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CLINICAL TRIAL REPORT

Effects of EnXtra® (*Alpinia galanga* Extract) and EnXtra® + Caffeine Combination on Mental Alertness and Fatigue in Healthy Adults: A Randomized, Double-Blind, Placebo-Controlled Study

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Purpose: To evaluate the efficacy and safety of EnXtra® (*Alpinia galanga* extract) alone, caffeine and its combination with caffeine on mental alertness and fatigue in healthy sleep-restricted adults through acute single-dose and sub-acute 28-day supplementation protocols.

Patients and Methods: This randomized, double-blind, placebo-controlled study consisted of two stages: an acute crossover design (n=128) and a sub-acute 28-day parallel design (n=127). In both the stages, participants aged 18–40 years with habitual caffeine intake received one of the following interventions: *A. galanga* extract (300 mg), caffeine (200 mg), *A. galanga* extract (300 mg) + caffeine (200 mg), or placebo (300 mg). The primary outcome was mental alertness evaluated using the Jin Fan Attention Network Test (ANT). Secondary outcomes included fatigue (Samn-Perelli Fatigue Scale (SPS)), psychomotor performance (Nine-Hole Peg Test), sustained attention (Continuous Performance Test), and safety parameters. Cognitive assessments were performed at 0, 1, 3, and 5 hours post-dose in controlled environments on each scheduled visit (Days 0, 5, 10, 15, 20, and 48).

Results: In both acute and sub-acute phases, *A. galanga* extract showed statistically significant improvements in alertness compared with placebo at selected time points. The combination group demonstrated greater improvements in alertness compared with placebo in several assessments. Improvements in fatigue scores were also observed with *A. galanga* extract alone and in combination with caffeine, with statistically significant reductions compared with placebo at certain time points. Trends toward improvements in psychomotor performance (NHPT) and sustained attention (CPT) were observed with *A. galanga* extract, although these changes were not consistently statistically significant. In the sub-acute phase, caffeine showed improvements in alertness and fatigue primarily at 1 hour post-dose, with limited effects at later time points.

Conclusion: *Alpinia galanga* extract, alone or combined with caffeine, significantly improved mental alertness and reduced fatigue without caffeine-associated rebound effects, with both interventions showing good safety profiles in healthy adults.

Keywords: *Alpinia galanga*, EnXtra®, caffeine, mental alertness, caffeine crash, cognitive enhancement, fatigue

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Introduction

Alertness plays a key role in cognitive function, reflecting an individual's ability to stay focused, react quickly, and maintain sensory awareness. This state is largely governed by activity in the cerebral cortex, which helps the brain interpret and respond to external input with speed and efficiency. This modulation is mostly mediated by the thalamo-cortical circuitry, specifically through the burst and tonic functional states of thalamic projection neurons. Information transport is often limited by the burst state, which results from a hyperpolarized resting membrane potential. On the other hand, the depolarized tonic state is more appropriate for effectively processing signals associated with alertness.[1,2]

Sleep restriction is increasingly recognized as a major factor affecting cognitive performance and daytime alertness. Epidemiological evidence indicates that a substantial proportion of adults experience insufficient sleep, with many reporting sleep durations below the recommended levels. Chronic or acute sleep restriction has been associated with impaired attention, slower reaction times, reduced executive function, and increased subjective fatigue.[3–5] These effects are thought to result from alterations in neurochemical signaling and cortical arousal associated with sleep loss.[6]

Caffeine, a Central Nervous System (CNS) stimulant from the methylxanthine class, is one of the most widely consumed psychoactive substances worldwide. Around the world, roughly four out of five people consume caffeine each day, with an average daily consumption of about 200 mg, or roughly three espresso shots.[7,8] During 2020–2021, global coffee consumption reached an estimated 166.62 million 60-kg bags.[9] The European Food Safety Authority (EFSA) acknowledges that even moderate caffeine doses (75–150 mg) can significantly improve alertness and attention.[10] These stimulant effects are primarily mediated through caffeine's antagonism of adenosine receptors, which inhibits adenosine-induced drowsiness, leading to increased wakefulness.[11] As the body metabolizes caffeine, adenosine gradually reattaches to its receptors, which can trigger a rebound effect often referred to as the "caffeine crash" marked by tiredness, mood dips, and slower cognitive function.[12]

Given this limitation, there is an increasing interest in identifying natural alternatives or complementary agents that provide the cognitive benefits of caffeine without the associated crash or tolerance effect. Among such options is *Alpinia galanga*, a rhizomatous herb known for its rich phytochemical profile, including flavonoids, essential oils, and terpenoids, which contribute to its wide range of pharmacological actions—anti-inflammatory, antimicrobial, antioxidant, and neuroprotective.[13]

Importantly, preclinical research has proved that *A. galanga* has stimulating effects on the CNS, as shown by improved mice performance on the rotarod and actophotometer tests.[14] Molecular docking studies have further provided the potential mechanisms involving dopaminergic modulation and acetylcholinesterase inhibition, both of which were relevant to cognitive enhancement.[15] Clinically, Srivastava et al reported that *A. galanga* improved mental alertness and sustained attention at 1-hour post-dose, and sustained improvements were observed up to 5 hours post-dose, particularly when combined with caffeine, and mitigated the caffeine crash commonly reported in habitual caffeine consumers.[16,17]

Based on the above evidence, we conducted a two-stage clinical study of EnXtra®, a proprietary extract of *A. galanga*, to comprehensively assess its cognitive benefits in sleep-deprived healthy adults. These sleep-restricted healthy adults were included in both study stages to replicate the cognitive challenges commonly experienced during everyday situations. The acute stage was designed to evaluate the immediate effects on alertness and fatigue following a single dose, while the sub-acute stage examined the consistency and sustainability of these effects, along with safety, over 28 days of repeated administration. This study aimed to evaluate and compare the efficacy of the *A. galanga* extract alone, caffeine and its combination with caffeine in improving alertness, orienting, and conflict resolution, fatigue, sustained attention, and psychomotor performance, while also assessing its safety and tolerability.

Materials and Methods

Ethics and Regulatory Compliance

This study was conducted in accordance with the Declaration of Helsinki (2013 revision), International Conference on Harmonization Good Clinical Practice (ICH-GCP) E6(R2) guidelines, and National Ethical Guidelines for Biomedical and Health Research involving Human Participants (ICMR, 2017). The protocol received approval from the Ethicare Ethics Committee (Maharashtra, India; ECR/224/Indt/MH/2015/RR-21) and was registered prospectively with ClinicalTrials.gov (NCT06560008) and Clinical Trials Registry India (CTRI/2024/09/073338). Written informed consent was obtained from all

participants before any study procedures. The study conformed to the Consolidated Standard Reporting of Trials (CONSORT) guidelines. The study was monitored and audited by Vedic Lifesciences' clinical research team to comply with the study protocol and applicable regulatory guidelines.

Study Design

This multi-center, randomized, double-blind, placebo-controlled study employed a two-stage design: (1) an acute stage utilizing a four-period crossover design with single-dose administration conducted over 4 non-consecutive days, each separated by a 4-day washout period, and (2) a sub-acute stage employing a parallel-group design with 28-days administration of the intervention. The first study participant was enrolled in October 2024, and the last participant completed the final visit as per protocol in March 2025. The crossover design in the acute stage minimized inter-individual variability, while the parallel design in the sub-acute stage allowed evaluation of sustained effects and tolerance development.

