

Reasearch

Effects of Cymbopogon Flexuosus, Alpinia Galanga, and Glycyrrhiza Glabra on Attention: A Randomized Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Rationale

The market focus is being diverted to caffeine-free natural psycho-stimulants with an onset and duration of action comparable to the caffeine but devoid of its crash effect. In an attempt to develop an efficient alternative or adjuvant, we designed a randomized, placebo-controlled study wherein we evaluated the effect of *C. flexuosus* (LG), *A. galanga* (AG1, AG2), and *G. glabra* (GG1, GG2) extracts in comparison with caffeine and placebo on the different aspects of attention along with the safety profile.

Methods

In this study, 70 caffeine-habituated subjects were assessed to determine the express effect on the mean response time (MRT), alertness, orientation and execution functions by Attention Network Test over a span of 5 hours on day 1 followed by a safety assessment on day 7.

Results

Among the studied groups, LG, AG2 and GG1 were unable to exhibit a beneficial effect in any of the outcome measures; caffeine reduced MRT at 3 hours by 3.94 % ($p = 0.07$) as compared to the baseline and placebo; AG1 exhibited a statistically significant and stable increase in alertness score compared to the baseline until 5 hours [107.31 % at 1 hour ($p = 0.07$); 119.27 % at 3 hours and 103.99 % at 5 hours]; GG2 also produced a positive effect on the alertness until 3 hours (33.79 %).

Conclusion

In summary, caffeine, AG1 and GG2 demonstrated an improvement in the separate aspects of the attention network. All the interventions were safe to use as no serious adverse event occurred throughout the study. These findings necessitate the profound assessment of the AG1 (Galanga water-soluble extract) as a potential psychostimulant.

Keywords: Alertness; Attention; Caffeine Crash; Dietary Supplement; Energy Drink; Mean Response Time (MRT).

List of Abbreviations

AA: Amino acid; AE: Adverse event; ANT: Attention network test; IP: Investigational product; CNS: Central nervous system; ICH:

International conference on harmonization; GCP: Good clinical practice; CRSD: Centre for research for safe driving; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRT: Mean response time.

Introduction

Energy drinks are known to improve the mental and cognitive performance as well as increase the subjective alertness and physical energy[1]. Most of these products contain caffeine (either synthetic or from natural sources) due to the popularity attributed to its perceivable and acute benefits for physiological, psychomotor and cognitive performance, as well as its beneficial effects on the mood. With regard to the cognitive performance, the domain of the attention appears to be most notably improved by the caffeine due to its psychostimulant effect [2,3].

Besides the psychostimulant benefits, it has an abuse potential and may induce a psychological and physical dependence[4]. The prolonged use of caffeine may lead to a range of adverse effects (insomnia, palpitations, jitters, headaches, occasional lightheadedness, gastrointestinal upset, headache, chest pain, and seizures). This altered psychosomatic state, generally termed as a 'caffeine crash', can produce an undue stress and depending upon the amount of caffeine consumed can produce troublesome social effects in many individuals (e.g. failure to meet social obligations). Thus, a high dose or in sensitive individuals, even a small amount of caffeine can exacerbate this perceived stressful state.

As several regulatory agencies have sounded their concerns related

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to the dose of the caffeine present in the energy drinks [5], there is a growing market interest in the caffeine-free natural alternatives with an onset and a duration of action comparable to that of the caffeine and devoid of any crash effect. Thus, there is an absolute need for an active and safe alternative psychostimulant.

Product development in the area of CNS stimulation and energy that is comparable to caffeine has many challenges, such as nature of the substance and safety concerns over uncontrolled daily use [6]. Many potential substances have been evaluated and reported by various groups worldwide. For example, amino acids (AAs) such as pyroglutamic acid, L-phenylalanine, and tyrosine have good CNS stimulation properties [7,8]; however, AAs were excluded from this product development program as the market is already crowded with the energy products containing AAs. The majority of the existing caffeine-free alternatives are mainly adaptogenic and have a slower onset compared to the caffeine. Traditionally reported medicinal plants such as *Celastrus paniculatus* (Jyotishmati) [9], *Bacopa monnieri* (Brahmi) [10], *Centella asiatica* (Mandukaparni) [11], and *Leptadenia Reticulata* (Jiwanti) [12] with a neuroprotective effect and the cognition enhancement have a good adaptogenic ability, however, are not profoundly explored for their CNS stimulant potential. Second, due to their medicinal nature, such ingredients may not be easily accepted in the items regulated as the foods and beverages. The herbs such *Citrus aurantium*, *Sida cordifolia*, and *Mucuna pruriens* have a CNS-stimulating effect but also have controversial safety profiles due to the presence of phytoconstituents which interfere with the normal functioning of the brain neurotransmitters [13-15].

