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A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans

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Abstract

The present study aimed to systematically assess acute, dose-related behavioural effects of an extract of guaraná plant for the first time in humans.

This double-blind, counterbalanced, placebo-controlled study ($n = 26$) assessed the acute mood and cognitive effects throughout the day of four different doses (37.5 mg, 75 mg, 150 mg and 300 mg) of a standardised guaraná extract (PC-102). Assessment included the Cognitive Drug Research computerized test battery and Bond-Lader mood scales.

Guaraná improved secondary memory performance and increased alert and content mood ratings. The two lower doses produced more positive cognitive effects than the higher doses.

This research supports previous findings of cognitive improvements following 75 mg guaraná and provides the first exploration of different dose effects of guaraná in humans. The findings suggest that the effects cannot be attributed to caffeine alone.

Keywords

guaraná, *Paullinia cupana*, memory, attention, caffeine, mood

Introduction

Guaraná (*Paullinia cupana*) seeds have a long history of usage as a stimulant by Amazonian tribes people (Henman, 1982). The putative stimulant properties are generally assumed to reflect the presence of caffeine, which comprises 2.5–5% of the extract's dry weight (Weckerle *et al*., 2003). However the psychoactive properties of guaraná may also be attributable to relatively high content of other potentially psychoactive components, including both saponins and tannins (Espinola *et al*., 1997). The latter may also account for antioxidant properties of the plant (Mattei *et al*., 1998).

Whilst guaraná is becoming progressively more common as a putatively psychoactive food additive in Western markets, its specific behavioural effects have been largely neglected in the human literature. Mattei *et al*. (1998) found that both acute and chronic administration of guaraná failed to modulate motor activity or pentobarbital-induced sleep parameters in rodents. Espinola *et al*. (1997) demonstrated that chronic (9 months) administration of a lower (but not a higher) dose of guaraná improved swimming time in mice, and reversed memory deficits in rats on a passive avoidance task. Acute administration of both low (3 mg/kg) and high (30 mg/kg) doses of guaraná and 1 mg/kg of caffeine also reversed scopolamine-induced deficits on passive avoidance performance in mice (Espinola *et al*., 1997).

In humans, improvements in performance were found between 2.00 PM and 4.00 PM (but not at other times) in sleep-deprived volunteers who had consumed a 500 mg guaraná drink at 7.15 AM (Alford and Atkins, 2003). Only one study to date has demonstrated psychoactive effects of guaraná in non-fatigued individuals.

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Kennedy *et al*. (2004) found that 75 mg guaraná was capable of producing improvements in secondary memory and speed of attention. Performance of serial subtractions of threes and sevens was also improved as well as speed of sentence verification.

Given the increasing use of guaraná and the lack of data regarding its behavioural effects in humans, it is important to further assess the plant's effects on mood and cognition, including determination of the optimum dose of guaraná needed to facilitate cognition and mood.

Method

Participants

Thirty participants entered the study of which 26 completed all phases of the experiment (18 female and 8 male, mean age 21.38 years, SEM 0.64). They were all undergraduate volunteers in good health and free from illicit, over-the-counter and medication drugs. All participants abstained from alcohol and caffeine for a minimum of 12 hours prior to the first testing session of the morning and throughout the day.

Cognitive and mood measures

Cognitive Drug Research (CDR) computerized assessment battery The tailored version of the CDR battery utilized here, including a description of the constituent tasks, are described in detail by Scholey and Kennedy (2004). The selection of computer controlled tasks was administered via laptop computers.

Primary cognitive outcome measures

As with previous studies assessing herbal treatments, the single task outcomes from the CDR battery were collapsed into the five cognitive outcome factors derived from the battery by a factor analysis conducted and described by Wesnes *et al*. (2000). The factor composition is described briefly below.

'Speed of Attention' factor: derived by combining the reaction times of the three attentional tasks – simple reaction time, choice reaction time and digit vigilance (units are summed milliseconds for the three tasks).

'Speed of Memory' factor: derived by combining the reaction times of numeric working memory, spatial memory, delayed word recognition, and delayed picture recognition (units are summed milliseconds for the four tasks).

'Accuracy of Attention' factor: derived by calculating the combined percentage accuracy across the choice reaction time and digit vigilance tasks. Accuracy of 100% across the two tasks would generate a maximum score of 100.