Participants

Healthy adults aged 18–40 years with regular caffeine consumption (≥2 cups of coffee/day) were eligible for participation. Key inclusion criteria included: body mass index (BMI) of 18.0–29.9 kg/m^2, baseline alertness score of 50±20 milliseconds (ms) on the Jin Fan ANT following 24-hour caffeine abstinence, Karolinska Sleepiness Scale (KSS) score >7 during caffeine abstinence, adequate computer literacy, and provision of informed consent.

Exclusion criteria encompassed: diagnosed sleep disorders, caffeine dependency (>3 cups/day), history of psychedelic drug use, recent trauma (within 3 months), concurrent use of psychoactive medications, abnormal thyroid function (Thyroid Stimulating Hormone (TSH) <0.40 or >5.0 μIU/mL), hypertension (systolic >140 mmHg and/or diastolic >90 mmHg), pregnancy or lactation, and any condition that compromised the study participation or safety.

Randomization and Blinding

Acute stage randomization employed sequence-based allocation using StatsDirect Software (version 3.1.17) at Day 0. Sub-acute stage randomization utilized stratified block randomization (block size 8) with 1:1:1:1 allocation at Day 20. Randomization schedules were generated independently and maintained in sealed envelopes. All participants, investigators, and study personnel remained blinded throughout the study duration.

Interventions

To ensure blinding, the four interventions were administered in identical capsules, with each group receiving only one of the following interventions: (1) One capsule of *Alpinia galanga* extract 300 mg (EnXtra®) + one capsule of placebo, (2) One capsule of caffeine 200 mg + One capsule of placebo, (3) One capsule of *Alpinia galanga* extract 300 mg + one capsule of caffeine 200 mg, and (4) Two capsules of placebo (Microcrystalline Cellulose (MCC) 300 mg). Participants were asked to take two capsules after breakfast orally once a day. All interventions were manufactured to pharmaceutical standards according to Good Manufacturing Practices (GMP) with verified potency and purity. The intervention duration was 4 days [1 (single dose) x 4 periods] for the acute stage and 28 days for the sub-acute stage.

Study Procedures

The acute stage comprised a randomized, double-blind, placebo-controlled, four-way cross-over design conducted over 4 days [1 (single dose) x 4 periods] with 4 days washout (to avoid carryover effect) between each period to assessing the immediate effects of *A. galanga* extract, caffeine, and their combination on alertness and fatigue. The sub-acute stage extended over 28 days to evaluate sustained efficacy and safety using a randomized, double-blind, placebo-controlled, parallel-group design. Participants underwent comprehensive screening, including medical history, physical examination, vital signs assessment, and laboratory evaluations. In the acute crossover stage, participants completed four intervention visits on Days 0, 5, 10, and 15, with a 4-day washout between each period. Participants underwent controlled sleep restriction (5–6 hours) and 24-hour caffeine abstinence, with study assessments initiated between 7:30 and 8:00 a.m. Cognitive assessments such as mental alertness was evaluated using the Jin Fan Attention Network Test (ANT), which

assesses efficiency of three attention networks—alerting, orienting, and executive control—by requiring participants to respond to directional cues and target stimuli. Fatigue was assessed using the Samn-Perelli Fatigue Scale (SPS), a validated 7-point subjective rating scale where participants self-report their perceived fatigue levels, ranging from "fully alert" to "completely exhausted". Psychomotor performance was evaluated with the help of Nine-Hole Peg Test (NHPT), a standardized task in which participants place and remove pegs from nine holes as quickly as possible, reflecting hand–eye coordination and fine motor skills. Sustained attention was assessed through Continuous Performance Test (CPT), which requires individuals to respond to specific stimuli over time while withholding responses to non-targets, thereby assessing vigilance and impulsivity control. Safety parameters were also performed. All assessments were performed at 0, 1, 3, and 5 hours (±15 minutes) post-dose in controlled environments.

The sub-acute stage involved baseline assessments (Day 20); at this point, participants were re-randomized into one of the aforementioned four intervention groups. Participants received daily supplementation for 28 days, maintaining dosing diaries, with endpoint evaluations conducted on Day 48 using the same assessment procedures as in the acute stage.

Outcome Measures (For Both Acute and Sub-Acute Stage)

Primary Outcome: Change in mental alertness assessed by the Jin Fan ANT, a validated computerized assessment measuring response time to visual stimuli with different cuing conditions. The alertness score was calculated as the difference between mean response times for no-cue versus center-cue conditions.

Secondary Outcomes: (1) Fatigue severity using the SPS, a 7-point Likert scale; (2) Fine psychomotor coordination assessed by the NHPT measuring peg placement/retrieval times; (3) Sustained attention evaluated by the CPT assessing response time and error rates; (4) Safety parameters including complete blood count, liver function tests, kidney function tests, vital signs, and adverse event monitoring.

Statistical Analysis

The sample size was calculated to detect a 10-millisecond difference in Jin Fan alertness scores, with 80% statistical power and a significance level of α=0.05. To accommodate a projected 15% attrition rate, a total of 128 participants were required. Statistical analyses were performed using R (version 4.0.5) and XLSTAT (2021.3.1). Continuous variables were compared using ANOVA or non-parametric tests as appropriate. For outcomes assessed at multiple time points, analysis of covariance (ANCOVA) models were applied, with treatment group as a fixed factor and baseline value as a covariate to adjust for baseline differences. Post hoc pairwise comparisons between groups were performed where applicable.The per-protocol population, defined as participants who completed the study without major protocol deviations, was used for efficacy analyses, while all randomized participants receiving at least one dose were included in safety analyses. Statistical significance was set at $p<0.05$.

Quality Assurance

The study was monitored and audited by the Contract Research Organization, Vedic Lifesciences (Mumbai, Maharashtra, India) to ensure compliance with the study protocol and with the ICH-GCP E6 (R2) guidelines.

Results

Participant Disposition and Demographic Characteristics

One hundred and sixty-five participants were screened, and 128 were randomized in the study. In the end, 127 completed it according to the protocol — only one participant dropped out due to lost to follow-up.

Baseline demographics were comparable across groups. All participants had established caffeine consumption patterns and demonstrated appropriate baseline cognitive scores after caffeine abstinence. During the sub-acute phase, participants were instructed to maintain a diet diary for two weekdays (any days from Monday to Friday) and one weekend day (Saturday or Sunday). The detailed participant disposition is presented in Figure 1.