This situation mandates a hunt for a functional food to improve the brain performance, mainly by enhancing the attention network-related functioning. Hence, ENovate Biolife attempted to identify an alternative with minimal unwanted side effects. Our team explored a plethora of herbs documented in the ancient scriptures and modern literature in order to locate the ones with beneficial effects on cognition, and we selected three such potential substances for the initial screening: *Cymbopogon flexuosus* (lemongrass), *Alpinia galanga* (galanga), and *Glycyrrhiza glabra* (licorice).

Lemongrass is widely reported for its traditional use as lemongrass tea for the freshness and as an energy booster [16]. It contains mainly volatile and nonvolatile terpenoids [17]. As per the literature, the central nervous system-stimulating activity of lemongrass is most likely due to the citral, though its exact mechanism remains unknown [18]. As reported by Karamkolly et al (2013), Geraniol, a phytochemical found in the lemongrass attenuates α -synuclein expression and neuromuscular impairment through an increase in dopamine content in MPTP intoxicated mice in a dose dependent manner and thus demonstrates a neuroprotective effects on 1-methyl-4-phenylpyridinium induced neuromuscular deficits and dopamine depletion [19]. Galanga is a widely eaten food biomass and popularly used in the form of a tea for its refreshing effects in Asian countries. Galanga rhizomes have a wide range of applications in traditional medicine [20]. and the extract generally contains phenolic compounds and flavonoids [21]. In addition,

various extracts have been studied pre-clinically and clinically and reported to have a CNS stimulant potential. As reported by Singh et al (2011) [22], treatment with *A. galanga* extract increased Na^+ K^+ ATPase and antioxidant activity depicting improvement in the brain membrane integrity and free radical scavenging. Also, AChE level was decreased to improve the cognition by enhancing cholinergic transmission. Thus, a neuro-protective and anti-amnesic effect was exerted by various fractions of *A. galanga*. It has been also reported that the alcoholic extracts of Galanga work via the dopaminergic pathway to enhance the CNS stimulation and alertness[23].

Licorice root contains the saponins and flavonoids as the most important bioactive components which are mainly responsible for its various pharmacological activities [24]. It has been reported by the various groups for its antidepressant effect. Dhingra et al (2006) [25] reported that the antidepressant-like effect of licorice extract was mediated by an increase in the brain norepinephrine and dopaminergic response. In addition, it has been reported to work on the serotonin re-uptake inhibition pathway to produce the CNS stimulation[26].

Though these plants have been previously reported for their effect on the memory, cognition, and other aspects of brain functioning, they have not yet been analyzed for the psychostimulant potential in the human subjects. Hence, we designed a randomized double-blind, placebo-controlled study to evaluate the effect of *C. flexuosus*, *A. galanga*, and *G. glabra* extracts in comparison with caffeine and placebo on the different aspects of the attention and also to assess the safety profile of these shortlisted ingredients. The designed dosage regimen for all of the investigational products was well-defined in a therapeutically active and safe range based on the reported values in the literature.

Methods

Study Design: This was a single center, randomized, double-blind, placebo-controlled study approved by the independent ethics committee: Aditya Ethics Committee (Ahmedabad, India; registered with the Office for Human Research Protections # IRB00006475). In order to provide a credible data, the study was designed, conducted, analyzed, and reported in an accordance with the guidelines laid by the International Conference on Harmonization - Good Clinical Practice (ICH-GCP). The investigations were carried out following the rules of the Declaration of Helsinki of 1975. The study was conducted by Vedic Life Sciences Pvt. Ltd and subjected to a quality assurance evaluation with scheduled monitoring and auditing.