'Secondary Memory' factor: derived by combining the percentage accuracy scores from delayed word recognition, delayed picture recognition, immediate word recall and delayed word recall tasks. Accuracy of 100% across the four tasks would generate a maximum score of 400 on this index.

'Working Memory' factor: derived by combining the percentage accuracy scores from the two working memory tests – spatial working memory, and numeric working memory. Accuracy of 100% across the two tasks would generate a maximum score of 200 on this index.

Bond-Lader mood scales (Bond and Lader 1974)

Scores from the 16 Bond-Lader visual analogue scales were combined as recommended by the authors to form three mood factors: 'alert', 'calm' and 'content'.

Extracts and treatments

Extracts

A standardized guaraná extract (PC-102, Pharmaton, SA) containing 11–12% caffeine was used. For a full description of the standardization process see Kennedy *et al*. (2004).

Treatments

On each study day participants consumed one capsule; these were of identical appearance on each occasion. The capsules contained either; 37.5 mg guaraná; 75 mg guaraná; 150 mg guaraná; 300 mg guaraná; or 0 mg guaraná (placebo).

Salivary caffeine levels

Saliva samples were taken, using salivettes, immediately prior to each assessment in order to confirm overnight caffeine abstinence and maximize compliance throughout the study day. Baseline saliva samples were immediately frozen at −20 °C until thawing for in-house batch analysis using the Emit system (Syva, Palo Alto, USA). This is an enzyme immunoassay intended to measure caffeine as a metabolite and is based on competition for antibody binding sites between caffeine and an enzyme-labelled drug.

Procedure

Each participant was required to attend a total of 6 study days, the first of which was a practice day identical to the others except that no treatment (placebo or active) was given. This served to eliminate practice effects, familiarize participants with procedure and to ensure performance was within established population ranges. Testing commenced at 9 AM each day and took place in a suite of laboratories with participants visually isolated from each other.

On arrival at their first session on the first day participants were randomly allocated to a treatment regime using a Latin square design which counterbalanced the order of treatments across the active days of the study.

Each of the 5 active study days comprised four identical testing sessions. Participants gave saliva samples then completed the CDR battery and the Bond-Lader mood scales, each assessment lasted 20–30 minutes. The first session was a pre-dose testing session which established baseline performance for that day, and was immediately followed by the day's treatment. Further testing sessions began at 1 hour, 3 hours and 6 hours following consumption of the day's treatment.

Table 1 Baseline and change from baseline scores for each measure from the CDR battery for each treatment condition. Means and SEMs are presented with F and *p* values from the primary ANOVA of treatment effects (see text).