As the acute stage was a cross-over study, all participants (N = 128) received each of the four study interventions—*A. galanga* extract, Caffeine, *A. galanga* extract + Caffeine, and Placebo in a randomized sequence. Therefore, to ensure

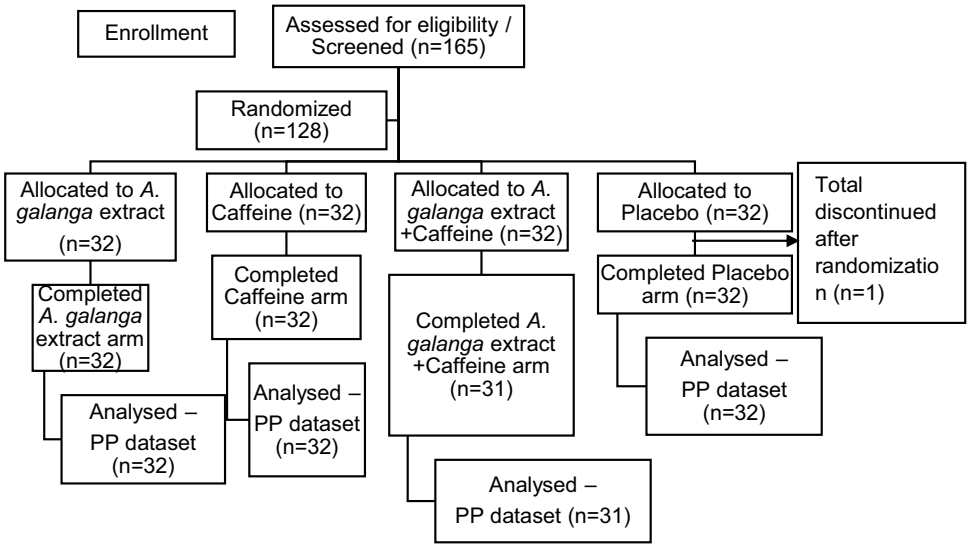

Figure 1 Participant Disposition The black arrow →denotes one participant who was discontinued after randomization in the placebo arm.

consistency, baseline characteristics were analyzed collectively without stratification by intervention arm. The mean age of participants was 28.28 (5.49) years, with a range of 18.00 to 39.00 years. The mean BMI was 23.89 (2.91) kg/m^2, with values ranging from 18.07 to 28.62 kg/m^2.

For the sub-acute stage, participants (N = 127) were randomized into four parallel intervention groups: *A. galanga* extract (N=32), Caffeine (N=32), *A. galanga* extract + Caffeine (N=31), and Placebo (N=32). The mean (±SD) age in the groups were 28.00 (±5.78), 28.09 (±5.50), 28.77 (±5.30), and 28.16 (±5.65) years, respectively. The BMI value ranged from 23.40 to 24.17 kg/m^2 across all groups. No statistically significant differences were observed across the groups in baseline demographics.

Other demographic details about the acute and sub-acute stages are presented in Table 1 and Table 2.

Table 1 Demographic and Baseline Characteristics - Acute Stage

Parameter	**Acute Stage**	
	Overall	
n	**128**	
	Mean (SD)	**Min, Max**
Age (years)	28.28 (5.49)	18.00, 39.00
Height (Meters)	1.64 (0.09)	1.45, 1.85
Weight (Kg)	64.11 (9.11)	47.00, 88.15
BMI (Kg/m^2)	23.89 (2.91)	18.07, 28.62
Gender n (%)	–	
Male	77 (60.2%)	
Female	51 (39.8%)	

Abbreviations: SD, Standard deviation; n, Number of participants; Min, Minimum; Max, Maximum; BMI, Body Mass Index.

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Table 2 Demographic and Baseline Characteristics - Sub-Acute Stage

Parameter	Sub-Acute Stage										P-value
	A. galanga Extract		Caffeine		*A. galanga* Extract + Caffeine		Placebo		Overall		
n	32		32		31		32		127		
	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	
Age (years)	28 (5.78)	18.00, 37.00	28.09 (5.50)	18.00, 37.00	28.77 (5.30)	20.00, 39.00	28.16 (5.65)	18.00, 38.00	28.25 (5.50)	18.00, 39.00	0.9453 (A)
Height (Meters)	1.62 (0.08)	1.47, 1.81	1.65 (0.10)	1.48, 1.85	1.65 (0.09)	1.48, 1.83	1.63 (0.08)	1.45, 1.74	1.64 (0.09)	1.45, 1.85	0.3153 (A)
Weight (Kg)	63.26 (10.04)	47.00, 88.15	64.02 (9.36)	47.00, 83.00	64.58 (8.39)	48.00, 77.20	64.46 (9.04)	49.00, 84.25	64.08 (9.14)	47.00, 88.15	0.9399 (A)
BMI (Kg/m^2)	24.13 (2.88)	19.00, 28.28	23.40 (2.76)	19.15, 28.35	23.75 (3.18)	18.07, 28.62	24.17 (2.89)	19.23, 28.59	23.86 (2.91)	18.07, 28.62	0.6916 (A)
Gender n (%)											0.7829 (C)
Male	17 (53.1%)		21 (65.6%)		19 (61.3%)		19 (59.4%)		76 (59.8%)		
Female	15 (46.9%)		11 (34.4%)		12 (38.7%)		13 (40.6%)		51 (40.2%)		

Notes: (A) p-value was calculated using One-way ANOVA. (C) p-value was calculated using Chi-square test. Percentages were calculated using respective column header count as denominator.
Abbreviations: SD, Standard deviation; n, Number of participants; Min, Minimum; Max, Maximum; BMI, Body Mass Index.

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Primary Efficacy Outcomes - Acute Stage

Alertness Score (Alerting Effect)

At 1-hour post-intervention, mean change of *A. galanga* + Caffeine showed the greatest improvement in alertness (+32.37 ± 23.43 ms), compared to placebo (+22.13 ± 21.25 ms), with statistically significant differences between the groups (p = 0.0031). Similarly, *A. galanga extract* alone demonstrated a mean change increase of +31.30 ± 27.42 ms, which was higher and also statistically significant when compared to the placebo (p = 0.0129).

At 3 hours post-intervention, the extract along showed a greater mean change in alertness score (+31.80 ± 29.74 ms) compared to placebo (+20.95 ± 26.04 ms), with a statistically significant difference (p = 0.0166). Additionally, the *A. galanga* group demonstrated a higher percent change in alertness (82.70 ± 78.18%) versus placebo (53.76 ± 65.81%), also with a statistically significant difference (p = 0.0190).

At 5 hours, placebo (−2.85 ± 19.81 ms) showed a decline in alertness compared to baseline. Similar decline in alertness was seen with caffeine (−1.71 ± 18.67 ms) indicating the typical "caffeine crash" effect. On the other hand, both *A. galanga extract* (+2.82 ± 19.26 ms) and *A. galanga extract* + Caffeine (+2.10 ± 20.36 ms) maintained alertness levels from baseline, suggesting avoidance of the usual decline associated with caffeine. (Tables 3, 4 and Figure 2)

Orienting Effect

At 3 hours, *A. galanga* extract + Caffeine showed a significant within-group improvement (−9.49 ± 40.22 ms; p = 0.0088), though between-group differences remained non-significant across timepoints. At 5 hours, this group (−3.30 ± 37.68 ms) showed greater reduction than other groups. (Supplementary Tables S1a, S1b and Supplementary Figure S1)

Conflict Effect (Executive Control)

Across post-dose timepoints, no statistically significant differences were observed between groups, and the interventions demonstrated limited and inconsistent changes in mean response times. (Supplementary Tables S2a, S2b and Supplementary Figure S2).

