16 males, 8 females)	Guarana complex (37.5 mg of guarana+ 12.5 mg ginseng +22.5 mg Vitamin C	Carbohydrate complex/ 67mg Caffeine/ Placebo	Cognitive performance during a 40-min submaximal exercise	1 preliminary session; 1 training session; 4 experiment-al sessions (2 per week)	Each participant was his own control
SCHOLEY A et al (2013)	Double-Blind, Placebo-Controlled, Randomized, Balanced Crossover Design	20 Healthy participants (mean age 28.35; 8 males, 12 females) + 5 Healthy participants (mean age 28.4) in fMRI testing	Multivitamin supplement with 222.2mg of guarana	Multivitamin supplement without guarana; placebo	Effects of multivitamin/ guarana preparation on cognitive performance and fMRI imaging.	1 practice visit and 3 study days	Each participant was his own control
VEASEY RC et al (2015)	Placebo-Controlled, Double-Blind, Randomized, Balanced Cross-Over Study	40 Healthy participants (Age: 21.4 ± 3.0 years; 40males, 0 females)	Multivitamin and mineral complex with guarana (222.2 mg)	Placebo	Effect of multivitamin preparation with guarana on the cognition and mental fatigue after fasted exercise	Visit 1; (at least after 48h) Visit 2; (at least after 48h) Visit 3; (at least after 7 days) Visit 4.	Each participant was his own control
WHITE DJ et al (2017)	Double-Blind, Placebo-Controlled, Randomized, Balanced Crossover Design Study	20 Healthy participants (mean age 28.35) of which 2 were excluded from SSVEP	Multivitamin supplement with guarana (222.2 mg)	Multivitamin supplement without guarana; placebo	Cognitive effects of multivitamins with/ without guarana and fMRI imaging	1 familiarization visit and 3 testing visits.	Each participant was his own control

= 0.42) and at 4 hours (p < 0.05; d = 0.31). Furthermore, at the picture recognition task, significant improvements were reported for the guarana treatment group in comparison with the placebo group at 1 hours (p < 0.05; d = 0.43), at 2.5 hours (p < 0.05 d=0.55) and at 4 hours (p < 0.005; d = 0.83). Finally, at the sentence verification task, statistically significant improvements were found for the treatment group in comparison with the placebo group at 2.5 hours (p = 0.001; d = 0.59), at 4 hours (p < 0.05; d = 0.36) and at 6 hours (p < 0.05; d = 0.35). Haskell C.F. et al. (2007) reported statistically significant improvements at reaction time for the guarana treatment group in comparison with the placebo group on the delayed word recognition task (p = 0.021; 37.5 mg dose d = 0.03; 75 mg dose d = 0.37; 150 mg dose d = 0.26; 300 mg dose d = 0.15). Veasey RC et al. (2015) reported a main effect of the guarana treatment for the picture recognition reaction time (p = 0.0496; d = 0.40) in comparison with the placebo. Kennedy DO et al. (2008) reported that the guarana treatment group performed faster at each post dose repetition of the RVIP task with the exception of the fifth in comparison with placebo (rep 1 p < 0.001, d = 0.33; rep 2 p < 0.001, d = 0.22; rep 3 p < 0.05, d = 0.12; rep 4 p < 0.001, d = 0.58; rep 5 p > 0.05 and at rep 6 p < 0.001, d = 0.37; repetitions 1–6 p < 0.05).Pomportes L et al. (2015) found improvements for reaction time at the go/no go task for the guarana group in comparison with the placebo group at the 45th minute (p < 0.05; d = 0.71), at the 60th minute (p < 0.05; d = 1.02) and at the 90th minute (p < 0.05; d = 1.21). Finally, Pomportes L et al. (2017) found a difference (81% likely effect) between guarana supplementation and placebo supplementation on the produced durations (reaction time) at the duration-production task (d = 0.38).

Accuracy of Performance

Statistically significant improvements in the accuracy of performance were reported across studies. Kennedy DO et al. (2008) reported that accuracy of performance significantly improved for the guarana treatment group in comparison with the placebo group at the RVIP task for each of the post-dose repetitions. Specifically, at rep 1 (p < 0.001; d = 0.27), at rep 2 (p < 0.001; d = 0.31), at rep 3 (p < 0.001; d = 0.51), at rep 4 (p < 0.001; d = 0.58), at rep 5 (p < 0.001; d = 0.53), and at rep 6 (p < 0.001; d = 0.37) [repetitions 1–6 (p < 0.001)]. Veasey RC et al. (2015) reported statistically significant improvement at the numeric working memory accuracy of performance (p = 0.001; d = 0.71) for the guarana treatment group in comparison with the placebo group. Statistically significant improvements for the guarana treatment group in comparison with the placebo group were reported by Haskell CF et al. (2007) at the accuracy of performance of the choice reaction time task (p = 0.03; 37 mg dose d = 0.39; 75 mg dose d = 0.41; 150 mg dose d = 0.13; 300 mg dose d = 0.36). Finally, Kennedy DO et al. (2004) reported a reduction in accuracy of performance at the choice reaction time task was at 1 hour (p = 0.003; d = 0.54) and at 4 hours (p = 0.009; d = 0.42) post-dose for the guarana treatment group, in comparison with the placebo group.