Measure	Treatment	Pre-dose baseline scores	Mean change from baseline score	Main effect
Immediate word recall accuracy (%)	Placebo	47.8±3.48	−4.55±3.37	F<1
	37.5 mg	49.5±3.33	−3.44±3.75	
	75 mg	49.2±4.21	−2.33±3.12	
	150 mg	45.4±3.52	1.22±2.71	
	300 mg	50.6±3.05	−5.13±2.85	
Simple reaction time (ms)	Placebo	288±7.36	14.7±4.85	F=1.29 $p>0.1$
	37.5 mg	293±8.61	3.89±7.21	
	75 mg	295±7.94	8.82±5.89	
	150 mg	286±8.82	9.75±5.92	
	300 mg	288±9.23	8.80±5.96	
Digit vigilance accuracy (%)	Placebo	95.8±1.08	−3.77±1.76	F<1
	37.5 mg	96.3±0.80	−3.56±1.75	
	75 mg	95.5±1.09	−3.14±1.83	
	150 mg	94.9±1.57	−2.57±2.02	
	300 mg	92.8±2.17	−1.83±1.42	
Digit vigilance reaction time (ms)	Placebo	441±9.46	21.0±7.22	F=2.11 $p=0.08$
	37.5 mg	426±9.75	22.5±7.65	
	75 mg	434±11.9	13.1±9.11	
	150 mg	436±9.80	13.1±6.79	
	300 mg	440±11.3	8.40±6.03	
Digit vigilance false alarms (number)	Placebo	1.10±0.24	−0.24±0.29	F=1.75 $p>0.1$
	37.5 mg	0.52±0.15	0.29±0.29	
	75 mg	0.62±0.17	0.05±0.22	
	150 mg	0.76±0.24	−0.05±0.31	
	300 mg	0.76±0.15	0.14±0.28	
Choice reaction time accuracy (%)	Placebo	95.2±0.71	0.95±0.68	F=2.72 $p=0.03$
	37.5 mg	96.8±0.67	−0.41±0.69	
	75 mg	96.8±0.54	−0.41±0.59	
	150 mg	95.3±0.78	0.48±0.73	
	300 mg	96.7±0.52	−0.48±0.84	
Choice reaction time (ms)	Placebo	454±11.2	4.78±8.39	F<1
	37.5 mg	443±9.39	2.54±9.44	
	75 mg	443±10.6	1.78±7.24	
	150 mg	440±10.7	2.80±8.33	
	300 mg	448±12.3	−2.53±10.9	
RVIP accuracy (%)	Placebo	59.1±4.82	−1.24±2.97	F=1.41 $p>0.1$
	37.5 mg	60.4±4.12	0.40±2.28	
	75 mg	63.3±4.26	−3.07±2.59	
	150 mg	57.3±4.52	0.99±2.42	
	300 mg	59.8±4.61	−1.64±2.28	
RVIP reaction time (ms)	Placebo	509±19.4	−11.5±16.5	F=1.21 $p>0.1$
	37.5 mg	508±16.9	−3.41±16.4	
	75 mg	498±21.6	11.8±17.8	
	150 mg	518±20.7	−11.1±15.2	
	300 mg	503±16.5	3.64±12.7	
RVIP false alarms (number)	Placebo	3.24±1.42	0.24±0.78	F=3.73 $p=0.006$
	37.5 mg	2.10±0.82	0.76±0.66	
	75 mg	1.33±0.38	1.00±0.73	
	150 mg	4.95±2.55	−0.87±0.83	
	300 mg	3.05±1.21	−0.92±0.74	
Spatial memory (sensitivity index)	Placebo	0.95±0.01	−0.05±0.03	F<1
	37.5 mg	0.92±0.02	−0.04±0.04	
	75 mg	0.94±0.01	−0.02±0.03	
	150 mg	0.95±0.01	−0.05±0.04	
	300 mg	0.96±0.01	−0.03±0.03	

Table 1 continued

Measure	Treatment	Pre-dose baseline scores	Mean change from baseline score	Main effect
Spatial	Placebo	584±21.1	−8.95±25.2	F=1.16 $p>0.1$
memory	37.5 mg	595±24.0	−28.8±18.7	
reaction	75 mg	587±22.7	−28.8±19.2	
time (ms)	150 mg	578±20.3	−25.8±14.1	
	300 mg	594±25.0	−43.2±16.1	
Logical	Placebo	0.75±0.06	0.02±0.04	F=1.80 $p>0.1$
reasoning	37.5 mg	0.82±0.04	−0.04±0.03	
accuracy	75 mg	0.85±0.04	0.01±0.03	
(sensitivity	150 mg	0.84±0.06	−0.05±0.04	
index)	300 mg	0.83±0.05	−0.02±0.04	
Logical	Placebo	2504±152	−34.9±129	F=1.77 $p>0.1$
reasoning	37.5 mg	2700±156	39.9±130	
reaction	75 mg	3056±187	−256±164	
time (ms)	150 mg	2840±202	−103±125	
	300 mg	2865±164	−97.4±183	
Numeric	Placebo	0.91±0.02	−0.02±0.02	F=3.55 $p=0.008$
working	37.5 mg	0.91±0.02	−0.01±0.02	
memory	75 mg	0.93±0.01	−0.04±0.02	
(sensitivity	150 mg	0.89±0.02	0.01±0.01	
index)	300 mg	0.92±0.01	−0.02±0.02	
Numeric	Placebo	610±33.7	−16.3±20.5	F=2.17 $p=0.073$
working	37.5 mg	629±30.2	−27.2±14.3	
memory	75 mg	611±25.7	7.10±19.2	
reaction	150 mg	603±29.9	−0.55±14.4	
time (ms)	300 mg	591±27.5	−11.8±14.9	
Delayed word	Placebo	37.0±3.75	−16.2±3.56	F<1
recall	37.5 mg	35.7±3.53	−12.2±3.60	
accuracy (%)	75 mg	34.1±4.03	−10.9±2.76	
	150 mg	34.1±3.94	−10.7±2.61	
	300 mg	36.5±3.86	−12.8±2.99	
Delayed word	Placebo	0.70±0.03	−0.08±0.04	F<1
recognition	37.5 mg	0.70±0.03	−0.10±0.04	
(sensitivity	75 mg	0.66±0.04	−0.05±0.04	
index)	150 mg	0.67±0.04	−0.11±0.05	
	300 mg	0.62±0.04	−0.08±0.04	
Delayed word	Placebo	712±36.1	42.0±24.1	F=2.93 $p=0.021$
recognition	37.5 mg	731±26.9	47.3±30.3	
reaction time (ms)	75 mg	802±78.5	−33.1±49.9	
	150 mg	720±30.6	10.9±21.4	
	300 mg	731±43.6	20.3±30.8	
Delayed	Placebo	0.69±0.05	−0.14±0.04	F=5.08 $p=0.001$
picture	37.5 mg	0.67±0.05	0.01±0.04	
recognition	75 mg	0.60±0.06	−0.01±0.05	
(sensitivity	150 mg	0.65±0.05	−0.08±0.06	
index)	300 mg	0.64±0.07	−0.02±0.05	
Delayed	Placebo	833±25.9	18.5±33.4	F<1
picture	37.5 mg	866±50.6	1.33±36.9	
recognition	75 mg	874±44.5	−10.1±34.4	
reaction time (ms)	150 mg	848±38.5	1.67±30.7	
	300 mg	853±45.4	−3.98±28.1	