Secondary Efficacy Outcomes – Acute Stage

Psychomotor Performance (Nine-Hole Peg Test)

Moving Duration

A. galanga extract + caffeine consistently showed improved task completion times across all timepoints. At 1 hour, the combination group demonstrated a reduction of (−933.77 ± 6425.23 ms) compared to placebo (−598.35 ± 7338.29 ms). At 3 hours from baseline, the reduction increased to −2937.17 ± 6497.55 ms (−7.49% improvement), and at 5 hours continued to improve to −3235.04 ± 6567.24 ms (−7.83% improvement), indicating sustained enhancement in psychomotor speed. The combination group showed greater reductions in moving duration compared to caffeine alone. None of these changes were significant between the groups. (Supplementary Tables S3a, S3b and Supplementary Figure S3)

Time Until First Peg Selection

Participants in all active groups began tasks more quickly than those in the placebo group. At 1 hour, Caffeine reduced the first peg selection time by −677.68 ± 2647.93 ms, the combination by −403.59 ± 4665.40 ms, and *A. galanga* extract alone by −361.18±3631.76 ms, compared to placebo (−219.28 ± 2158.71 ms). At 3 hours, the combination group demonstrated the greatest improvement (−1197.54 ± 3418.19 ms) compared with the other groups [Caffeine: −753.26 ± 2715.68; *A. galanga* extract: −532.42 ± 4010.66; Placebo: −288.33 ± 3040.98], while at 5 hours, Caffeine [−1006.28 ± 2456.13] showed a greater reduction than other groups, whereas *A. galanga* extract alone maintained superior performance (−732.16 ± 3407.90 ms). However, none of these changes were statistically significant between the groups. (Supplementary Tables S4a, S4b and Supplementary Figure S4)

Transport Drops

At 3 hours, the combination group showed a decrease in transport drops (−0.33 ± 1.96 units; −6.01% improvement) as compared to placebo (−0.01 ± 2.02 units; 10.94% increase) and caffeine (−0.20 ± 2.30 units; 11.76% increase), indicating

Table 3 Alertness Score (Acute Stage)

Timepoint	*A. galanga* Extract (N=127)		Caffeine (N=127)		*A. galanga* Extract + Caffeine (N=127)		Placebo (N=127)		p-value [a]
	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	
0 Hour (pre – IP consumption)	40.65 (7.88)	30.01,66.77	40.44 (7.90)	30.11, 69.79	41.72 (8.06)	30.08, 65.94	42.46 (8.77)	30.34,69.46	0.1646
1 Hour (post– IP consumption)	71.95 (27.78)	11.30, 159.02	68.08 (21.47)	22.34, 122.78	74.09 (25.86)	24.20, 172.81	64.59 (20.91)	16.87, 120.49	0.0096*
p-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change at 1 hour (post– IP consumption)	31.30 (27.42)	−32.71, 121.26	27.64 (20.01)	−18.88, 81.68	32.37 (23.43)	−12.62, 119.51	22.13 (21.25)	−29.17, 84.10	
Percent Change at 1 Hour (post– IP consumption)	80.29 (72.91)	−74.33, 321.04	70.52 (52.02)	−45.80, 248.99	78.79 (56.62)	−31.50, 271.09	56.64 (56.93)	−63.36, 244.03	
3 hours (post– IP consumption)	72.45 (29.63)	21.68, 171.38	66.09 (26.45)	17.90, 141.38	69.98 (30.49)	4.91, 166.98	63.40 (25.59)	14.27, 158.79	0.0517
P-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change at 3 hours (post– IP consumption)	31.80 (29.74)	−24.76, 129.11	25.66 (25.38)	−18.89, 102.01	28.26 (29.22)	−40.04, 124.15	20.95 (26.04)	−33.07, 105.47	
Percent Change at 3 Hour (post– IP consumption)	82.70 (78.18)	−49.12, 311.97	65.80 (67.11)	−47.37, 259.10	69.40 (70.74)	−89.08, 307.70	53.76 (65.81)	−65.28, 278.02	
5 hours (post– IP consumption)	43.47 (18.72)	13.35, 102.80	38.73 (18.55)	12.42, 103.17	43.82 (20.86)	8.88, 107.01	39.60 (19.79)	2.75, 103.23	0.0782
p-value [c]	0.1015		0.3044		0.2484		0.1070		
Change at 5 hours (Post– IP consumption)	2.82 (19.26)	−42.48, 65.03	−1.71 (18.67)	−42.63, 69.10	2.10 (20.36)	−49.04, 66.77	−2.85 (19.81)	−48.01, 67.54	
Percent Change at 5 Hour (post– IP consumption)	9.52 (49.87)	−73.95, 185.98	−2.82 (45.70)	−76.69, 202.79	6.22 (48.32)	−81.33, 182.07	−4.98 (48.98)	−93.32, 197.00	

Notes: [a] p-value was calculated using ANOVA Type III (A) for intervention effect. [c] p-value was calculated using paired *t*-test (t) for within-group change. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

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Table 4 Alertness Score (Acute Stage - p-value comparisons)

Timepoint	p-value (*A. galanga* Extract vs Placebo) [b]	p-value (*A. galanga* Extract + Caffeine vs Placebo) [b]	p-value (Caffeine vs Placebo) [b]
0 Hour (pre – IP consumption)	0.2926	0.8911	0.1993
1 Hour (post– IP consumption)	0.0733	0.0099*	0.6583
Change at 1 hour (post– IP consumption)	0.0129$*	0.0031$*	0.2831$
Percent Change at 1 Hour (post– IP consumption)	0.0285$*	0.0240$*	0.4979$
3 hours (post– IP consumption)	0.0517	0.2450	0.8715
Change at 3 hours (post– IP consumption)	0.0166$*	0.1727$	0.6425$
Percent Change at 3 Hour (post– IP consumption)	0.0190$*	0.3571$	0.7954$
5 hours (post– IP consumption)	0.3912	0.3130	0.9842
Change at 5 hours (Post– IP consumption)	0.1985$	0.2263$	>0.9999$
Percent Change at 5 Hour (post– IP consumption)	0.1548$	0.3008$	>0.9999$

Notes: [b] p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. $Adjusted p-values were derived from an ANCOVA model with intervention as factor and baseline as a covariate, using Tukey's adjustment for multiple comparisons. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

improved fine motor control. At 5 hours, both the combination and caffeine groups maintained the mean change reductions of −0.17 drops each. The reduction in transport drops with the combination group at 3 hours, and sustained effects at 5 hours, suggest improved and prolonged fine motor control compared to placebo. None of these changes were significant between the groups. (Supplementary Tables S5a, S5b and Supplementary Figure S5)

Sustained Attention (Continuous Performance Test)

At 1 hour, both *A. galanga* extract alone (−0.04 ± 8.63 ms) and the combination group (−0.13 ± 7.06 ms) showed a reduction in mean response time, which indicated an improvement in sustained attention, while the placebo showed