Secondary Memory Factor

Kennedy DO et al. (2004) and Haskell CF et al. (2007) reported statistically significant improvements at the Secondary Memory factor for the guarana treatment group in comparison with the placebo group. For this outcome, Kennedy DO et al. (2004) reported a p-value of 0.002 (d = 0.56) at 2.5 hours of testing, while Haskell CF et al. (2007) reported a p-value of 0.003 for the 75 mg dose and 0.03 for the 37.5 mg dose (Cohen's D could not be calculated).

Serial of 3s and 7s

At the Serial of 3s task Kennedy DO et al. (2004) found no effect on the total number of subtractions, but reported a significant reduction in errors during the task at 2.5 hours (p = 0.03; d = 0.54) and at 4 hours (p = 0.049; d = 0.36) for the guarana treatment group in comparison with the placebo group. At the Serial of 7s task, an increase in the total number of subtractions was achieved for the 75 mg guarana dose group at 1 hour (p < 0.001; d = 0.2), 2.5 hours (p = 0.05; d = 0.63), 4 hours (p = 0.011; d = 0.44) and at 6 hours (p = 0.012; d = 0.50), while accuracy of performance for the same dose, decreased, with this effect reaching significance at a single time point [4 hours (p = 0.032), d = 0.42]. Finally, Scholey A et al. (2013) found a statistically significant improvement (p = 0.006) at the Serial of 3s task for both accuracy of performance and reaction time for the guarana treatment group, in comparison with the placebo group.

Other Findings

Kennedy DO et al. (2004) reported statistically significant improvements in Speed of Attention factor at 1 hour (p = 0.011; d = 0.55), 4 hours (p = 0.007; d = 0.39) and at 6 hours (p = 0.025; d = 0.31) post dose for the guarana treatment group in comparison with the placebo group. Speed of Memory factor showed statistically significant improvements at 1 hour (p = 0.043; d = 0.27), at 2.5 hours (p = 0.0014; d = 0.17) and at 4 hours (p = 0.001; d = 0.33) and reached significance at 6 hours (p = 0.06) post dose for the guarana treatment group in comparison with the placebo group. Haskell CF et al. (2007) reported statistically significant improvement at the numeric

working memory (p = 0.008; 37.5 mg dose d = 0.1; 75 mg dose d = 0.2; 150 mg dose d = 0.26, 300 mg dose d = 0) and the delayed picture recognition (sensitivity index) (p = 0.001; 37.5 mg dose d = 0.75; 75 mg dose d = 0.57; 150 mg dose d = 0.23; 300 mg dose d = 0.006) for the guarana treatment group in comparison with the placebo group. Pomportes L et al. (2017) found a difference (92% likely effect) in variance between guarana supplementation and placebo (d = 0.31).

Functional Imaging of Participants Supplemented with Guarana

FMRI imaging was performed to assess the effects of guarana in the central nervous system. The use of fMRI on participants revealed that the multivitamin supplement with guarana produced greater activation of the right precentral gyrus, the left middle frontal gyrus, frontal medial gyri and the left and right superior parietal lobes in comparison with the multivitamin supplement without guarana for Scholey A et al. (2013). White DJ et al. (2017) reported that the guarana supplement led to greater phase advance across fronto-central regions, but this effect did not extend to the prefrontal regions, in comparison with the multivitamin supplement without guarana.

Guarana versus Caffeine

Five studies enabled us to evaluate the differences in cognitive enhancement between guarana and coffee. Haskell CF et al. (2007) and Kennedy DO et al. (2004) examined doses of guarana were the caffeine content of the herb was incapable of producing cognitive enhancing effects (75 mg or 37.5 mg of guarana, 10% caffeine < 9 mg of caffeine). Galduroz JC, Carlini EDE A (1994) examined the effects of 500 mg of guarana (2% caffeine; 10 mg of caffeine) in comparison with 12.5 mg of caffeine. Lastly, the studies of Pomportes L et al. (2017) and Pomportes L et al. (2014) were also used, as they compared guarana interventions with caffeine.Pomportes L et al. (2017) reported that the caffeine intervention produced shorter reaction times in comparison with the guarana/multivitamin/ginseng intervention. While Pomportes L et al. (2014) reported that faster reaction time was observed at the guarana/ginseng complex at the 60th minute of the go/no-go task, in comparison with caffeine. Furthermore, at the end of the task, mental fatigue was observed at the 120th minute for caffeine and at the 150th minute for the guarana/ginseng intervention.