Participants: Seventy subjects (male and female) between 18-40 years of age with a body mass index (BMI) of 18–25 kg/m², a resting blood pressure \leq 140/90 mm Hg, and habituated to > 400 mg/day caffeine consumption (to avoid any effect due to caffeine hypersensitivity)[27] were considered eligible for this study. Only right-handed subjects were included in the study to avoid spatial bias [28]. Subjects had to refrain from caffeine products and vigorous physical activity 12 hours prior to the study visit. Subjects were allowed to consume the caffeine containing products

during the interim study period (day 2 to 7) as only the data pertaining to safety profile was planned to be captured on the day 7 study visit. As caffeine abstinence tends to increase sleepiness, consequently reducing the alertness score, the included subjects had to have an Epworth's sleepiness scale ≥ 10 [29]. The subjects had to be nonsmokers and were instructed to refrain from an alcohol intake throughout the study. Pregnant or breastfeeding women were excluded and the female subjects who were currently in their menstrual period [30] were included only after the last day of menstrual flow. Those who were currently using the oral contraceptives were included in the study after a washout period of seven days and were advised to opt for barrier contraceptives for the duration of the study. Subjects with a history or a presence of clinically significant disease conditions were excluded from the study. Concomitant therapy was strictly prohibited during the course of the study to exclude any significant effects on the study results. All the subjects were thoroughly instructed about the study procedures. An ethics committee-approved informed consent form to participate in the study and an authorization for the release of the relevant protected health information to the study investigator was obtained from each of the enrolled subjects.

Interventions: Block randomization was carried out by an independent biostatistician using the Stats Direct software version 3. On the day 1, subjects were randomized in one of the arms to receive either the investigational product (IP), comparator (Caffeine: CF), or the placebo. The IPs included: Spray-dried microencapsulated inclusion complex powder of *C. flexuosus* oil (LG), water-soluble and water-insoluble extracts of *A. galanga* (AG1 and AG2, respectively), and water-soluble and water-insoluble extracts of *G. glabra* (GG1 and GG2, respectively). The manufacture and packaging of the standardized herb extracts were carried out at a GMP-certified contract manufacturing facility. Pure anhydrous caffeine (99.7%) was used as a comparator and constituted the CF group, and microcrystalline cellulose was used as a placebo. The composition details of all the treatments are listed in (Table 1). All the interventions were provided to the study site in the form of the identical capsules which were averaged to a weight of 500 mg and packed in the duly labeled HDPE bottles. The blinding codes were secured at the study site in the tamper-evident sealed envelopes with no access to the study team. Thus, the double-blind nature of the study was ensured and strictly followed.

Test Visit Procedure: This was a seven day pilot study. On the day 1, all the subjects reported to the clinic during the morning hours and the testing began at an early time of the day (8:00–9:00 a.m.) to avoid an influence of the daily challenges (related to mental and physical stress) on study outcomes. A Twenty-fourhours of abstinence from caffeine and caffeine-containing products or any other psychostimulants was mandated. Upon arrival, subjects were asked to rest quietly for 15–20 minutes, followed by the physical examination and recording of the caffeine history. The subjects were asked to fill up the Epworth's sleep scale questionnaire to rate their sleepiness. A standardized meal of approximately 300-500 calories was provided to maintain the normo-glycemic state and

to avoid any variations from the possible digestion confounds. The baseline data for the mean response time, alertness, orientation, and executive attention by ANT was collected 30 minutes after the breakfast followed by the administration of an IP (two capsules of the product with a glass of water) by the trial coordinator at the investigational site. Post IP- ingestion, data by ANT were collected at 1, 3, and 5 hours. No other food or calorie-containing beverages were provided during the clinic stay period. The subjects were allowed to drink water as desired and relax in an isolated room at a comfortable temperature with the free use of a computer and the magazines along with a restricted access to the mobile phones.

From the days 2 to 6, the participants were advised to take two capsules daily until the day 6. On the day 7 visit, subjects followed the exactly same schedule as that of the day 1. To ensure the treatment compliance, the product accountability was monitored by a clinical research coordinator on the day 7.

Outcome Measures: The attention system of the human brain is anatomically separate from the processing systems, which handle incoming stimuli, make decisions, and produce outputs. It is comprised of an alerting network, which focuses on the brain stem arousal systems along with right hemisphere systems related to the sustained vigilance; an orienting network which focuses on, among other regions, parietal cortex; and an executive network, which includes midline frontal/anterior cingulate cortex, [31] The Attention Network Test (ANT) is a validated tool developed by Dr. Jin Fan in 2002 based on the Posner's ANT [32]. It has been used to examine the efficiency of attention networks and to explore the efficiency of the alerting, orienting, and executive control networks of attention and mean response time with respect to different psychological and physiological states. It also provides an opportunity to examine the brain activity of these three networks within the context of a quick, simple and integrated computerized task [33].