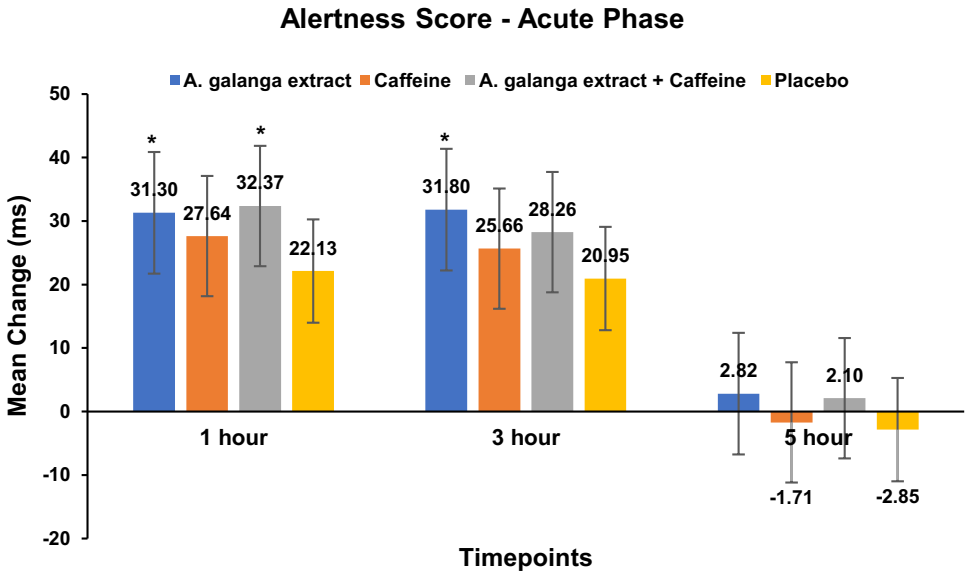

Figure 2 Mean Change in Alertness Score – Acute Stage p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. *p<0.05 significance over placebo.
Abbreviation: ms, milliseconds.

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slight deterioration (+0.70 ± 7.21 ms). Across hours, there were no statistically significant differences observed between groups. (Supplementary Tables S6a, S6b and Supplementary Figure S6)

Fatigue Reduction (Samn-Perelli Fatigue Scale)

At 1 hour post-intervention, *A. galanga* extract + caffeine exhibited the most significant fatigue reduction (−2.20 ± 1.32 units vs −1.91 ± 1.18 units placebo; p=0.0367), representing a −34.78% improvement compared to −29.96% for placebo. *A. galanga* extract alone (−2.08 ± 1.37 units; −32.33%) and caffeine (−2.07 ± 1.09 units; −32.38%) also demonstrated substantial reductions in fatigue.

At 3 hours, fatigue reduction was sustained across all groups: *A. galanga* extract alone (−2.04 ± 1.42 units; −31.31%), combination group (−1.99 ± 1.33 units; −31.13%), and caffeine (−1.92 ± 1.26 units; −30.23%) compared to placebo (−1.79 ± 1.41 units; −28.12%), though differences were not statistically significant.

At 5 hours, the combination group demonstrated greater fatigue reduction (−0.61 ± 1.17 units; −8.95%), compared to other groups [caffeine (−0.53 ± 1.13 units; −7.69%), *A. galanga* extract alone (−0.46 ± 1.17 units; −5.96%), and placebo (−0.41 ± 1.20 units; −5.74%)]. Across all timepoints, all active interventions produced greater fatigue reductions than placebo, with the combination group showing the largest improvement at 1 hour and maintaining the most favorable reduction at 5 hours. (Tables 5, 6 and Figure 3).

Primary Efficacy Outcomes – Sub-Acute Stage (Day 48)

Alertness Score (Alerting Effect)

At 1 hour, the combination group showed the highest improvement in alertness (+44.41 ± 36.48 ms vs +10.72 ± 20.03 ms Placebo; p<0.0001), with the extract alone also demonstrating statistically significant enhancement (+30.36 ± 25.23 ms; p = 0.0263) along with caffeine (+35.27 ± 30.08 ms; p = 0.0073) over placebo (+30.36 ± 25.23 ms; p=0.0263).

At 3 hours, *A. galanga* extract + Caffeine maintained superior cognitive performance (+43.28 ± 35.12 ms) with continued statistical significance over placebo (+18.94 ± 25.32 ms) (p = 0.0142).

At 5 hours, only *A. galanga* extract-containing interventions maintained positive changes: *A. galanga* extract + Caffeine (+9.40 ± 23.21 ms; p=0.0016 vs Placebo) and extract alone (+3.28 ± 20.22 ms), while Caffeine (−4.51 ± 18.01 ms) and Placebo (−9.05 ± 14.85 ms) declined below baseline. At the end of 5 hours, *A. galanga* extract + Caffeine group showed significant positive results compared to Placebo as well as Caffeine group which experienced caffeine crash, demonstrating negative results. It should be noted that the combination group showed significantly better results over Placebo, with improvements observed at 1 hour (p<0.0001), 3 hours (p=0.0142), and 5 hours (p=0.0016) (Tables 7, 8 and Figure 4)

Orienting Effect

The mean change in orienting effect showed no significant change across time points, indicating high variability and minimal effect between-group differences. At 3 and 5 hours, the combination group showed continuous mean change reduction at −7.39 ± 40.50 ms and −8.35 ± 38.08 ms, whereas the placebo showed an increase at 4.50 ± 47.04 ms and 10.62 ± 48.61. The consistent reductions in the combination group at 3 and 5 hours suggest a potential toward improved orienting effect compared with placebo. None of these changes were significant between the groups. (Supplementary Tables S7a, S7b and Supplementary Figure S7)

Conflict Effect (Executive Control)

At 1 hour, *A. galanga* extract alone (−4.08 ± 44.21 ms) and the combination group (−1.73 ± 27.77 ms) showed slight improvements in orienting effect from baseline, similar to placebo (−2.82 ± 37.86 ms), whereas caffeine alone demonstrated a small increase (+5.82 ± 34.44 ms), indicating no meaningful or consistent change across groups. At 5 hours, changes remained minimal with extract alone (−0.70 ± 40.99 ms) and the combination (+2.63 ± 30.49 ms) showing smaller shifts compared to Placebo (−8.60 ± 35.11 ms). Conflict effect scores showed no significant differences between groups at any time point. (Supplementary Tables S8a, S8b and Supplementary Figure S8).

Table 5 Total Score- Samn-Perelli Fatigue Scale (Acute Stage)