Data analysis

Prior to analysis of change from baseline data, mean pre-dose raw baseline scores for all five conditions for each outcome were subjected to a one-way, repeated-measures ANOVA. In order to identify main effects a repeated measures ANOVA (General Linear Model) was carried out (not reported). The primary statistical analysis followed the recommendation of Keppel (1991), and was carried out using planned comparisons, which were made between placebo and each of the active treatments utilizing t tests with the mean squares for 'Dose*Time*Participants' from an omnibus ANOVA as an error term. In this brief communication only main effects of treatment are reported (see Table 1).

Results

Salivary caffeine levels

Salivary analysis revealed that five participants had not complied with instructions to avoid caffeine-containing products. All data from these participants were excluded from further analyses. Data for the remaining 21 participants confirmed compliance with overnight abstinence, mean baseline values were 0.26 µg/ml (levels below 1 µg/ml have been reported for overnight caffeine abstinence – Evans and Griffiths, 1999).

Baseline scores

There was one significant baseline difference for accuracy of choice reaction with all but the 150 mg guaraná pre-dose performing significantly better than placebo.

Cognitive outcome measures

Secondary Memory factor: Compared with placebo, secondary memory performance was enhanced by the 75 mg dose [$t(160)=2.96$, $p=0.003$] and the 37.5 mg dose [$t(160)=2.13$, $p=0.03$], see Fig. 1a.

Bond-Lader mood scales

Alert: There was a significant increase in alert ratings following the 300 mg dose [$t(160)=2.37$, $p=0.042$], see Fig 1b.

Content: There were significant improvements in content ratings following all doses of guaraná: 37.5 mg [$t(160)=3.12$, $p=0.002$]; 75 mg [$t(160)=3.59$, $p=0.01$]; 150 mg [$t(160)=2.62$, $p=0.01$]; 300 mg [$t(160)=2.64$, $p=0.009$], see Fig 1c.

Calm: Decreases in calm ratings following the active treatments did not quite reach significance [$F=2.14$ $p=0.076$].