Galduroz JC, Carlini EDE A (1994) supplemented one group of participants with a 500 mg dose of guarana containing approximately 10 mg of caffeine and another group of participants with 12.5 mg dose of caffeine. None of the two groups showed significant improvements in cognitive tasks when compared with the placebo group.

Haskell CF et al. (2007) and Kennedy DO et al. (2004) both reported statistically significant improvements of performance at the Secondary Memory factor in comparison with the placebo (this effect was done at the 37.5 mg and 75 mg for Haskell CF et al. [2007] and at 75 mg for Kennedy DO et al. [2004]). Additionally, Kennedy DO et al. (2004) reported statistically significant improvements in speed of attention factor, speed of memory factor, reaction time at the digit vigilance task, the choice reaction task and the sentence verification task. Improvements were also found at the accuracy of performance at the serial of 3s task; while at the serial of 7s task, participants increased the total number of subtractions. Accuracy of performance at the same task decreased at 4 hours, and at the choice reaction time task, it was decreased at 1 hour and 4 hours.

All in all, the two studies by Pomportes L. et al. were thought to be useful for this comparison, but eventually, they were not conclusive. The study of Galduroz JC, Carlini, EDE A (1994) provided no evidence for a possible synergy between caffeine and other compounds found in guarana, as no significant outcome improvements were found from a high dose of guarana containing low doses of caffeine. On the other hand, results from Haskell CF et al. (2007) and Kennedy DO et al. (2004) tend to support the claim that cognitive enhancing effects of guarana are not solely attributed to the caffeine content of the herb, but to other compounds as well. These two studies report that guarana interventions with low doses of caffeine provided significant improvements in certain cognitive domains.

Results of Low Risk of Bias Studies

In this section of the results, we present the findings of studies with a relatively low risk of bias. Studies included in this section of the results needed to have at least 4/7 'low risk' of bias grades at the Cochrane tool of assessing risk of bias. This criterion was set to ensure that > 50% of the potential biases across studies were eliminated. Furthermore, studies included in this section of the results also needed to use an intervention consisting solely of guarana or a guarana intervention with multivitamins. Randomized clinical trials using interventions with guarana and ginseng were not considered as low risk of bias studies even if the clinical trial was set in a manner to eliminate bias. Consequently, only the results of Kennedy DO et al. (2008), Scholey A et al. (2013) and Veasey RC et al. (2015) are presented in this section of the results.

All three studies used an intervention consisting of 222.2 mg of guarana (40 mg of caffeine), multivitamins and minerals.

All three studies found statistically significant improvements at reaction time and accuracy of performance. Specifically, Kennedy DO et al. (2008) reported that the guarana treatment group performed faster at each post dose repetition of the RVIP task with the exception of the fifth in comparison with placebo (rep 1 $p < 0.001$, $d = 0.33$; rep 2 $p < 0.001$, $d = 0.22$; rep 3 $p < 0.05$, $d = 0.12$; rep 4 $p < 0.001$, $d = 0.58$; rep 5 $p > 0.05$ and at rep 6 $p < 0.001$, $d = 0.37$; repetitions 1–6 $p < 0.05$). Veasey RC et al. (2015) reported a main effect of the guarana treatment for the picture recognition reaction time ($p = 0.0496$; $d = 0.40$) in comparison with the placebo, while Scholey A et al. (2013) found a statistically significant improvement ($p = 0.006$) at the Serial of 3s task for both reaction time and accuracy of performance. Regarding accuracy of performance, Kennedy DO et al. (2008) reported that accuracy of performance significantly improved for the guarana treatment group in comparison with the placebo group at the RVIP task for each of the post-dose repetitions. Specifically, at rep 1 ($p < 0.001$; $d = 0.27$), at rep 2 ($p < 0.001$; $d = 0.31$), at rep 3 ($p < 0.001$; $d = 0.51$), at rep 4 ($p < 0.001$; $d = 0.58$), at rep 5 ($p < 0.001$; $d = 0.53$), and at rep 6 ($p < 0.001$; $d = 0.37$) [repetitions 1–6 ($p < 0.001$)]. Veasey RC et al. (2015) reported statistically significant improvement at the numeric working memory accuracy of performance ($p = 0.001$; $d = 0.71$) for the guarana treatment group in comparison with the placebo group. All in all, the three studies with a relatively low risk of bias indicate that guarana interventions with multivitamins and minerals may enhance the reaction time and accuracy of performance at tasks.