Timepoint	*A. galanga* Extract (N=127)		Caffeine (N=127)		*A. galanga* Extract + Caffeine (N=127)		Placebo (N=127)		p-value [a]
	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	
0 Hour (pre – IP consumption)	6.15 (0.75)	3.00, 7.00	6.26 (0.61)	4.00, 7.00	6.15 (0.59)	3.00, 7.00	6.19 (0.66)	4.00, 7.00	0.4943
1 Hour (post– IP consumption)	4.07 (1.08)	2.00, 6.00	4.19 (0.87)	2.00, 6.00	3.94 (1.09)	2.00, 7.00	4.28 (1.01)	2.00, 7.00	0.0484*
p-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change at 1 hour (post– IP consumption)	−2.08 (1.37)	−5.00, 2.00	−2.07 (1.09)	−5.00, 0.00	−2.20 (1.32)	−5.00, 2.00	−1.91 (1.18)	−4.00, 1.00	
Percent Change at 1 Hour (post– IP consumption)	−32.33 (21.39)	−71.43, 50.00	−32.38 (15.59)	−71.43, 20.00	−34.78 (21.03)	−71.43, 66.67	−29.96 (17.96)	−66.67, 25.00	
n	126		127		127		127		
3 hours (post– IP consumption)	4.10 (1.06)	1.00, 7.00	4.34 (1.17)	1.00, 7.00	4.16 (1.03)	1.00, 6.00	4.40 (1.26)	2.00, 7.00	0.1133
P-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change at 3 hours (post– IP consumption)	−2.04 (1.42)	−6.00, 2.00	−1.92 (1.26)	−6.00, 1.00	−1.99 (1.33)	−6.00, 2.00	−1.79 (1.41)	−5.00, 1.00	
Percent Change at 3 Hour (post– IP consumption)	−31.31 (23.51)	−85.71, 66.67	−30.23 (19.42)	−85.71, 16.67	−31.13 (20.96)	−85.71, 66.67	−28.12 (21.57)	−71.43, 20.00	
n	127		127		127		127		
5 hours (post– IP consumption)	5.69 (0.95)	2.00, 7.00	5.73 (1.03)	1.00, 7.00	5.54 (1.00)	3.00, 7.00	5.78 (1.08)	3.00, 7.00	0.2508
p-value [c]	<0.0001*		<0.0001*		<0.0001*		0.0002*		
Change at 5 hours (Post– IP consumption)	−0.46 (1.17)	−3.00, 3.00	−0.53 (1.13)	−5.00, 2.00	−0.61 (1.17)	−3.00, 3.00	−0.41 (1.20)	−4.00, 2.00	
Percent Change at 5 Hour (post– IP consumption)	−5.96 (21.44)	−60.00, 100.00	−7.69 (18.63)	−83.33, 50.00	−8.95 (20.32)	−50.00, 100.00	−5.74 (19.19)	−57.14, 40.00	

Notes: [a] p-value was calculated using ANOVA Type III (A) for intervention effect. [c] p-value was calculated using paired *t*-test (t) for within-group change. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

Table 6 Total Score- Samn-Perelli Fatigue Scale (Acute Stage - p-value comparisons)

Timepoint	p-value (*A. galanga* Extract vs Placebo) [b]	p-value (*A. galanga* Extract + Caffeine vs Placebo) [b]	p-value (Caffeine vs Placebo) [b]
0 Hour (pre – IP consumption)	0.9637	0.9637	0.8243
1 Hour (post– IP consumption)	0.3421	0.0406*	0.8804
Change at 1 hour (post– IP consumption)	0.3232$	0.0367$*	0.9041$
Percent Change at 1 Hour (post– IP consumption)	0.4850$	0.0463$*	0.9122$
n			
3 hours (post– IP consumption)	0.1572	0.3172	0.9710
Change at 3 hours (post– IP consumption)	0.1407$	0.2944$	0.9827$
Percent Change at 3 Hour (post– IP consumption)	0.3439$	0.4112$	0.9747$
n			
5 hours (post– IP consumption)	0.8809	0.2243	0.9827
Change at 5 hours (Post– IP consumption)	0.8949$	0.2383$	0.9725$
Percent Change at 5 Hour (post– IP consumption)	0.9810$	0.2897$	0.9791$

Notes: [b] p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. $Adjusted p-values were derived from an ANCOVA model with intervention as factor and baseline as a covariate, using Tukey's adjustment for multiple comparisons. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

Secondary Efficacy Outcomes – Sub-Acute Stage (Day 48)

Psychomotor Performance (Nine-Hole Peg Test)

Moving Duration

At 1 hour, all active groups showed an increase in moving duration, with the smallest increase in *A. galanga* extract + caffeine (+936.32 ± 9427.37 ms; +9.38%), followed by caffeine (+1449.44 ± 8061.63 ms; +7.50%) and extract alone

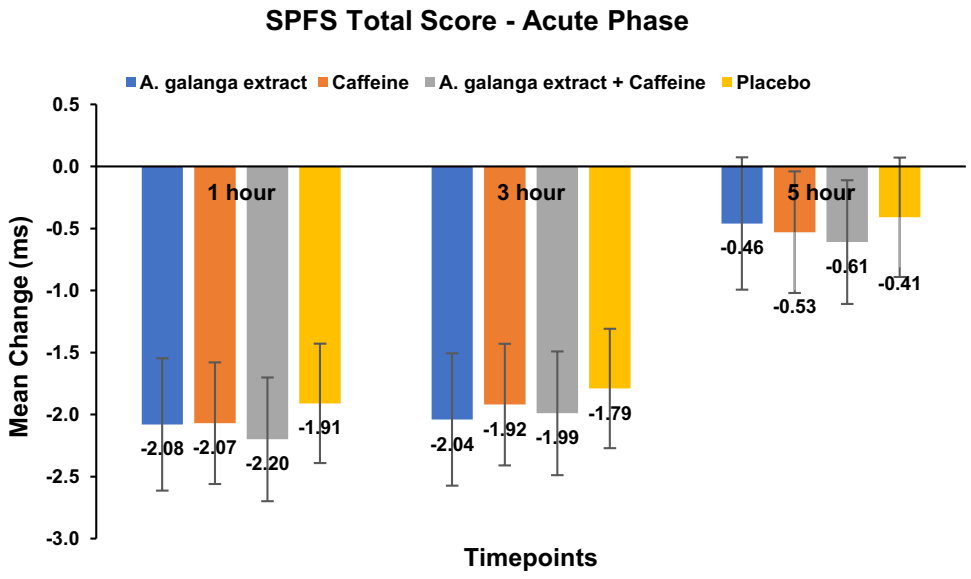

Figure 3 Mean Change in Samn-Perelli Fatigue Score – Acute Stage p-value was calculated using Tukey's HSD test (T) for pairwise comparisons.
Abbreviation: ms, milliseconds.

Table 7 Alertness Score (Sub-Acute Stage)