A validated adaptation of ANT, termed as 'CRSD-ANT' (Centre for Research on Safe Driving Attention Network Task) [34] was used to evaluate the effect of the products on the aspects of attention network. Caffeine is well reported to reduce a response times in the tasks such as simple reaction time and choice reaction time, and the results have been inversely correlated with the mental alertness [35]. Also, it has shown improvement in the alertness and executive control function on ANT in a dose-dependent manner without any effect on the orientation [36, 37]. As caffeine was the comparator extract in this study, we decided to assess all of the IPs for the effect on the MRT and other aspects of attention network.

The primary efficacy variable was the mean response time measured in milliseconds (ms). The secondary efficacy variables were alertness score, orientation score and conflict (executive) score expressed in ms. The subject was seated in a silent and secluded room. All external distractions were avoided and subject was asked to give complete attention to the ANT. The ANT is a combination of a flanker task (with arrows) and a cued reaction time task. Participants indicate the direction of a central arrow that is flanked by four arrows (two per side) pointing in the same direction as the

Table 1. Treatment Composition

Interventions	Ingredient	Quantity of active ingredient /capsule (mg)	Quantity of excipient/ capsule (mg)	Total content/ capsule (mg)	Total no. of capsules	No. of placebo capsules	No. of active capsules	Total dose/day (mg)
Placebo	Microcrystalline cellulose (MCC)	-	500	500	2	2	0	-
Caffeine (CF)	Anhydrous caffeine	120	380	500	2	0	2	240
LG	<i>Cymbopogon flexuosus</i> essential oil from leaves	148.75	351.25	500	2	0	2	297.5
AG1	<i>Alpinia galanga</i> water-soluble extract	300	200	500	2	1	1	300
AG2	<i>Alpinia galanga</i> water-insoluble extract	300	200	500	2	1	1	375
GG1	<i>Glycyrrhiza glabra</i> water-soluble extract	500	-	500	2	1	1	500
GG2	<i>Glycyrrhiza glabra</i> water-insoluble extract	500	-	500	2	1	1	500

central arrow (congruent condition) or in the opposite direction (incongruent condition), in the neutral condition, either straight lines flank the central arrow or the central arrow is presented alone. The arrows are preceded by one of three types of cues (center cue, double cue, spatially informative cue; all of which are temporally informative) or no cue (a temporally uninformative condition). The center and double cues indicate that the arrow stimulus will occur soon, and the spatially informative cue is 100% predictive of the target location. The software-generated mean response time and attention networks scores in (ms) were used as such for the interpretation without a further need for the data refinement.

Statistical Analysis: The sample size was calculated using “PS: Power and Sample Size Calculation version 3.1.2, 2014”. A continuous response variable from the intervention groups was matched to that of the placebo group. Prior in-house data indicated that the difference in the response of matched pairs is normally distributed with standard deviation of 2. Considering the mean response of matched pairs is 2, we required a minimum of 8 subjects/ arm to reject the null hypothesis with a type I error probability of 0.1. The derived results were represented graphically as individual subject data sets for each treatment group in comparison with placebo. The data were also analyzed by student’s t-test for inter-group significance ($p < 0.1$) in comparison with placebo.

Results

A total of 95 subjects were screened in the recruitment process, during which 25 subjects failed to qualify for the study with primary reasons of weak caffeine history, high blood pressure, and a low body weight. Finally, 70 subjects were recruited from which 64 subjects completed the study and 6 subjects were withdrawn due to non-compliance to the protocol. The disposition of subjects is presented in Figure 1 as CONSORT flow diagram. Data pertaining to the demographic characteristics are presented in Table 2. The results of the efficacy variables are presented in Table 3 and Figures 2 and 3.

With respect to the primary efficacy variable, none of the treatment groups except caffeine group showed any reduction in the mean response time. The caffeine group showed statistically significant reduction at 3 hours as evident by 3.94 % decrease in mean response time, ($p = 0.07$), followed by an increase in the response time. The subjects in the LG group showed maximum increase in the MRT at 1 h (14.18 % increases). The individual response for a change in the MRT in various IP groups in comparison with placebo is presented in Figure 2(A-F). None of the treatment groups showed a decrease in MRT at 5 hours.