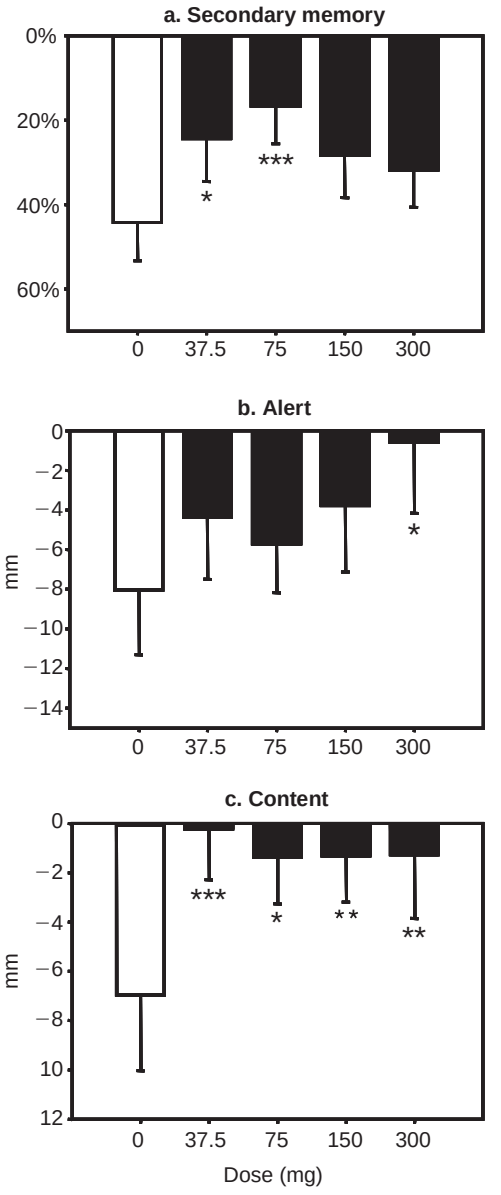

Figure 1 Effects of guaraná on cognitive performance and mood. Bars depict mean change from baseline (±SEM) following placebo (0), 37.5 mg, 75 mg, 150 mg, and 300 mg guaraná extract with more positive values representing better performance and/or mood. Significant treatment effects are shown for (**a**) secondary memory (summed percentage), and visual analogue scale-derived mood measures (mm) corresponding to (**b**) alertness, (**c**) contentedness. Significant differences compared with placebo are indicated (*, $p<0.05$; **, $p<0.01$; ***$p<0.005$).

Discussion

The results of the current study confirm that guaraná can improve cognitive performance and mood in healthy young adults. These improvements support previous findings of effects of guaraná on accuracy of secondary memory (Kennedy *et al*., 2004). The study provides the first demonstration of effects of guaraná on mood with dose-dependent increases in alertness and contentedness. Moreover the two lower doses in this study provided more beneficial cognitive effects than the two higher doses. Conversely, only the highest dose increased alertness ratings and contentedness ratings were most significantly improved by the highest dose but each of the other doses also led to some improvements.

Given that the guaraná extract contained only 11–12% caffeine, it seems unlikely that the effects seen here can be solely attributed to guaraná's caffeine content. The highest dose of guaraná contained around 36 mg of caffeine, which is above its accepted psychoactive threshold. However the fact that only the 37.5 mg and 75 mg doses, containing 4.5 mg caffeine and 9 mg caffeine respectively, produced beneficial cognitive effects lends further support to this proposal. This is consistent with Espinola *et al*.'s (1997) observations in rodents that doses of guaraná with minimal total caffeine content were more beneficial than tenfold doses of guaraná. Additionally different patterns of enhancement may have been observed by Alford and Atkins (2003) had a range of guaraná doses been assessed. Obviously the lower doses of guaraná utilised in this study also contain lower doses of any other potential active ingredients. However little is known about the other constituents of guaraná – its effects so often being assumed to be attributable to caffeine – it is difficult to assess what level of these constituents is the optimum or indeed what level is present. It is also possible that at the higher doses the effects of higher caffeine levels are in some way masking the effects of the other active ingredients. Herbal extracts have complex dose–effect relationships on behaviour (Scholey *et al*., 2005), and it is possible that, at lower doses, guaraná's constituents are acting synergistically.

One further point here is that the positive effects of caffeine have been attributed to reversal of caffeine withdrawal (Rogers *et al*., 2003), although see also e.g. Haskell *et al*. (2005) for an alternative explanation. It seems improbable that the caffeine content of the effective doses of guaraná here would be sufficient to alleviate any such withdrawal. Furthermore it is highly unlikely that participants in this study were in a state of 'guaraná withdrawal'.

In the current study the tasks which were affected by guaraná are not those generally accepted as being sensitive to the effects of caffeine (and it seems unlikely that the single baseline difference in choice reaction time would have obscured any effects on attentional performance). However, it should be pointed out that very little is known about the effects of very low doses of caffeine (equivalent to those employed here) and further exploration of these effects is warranted as well as investigating the properties of the other constituents of guaraná.

The results obtained here in a sample of young healthy participants provide further support for the cognitive and mood enhancing properties of guaraná. The findings suggest that within the range of doses employed in the present study, lower doses produce more beneficial cognitive effects than higher ones and all doses are capable of affecting mood. This implies a role for components other than caffeine; however, further exploration of this extract is needed, including comparison with decaffeinated guaraná, in order to fully understand its action.

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