Timepoint	*A. galanga* Extract (N=32)		Caffeine (N=32)		*A. galanga* Extract + Caffeine (N=31)		Placebo (N=32)		p-value [a]
	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	
VISIT 6 – Re-Randomization – Day 20 (20 ± 1) (ms)									
0 Hour (Pre – IP Consumption)	45.80 (11.00)	30.55, 66.71	43.58 (9.92)	30.97, 69.57	43.75 (11.23)	30.23, 68.97	46.11 (9.86)	31.06, 67.48	0.6773
VISIT 7 – End of Study - Day 48 +2 (ms)									
1 Hour (Post– IP Consumption)	76.16 (20.12)	29.69, 123.96	78.85 (28.62)	26.49, 168.39	88.15 (37.05)	33.28, 207.00	56.83 (19.41)	30.45, 99.55	0.0001*
p-value [c]	<0.0001*		<0.0001*		<0.0001*		0.0049*		
Change from 1 Hour (Post– IP Consumption)	30.36 (25.23)	−21.51 90.43	35.27 (30.08)	−30.64 114.24	44.41 (36.48)	−2.80 151.83	10.72 (20.03)	−36.73 55.12	
Percent change from 1 Hour (Post– IP Consumption)	78.01 (72.43)	−34.89, 269.64	88.02 (73.38)	−44.04, 214.76	108.47 (85.43)	−4.96, 292.77	26.46 (41.41)	−54.67, 124.04	
3 Hour (Post– IP Consumption)	76.86 (26.31)	39.83, 129.24	74.11 (31.71)	32.63, 167.44	87.02 (32.06)	30.43, 149.10	65.05 (26.81)	27.06, 122.64	0.0334*
p-value [c]	<0.0001*		<0.0001*		<0.0001*		0.0002*		
Change from 3 Hour (Post– IP Consumption)	31.06 (27.81)	−16.36 88.42	30.53 (31.37)	−21.39 130.98	43.28 (35.12)	−17.29 113.80	18.94 (25.32)	−24.81 80.28	
Percent change from 3 Hour (Post– IP Consumption)	76.16 (72.31)	−24.53, 269.51	74.73 (81.08)	−39.60, 359.24	112.18 (95.34)	−25.07, 322.31	42.73 (57.80)	−47.84, 198.65	
5 Hour (Post– IP Consumption)	49.08 (19.07)	21.20, 105.32	39.07 (17.40)	16.85, 88.68	53.14 (20.64)	18.68, 90.08	37.06 (12.63)	18.93, 73.36	0.0007*
p-value [c]	0.3665		0.1664		0.0317*		0.0016*		
Change from 5 Hour (Post– IP Consumption)	3.28 (20.22)	−31.44, 48.67	−4.51 (18.01)	−38.05, 52.22	9.40 (23.21)	−29.96, 52.63	−9.05 (14.85)	−32.43, 32.95	
Percent change from 5 Hour (Post– IP Consumption)	76.16 (72.31)	−24.53, 269.51	74.73 (81.08)	−39.60, 359.24	112.18 (95.34)	−25.07, 322.31	42.73 (57.80)	−47.84, 198.65	

Notes: [a] p-value was calculated using ANOVA Type III (A) for intervention effect. [c] p-value was calculated using paired *t*-test (t) for within-group change. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product; ms, millisecond.

Table 8 Alertness Score (Sub-Acute Stage - p-value comparisons)

Timepoint	p-value (*A. galanga* Extract vs Placebo) [b]	p-value (*A. galanga* Extract + Caffeine vs Placebo) [b]	p-value (Caffeine vs Placebo) [b]
VISIT 6 – Re-Randomization – Day 20 (20 ± 1) (ms)			
0 Hour (Pre – IP Consumption)	0.9994	0.8091	0.7712
VISIT 7 – End of Study - Day 48 +2 (ms)			
1 Hour (Post– IP Consumption)	0.0263*	<0.0001*	0.0082*
Change from 1 Hour (Post– IP Consumption)	0.0263$*	<0.0001$*	0.0073*$
Percent change from 1 Hour (Post– IP Consumption)	0.0084$*	<0.0001$*	0.0045*$
3 Hour (Post– IP Consumption)	0.3766	0.0184*	0.6055
Change from 3 Hour (Post– IP Consumption)	0.3683$	0.0142$*	0.5431$
Percent change from 3 Hour (Post– IP Consumption)	0.2730$	0.0042$*	0.5195$
5 Hour (Post– IP Consumption)	0.0370*	0.0025*	0.9687
Change from 5 Hour (Post– IP Consumption)	0.0341$*	0.0016$*	0.9356$
Percent change from 5 Hour (Post– IP Consumption)	0.2730$	0.0042$*	0.5195$

Notes: [b] p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. $Adjusted p-values were derived from an ANCOVA model with intervention as factor and baseline as a covariate, using Tukey's adjustment for multiple comparisons. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product; ms, millisecond.

(+1960.59 ± 7227.60 ms; +10.82%). Placebo showed a decrease (−78.41 ± 7410.81 ms; +3.56%), thereby showing improvement.

At 3 hours, caffeine (−222.88 ± 7181.18 ms) and placebo (−624.28 ± 6638.51 ms) showed reductions.

At 5 hours, the extract alone demonstrated improvement in moving duration (−594.41 ± 7324.08 ms; +1.85%), preventing the crash found in other groups, whereas the combination group showed a delayed increase (+1448.39 ± 10,445.63 ms;

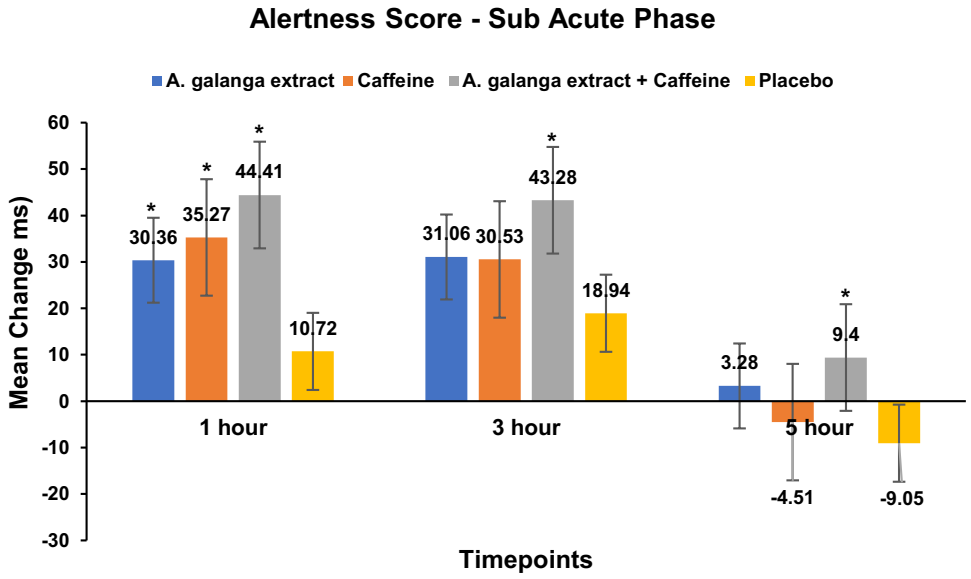

Figure 4 Mean Change in Alertness Score – Sub-acute Stage p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. *p<0.05 significance over placebo.
Abbreviation: ms, milliseconds.

+11.45%), indicating variable recovery patterns among groups. None of these changes were significant compared to baseline as well as between the groups. (Supplementary Tables S9a, S9b and Supplementary Figure S9)

Time Until First Peg Selection

At 1 hour, only the combination group showed a reduction in mean change (−53.74 ± 2947.64 ms; +16.83%) compared to other groups. At 3 hours, this combination group achieved further reduction in time for first peg selection (−457.00 ± 2441.66 ms; +1.84%). By 5 hours, the combination group achieved the highest reduction (−355.84 ± 3029.39 ms), showed sustained effect, followed by the extract alone (−22.34 ± 1173.05 ms; +5.51%), whereas both placebo and caffeine groups showed an increase in first peg selection time. These findings suggest that the combination group supported faster task initiation over time compared to the caffeine and placebo groups. None of these changes were significant compared to baseline as well as between the groups. (Supplementary Table S10a, S10b and Supplementary Figure S10)

Transport Drops

Mean change of all groups demonstrated minimal and non-significant changes across all timepoints. However, *A. galanga* extract + caffeine showed slight improvements in transport drops at most timepoints (−0.16 ± 1.75 drops at 1 hour, −0.26 ± 1.18 drops at 3 hours, −0.10 ± 1.60 drops at 5 hours), unlike other groups, which showed inconsistent trends or increased values. (Supplementary Tables S11a, S11b and Supplementary Figure S11)

Sustained Attention (Continuous Performance Test)

A. galanga extract alone showed slight increases from baseline (+2.06 ± 11.14 ms at 1 hour, +2.30 ± 11.62 ms at 3 hours, +3.59 ± 12.22 ms at 5 hours), while caffeine demonstrated reductions (−2.44 ± 19.35 ms, −4.45 ± 40.77 ms, −2.33 ± 18.62 ms, respectively), though no between-group differences reached statistical significance. (Supplementary Tables S12a, S12b and Supplementary Figure S12)

Fatigue Reduction (Samn-Perelli Fatigue Scale)

At 1-hour post-dose on Day 48, all active interventions significantly outperformed placebo: *A. galanga* extract alone (−2.16 ± 1.30 units; $p = 0.0282$), extract combination with Caffeine (−2.29 ± 1.35 units; $p = 0.0334$) and Caffeine (−2.34 ± 1.38 units; $p = 0.0151$) compared to placebo.