It is evident from the data for secondary efficacy variables that

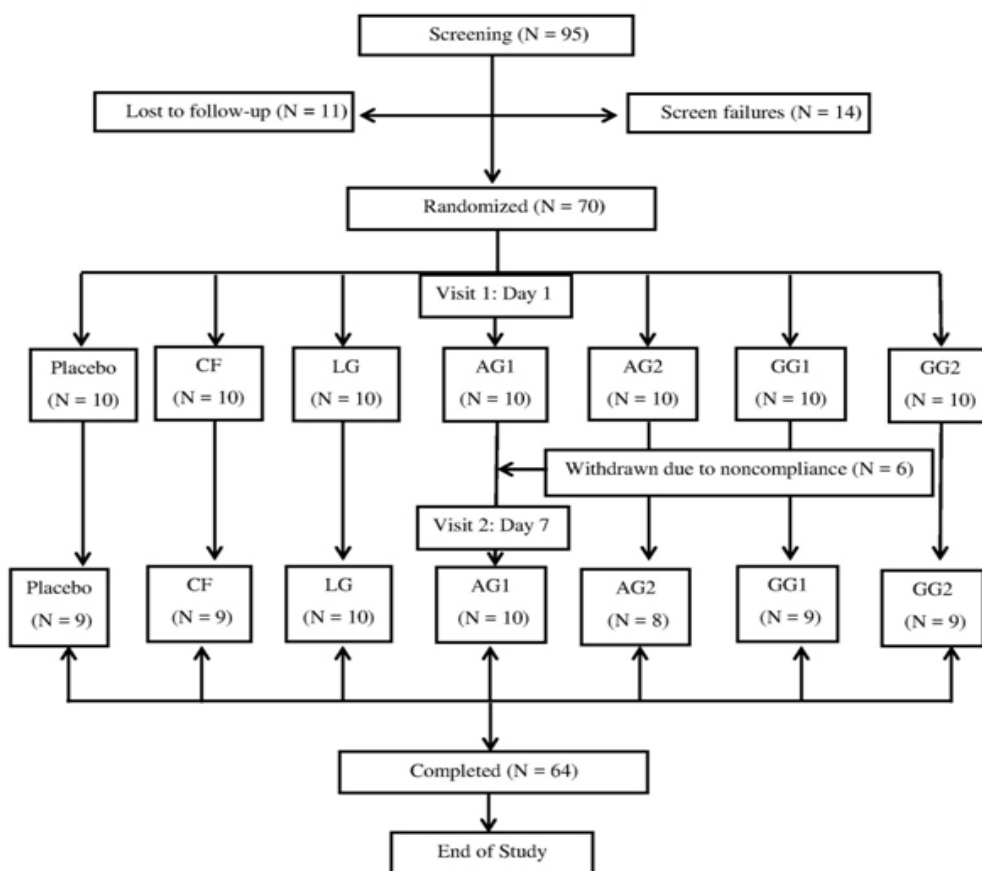


Figure 1. CONSORT Flow Diagram

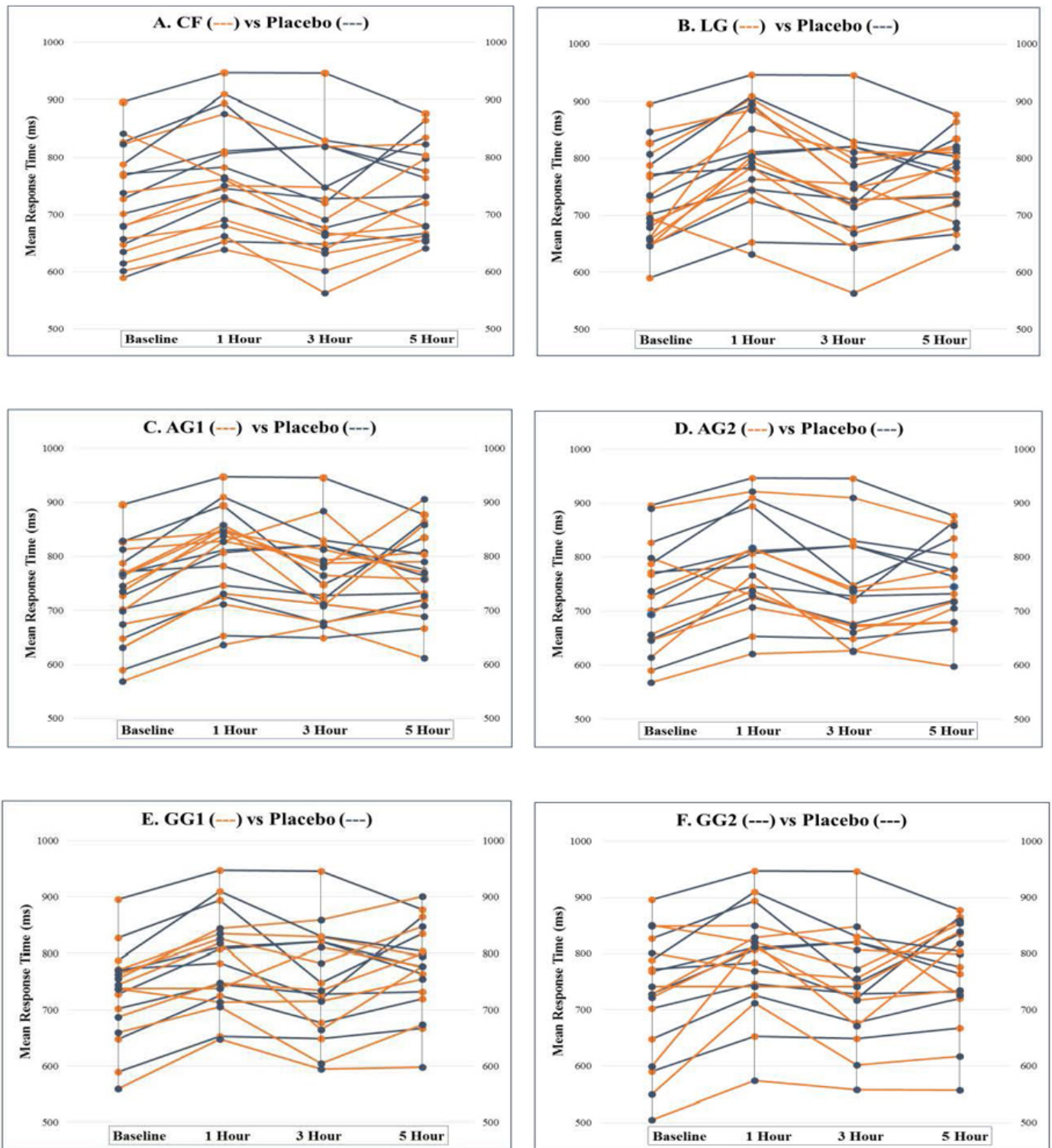


Figure 2. Effect of IP on Mean Response Time

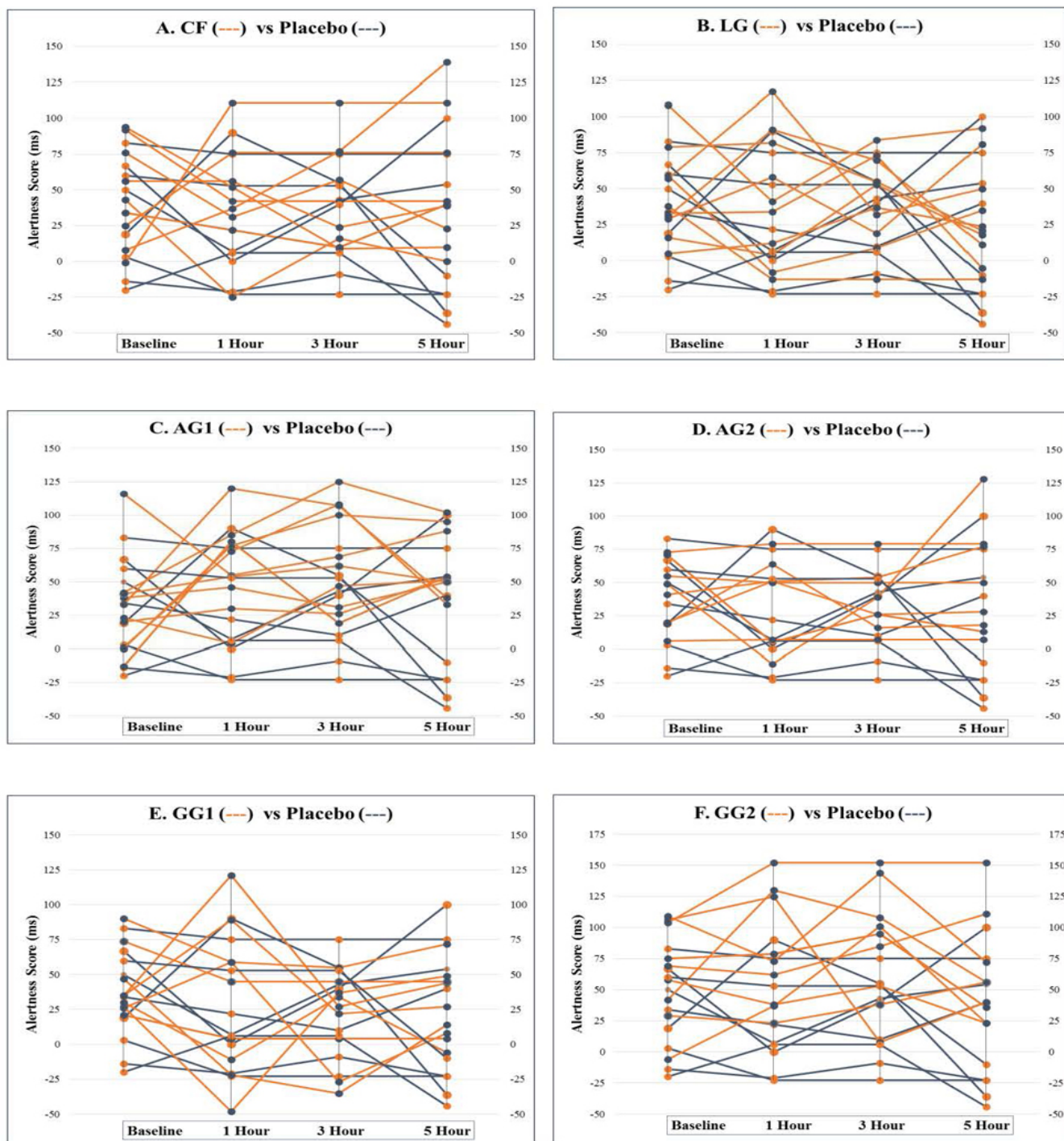


Figure 3. Effect of IP on Alertness

Table 2. Demographic Characteristics

Interventions	No. of subjects	Mean age (Years ± Months)	BMI (kg/m ²) (Mean ± SD)
Placebo	10	31 ± 6	22.15 ± 2.49
CF	10	23 ± 5	22.06 ± 2.53
LG	10	31 ± 7	22.86 ± 2.28
AG1	10	32 ± 7	23.25 ± 1.54
AG2	10	25 ± 7	23.42 ± 2.59
GG1	10	30 ± 7	22.90 ± 2.72