DISCUSSION

To our knowledge, this is the first systematic review of controlled clinical trials for the effect of guarana (Paullinia cupana) on the cognition of young healthy adults. Our primary goal was to examine the effects of guarana on cognition. A secondary goal was to compare guarana with pure caffeine on the cognitive performance of young healthy adults.Regarding our primary outcome, a total of nine studies were used, the majority of which had an unclear or high risk of bias. Most of the studies found statistically significant improvements in reaction time and accuracy of performance at tasks. Two studies also found statistically significant improvements in the secondary memory factor. In order to clarify the results of our systematic review, we presented results from low risk of bias studies both at the main findings section, and individually. The three studies with a relatively low risk of bias used a multivitamin supplement with 222.2 mg of guarana. All three studies reported statistically significant improvements in reaction time and accuracy of performance at cognitive tasks. All in all, guarana seems to improve the reaction time and the accuracy of performance at tasks, but these findings are not definite.For our secondary aim, a total of six studies were used. No firm results were found to support a potential synergy of compounds in the guarana herb, or to evaluate the comparison between guarana and caffeine. Specifically, two studies using multivitamin supplements with guarana and ginseng, while comparing them with pure caffeine, found contradicting results. A third study found no significant results for a high dose of guarana containing low doses of caffeine in comparison with a low dose of caffeine. Finally, two studies found statistically significant improvements in reaction time, accuracy of performance and at the secondary memory factor. Even though these 2 studies found positive results on the guarana-caffeine comparison, we must highlight that both studies are not randomized controlled trials, and thus, they most probably have a high risk of bias. All in all, no definite conclusions can be made for the comparison of guarana with pure caffeine and the potential synergy between guaranine and other compounds of the herb.

Our systematic review provides some evidence of the nootropic effects of guarana. This effect was limited only to the domains of reaction time and accuracy of performance. Furthermore, the results are not conclusive. Most of the studies included have a relatively high risk of bias, do not use interventions consisting solely of guarana and include a low number of participants (total participants included = 369; mean participants per study = 41). Thus, more research is needed to rigorously examine the effects of guarana on cognition. Future research should focus on providing high quality randomized controlled clinical trials, with a low risk of bias, a large number of participants and interventions consisting solely of guarana. Studies using guarana interventions with a low caffeine content or studies using comparisons with pure caffeine are also valuable.

Limitations

The main limitations of our review were set by the low quality of the individual studies included and the mixed interventions used by the included studies. Specifically, only 4 out of the 9 studies included in our review had a relatively low risk of bias. Biases across studies were assessed with the Cochrane tool of assessing risk of bias. Low risk of bias studies were defined as the studies scoring 'low risk of bias' in 4/7 points of the Cochrane scale. Only 4 studies met this criterion, all of which used mixed guarana interventions. Consequently, most of the studies included in our review have a relatively high risk

of bias. Furthermore, the assessment of a potential synergy between guarana caffeine and other compounds in the herb or a comparison between caffeine with pure guarana was highly limited, as the studies available for this outcome also had a high risk of bias.Finally, we wished to perform a meta-analysis of the outcome results, but eventually this was not possible. Heterogeneity across studies deterred us from this goal. Firstly, there was heterogeneity of interventions across studies. Secondly, there was heterogeneity at the methods used to measure the study outcome across studies. Furthermore, some studies did not report the p-values or effect sizes of the measured outcomes. Finally, most of the included studies had an unclear or a high risk of bias. All of these factors deterred us from performing a meta-analysis of the results.

CONCLUSION

This systematic review was conducted out of pure interest for the effects of guarana on cognition. Our main goal was to assess the effects of guarana on the cognitive performance of young healthy adults. A secondary goal was to compare guarana with pure caffeine and to examine a potential synergy between guaranine and other compounds found in guarana.

The completion of the study revealed some positive findings on our first goal, but these findings were not conclusive. The findings for our second goal were significantly limited. Specifically, regarding guarana's effects on cognition; only certain cognitive domains showed improvement, such as reaction time, accuracy of performance and the secondary memory factor. For our second goal, no firm evidence was found to support a different behavioural profile of guarana in comparison with caffeine or a potential synergy between different compounds found in guarana.

We hope that this systematic review proves to be informative for the effects of guarana on cognition, and the comparison of guarana with caffeine. Future research should focus on providing high quality clinical trials with interventions consisting solely of guarana. Doses of guarana with a low caffeine content and comparisons with pure caffeine should also be used. We encourage further research of the herb and hope our systematic review fuels the interest of researchers towards guarana and herbal medicine.

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ETHICAL APPROVAL

As no new data was collected for this study (systematic review), no ethical approval was necessary.

INFORMED CONSENT

As no new data was collected for this study (systematic review), no informed consent was required.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in conducting this review.

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