GG2	10	25 ± 7	22.42 ± 2.49

Table 3. Percentage Change in Efficacy Variables

Treatment Group	% change in MRT Compared to Baseline			% change in Alertness Score Compared to Baseline		
	1 hour	3 hours	5 hours	1 hour	3 hours	5 hours
PL	8.30	3.29	4.78	-25.89	-11.35	-52.84
CF	4.58	-3.94	4.80	-5.85	-1.17	12.41
LG	14.18	2.22	6.18	-9.00	-18.01	-24.41
AG1	10.38	5.08	5.56	107.31	119.27	103.99
AG2	9.10	0.77	2.82	-11.38	-11.08	19.76
GG1	7.17	2.82	7.90	-23.12	-57.92	-33.25
GG2	9.17	2.24	7.23	22.70	33.79	-2.90

among all the treatment groups, only AG1 group showed a consistent and statistically significant increase in the alertness score in comparison with the placebo at 1 hour 107.31%, $p = 0.07$), 3 hours (119.27 %, $p = 0.05$) and 5 hours (103.99 %, $p < 0.05$), indicating the sustained alertness. Also, the GG2 group exhibited an increase in the alertness score at 1 and 3 hours (22.70 and 33.79%, respectively), however the score dropped at 5 hours, implying its inefficiency to maintain the alertness over a span of 5 hours. The changes in the other groups were not as appreciable. Figure 3 depicts a graphical representation of these results.

In terms of orientation and executive attention, none of the investigated extracts and the comparator demonstrated any significant effect on the respective scores as compared to the baseline and the placebo.

The safety of the IPs was determined primarily by analyzing the vital parameters (blood pressure and pulse rate) and an occurrence of cardiogenic, gastric or any other systemic events. A total of six adverse events, all classified as mild, were observed during the study period. No treatment was required and the events were resolved on their own. None of the adverse events (AEs) had any specific repetitive nature and no serious AEs were reported during the study. Table 4 lists the details of the AEs. According to the investigator's opinion, the AE observed in LG, CF and AG1 groups might be due to the hypersensitivity to the investigational products or other conditions. The AE observed in GG2 group can be correlated with the presence of phytoestrogenic compounds

which activate and modulate the estrogen receptors, thus delaying the menstrual cycle[38].

Discussion and Conclusion

This study was undertaken to evaluate the efficacy and safety of natural product extracts in the subjects with caffeine dependence. We screened several extracts to elucidate the psycho stimulant potential of the selected natural sources. Unlike other studies which report findings on the basis of subjective feelings, this study objectively compared the effects of the IPs on the different aspects of the attention network using ANT, which is the only standardized and validated tool for an independent analysis of the different aspects of the attention network.

A decrease of the MRT in the caffeine group at 3 hours ascertains its literature-reported positive effect on the mental attention. This finding also validated the reliability of the ANT as an assessment tool for the attention-related studies.

Among the other studied extracts (LG, AG1, AG2, GG1, and GG2), the ANT data revealed that LG did not exhibit any beneficial effects in any of the outcome measures. Therefore, it can be postulated that this particular extract from *Cymbopogon* species does not contain any phytoconstituents responsible for the psychostimulant activity. AG1 showed a consistent improvement in the alertness at 1, 3, and 5 hours as compared to the baseline and placebo. This can be attributed to the bioactive constituents such as polyphenols, pyrocatecollic type tannins, and polysaccharides

Table 4. Nature of Adverse Events

Subject ID	Concerned IP	Adverse Events
ER/SR/02	CF	Numbness on fingertips
ER/SR/02	CF	Chills
ER/SR/19	GG2	Delay in menstrual cycle by 12 days
ER/SR/28	AG1	Papular eruption on cheeks; cough and cold
ER/SR/38	Placebo	Decreased stamina during the study duration
ER/SR/53	LG	Delay in menstrual cycle by 5 days

present in *A. galanga*, which were skillfully extracted in the water-soluble extract.

GG1 did not demonstrate any effect on alertness, while GG2 was able to produce a positive effect until 3 hours. Both did not show any effect 5 hours after administration compared to the baseline. The beneficial effect of the latter extract can be due to the fact that this particular extract contains triterpenoids, saponins, and flavonoids [39], reported to have neuroprotective and antidepressant effects [40].

The water soluble *A. galanga* extract used in the study has a rich phytochemical profile in addition to the alkaloids. Moreover, the polyphenols and flavonoids of AG1 may be helpful in combating the caffeine-like “crash effect.” As we observed the alertness enhancing effect in the AG1 group, we postulate that the neuroenergetic effect responsible for improving the alerting network cannot be solely attributed to the widely acknowledged purine-like alkaloids such as caffeine or the acrine.

In conclusion, our findings cumulatively support the predominance of AG1 as a potent psycho stimulant among the investigated products. Although, the acquired data serves as an encouraging base, future studies with a fine-tuned study design and a larger sample size are warranted to conclusively determine the effect of AG1 on the alertness. Additionally, an organized study to compare the activity of *A. galanga* with other species of *Alpinia* (such as *Alpinia officinarum*) would be helpful.

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Declarations

Author Contributions

SS is responsible for conceptualization, project administration, data curation, and review & editing of the manuscript. SP is responsible for preparation of the original draft of the manuscript. SS agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the

work are appropriately investigated and resolved. All the authors read and approved the final manuscript.

Conflicts of Interest

Enovate Biolife funded the trial, provided the investigational products and approved the manuscript submission to the journal. Enovate Biolife provided support in the form of salaries to SS and SP, who hold full-time positions with the organization. This does not alter author’s adherence to journal’s policies on sharing the study data and materials.

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