At 3 hours, the combination group demonstrated the most pronounced and sustained effect vs placebo (−2.81 ± 1.60 units; $p = 0.0019$). It maintained superiority over other groups as well.

By 5 hours, only the combination group maintained statistical significance compared with placebo (−1.00 ± 1.34 units; $p = 0.0021$), while placebo showed a slight increase in fatigue (+0.06 ± 1.05 units). The *A. galanga* extract alone group also showed a reduction in fatigue; however, the difference did not reach statistical significance ($p = 0.0778$). (Tables 9, 10 and Figure 5).

Safety Outcomes

Alpinia galanga extract intervention demonstrated a strong safety profile throughout the study period. No serious adverse events were reported, and mild events such as headache and gastrointestinal discomfort were evenly distributed across groups, with a total of eight incidents (six during the acute stage, two during the sub-acute stage). All reported adverse events were resolved and were not related to the interventions. Laboratory findings — including complete blood counts and assessments of liver and kidney function — remained within normal limits for all participants, and vital signs showed no clinically meaningful deviations from baseline. (Supplementary Tables S13 and S14–S19).

Discussion

Alertness is a critical aspect of cognitive performance, especially under conditions of fatigue and sleep deprivation. Caffeine, while widely used to increase alertness, is often associated with a rebound "crash" once its effects subside. *Alpinia galanga* (EnXtra®), a botanical extract with psychostimulant potential, has shown promise in sustaining alertness without this drawback.[15,18] Based on previous clinical findings, this randomized, double-blind, placebo-controlled

Table 9 Total Score- Samn-Perelli Fatigue Scale – Sub-Acute Stage

Timepoint	*A. galanga* Extract (N=32)		Caffeine (N=32)		*A. galanga* Extract + Caffeine (N=31)		Placebo (N=32)		p-value [a]
	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	Mean (SD)	Min, Max	
VISIT 6 – Re-Randomization – Day 20 (20 ± 1)									
0 Hour (Pre – IP Consumption)	6.03 (0.54)	5.00, 7.00	6.13 (0.71)	4.00, 7.00	6.13 (0.72)	4.00, 7.00	6.00 (0.57)	5.00, 7.00	0.7992
VISIT 7 – End of Study - Day 48 +2									
1 Hour (Post– IP Consumption)	3.88 (1.01)	2.00, 6.00	3.78 (0.87)	2.00, 6.00	3.84 (0.93)	2.00, 6.00	4.53 (0.98)	3.00, 7.00	0.0058*
p-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change from 1 Hour (Post– IP Consumption)	−2.16 (1.30)	−5.00, 0.00	−2.34 (1.38)	−5.00, 2.00	−2.29 (1.35)	−5.00, 1.00	−1.47 (1.14)	−3.00, 1.00	
Percent change from 1 Hour (Post– IP Consumption)	−34.76 (19.13)	−71.43, 0.00	−36.29 (22.39)	−71.43, 50.00	−35.77 (20.40)	−71.43, 25.00	−23.85 (17.83)	−50.00, 16.67	
3 Hour (Post– IP Consumption)	4.06 (1.13)	1.00, 6.00	4.00 (1.46)	1.00, 6.00	3.32 (1.30)	1.00, 5.00	4.50 (0.98)	3.00, 6.00	0.0030
p-value [c]	<0.0001*		<0.0001*		<0.0001*		<0.0001*		
Change from 3 Hour (Post– IP Consumption)	−1.97 (1.33)	−5.00, 1.00	−2.13 (1.90)	−6.00, 1.00	−2.81 (1.60)	−6.00, 0.00	−1.50 (1.16)	−4.00, 0.00	
Percent change from 3 Hour (Post– IP Consumption)	−31.80 (21.52)	−83.33, 20.00	−32.49 (27.85)	−85.71, 20.00	−44.52 (23.49)	−85.71, 0.00	−24.24 (18.30)	−57.14, 0.00	
5 Hour (Post– IP Consumption)	5.47 (0.84)	4.00, 7.00	5.56 (1.22)	3.00, 7.00	5.13 (1.06)	3.00, 7.00	6.06 (0.76)	5.00, 7.00	0.0032
p-value [c]	0.0059*		0.0593		0.0003*		0.7375		
Change from 5 Hour (Post– IP Consumption)	−0.56 (1.08)	−3.00, 1.00	−0.56 (1.63)	−4.00, 2.00	−1.00 (1.34)	−4.00, 1.00	0.06 (1.05)	−2.00, 2.00	
Percent change from 5 Hour (Post– IP Consumption)	−8.36 (17.82)	−42.86, 20.00	−7.06 (25.42)	−57.14, 40.00	−14.83 (20.87)	−57.14, 25.00	2.19 (17.69)	−28.57, 40.00	

Notes: [a] p-value was calculated using ANOVA Type III (A) for intervention effect. [c] p-value was calculated using paired *t*-test (t) for within-group change. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

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Table 10 Total Score- Samn-Perelli Fatigue Scale – (Sub-Acute Stage - p-value comparisons)

Timepoint	p-value (*A. galanga* Extract vs Placebo) [b]	p-value (*A. galanga* Extract + Caffeine vs Placebo) [b]	p-value (Caffeine vs Placebo) [b]
VISIT 6 – Re-Randomization – Day 20 (20 ± 1)			
0 Hour (Pre – IP Consumption)	0.9973	0.8527	0.8613
VISIT 7 – End of Study - Day 48 +2			
1 Hour (Post– IP Consumption)	0.0331*	0.0232*	0.0107*
Change from 1 Hour (Post– IP Consumption)	0.0282$*	0.0334$*	0.0151*$
Percent change from 1 Hour (Post– IP Consumption)	0.0434$*	0.0848$	0.0554$
3 Hour (Post– IP Consumption)	0.4890	0.0013*	0.3693
Change from 3 Hour (Post– IP Consumption)	0.4950$	0.0019$*	0.4626$
Percent change from 3 Hour (Post– IP Consumption)	0.4835$	0.0024$*	0.6353$
5 Hour (Post– IP Consumption)	0.0800	0.0015*	0.1821
Change from 5 Hour (Post– IP Consumption)	0.0778$	0.0021$*	0.2388$
Percent change from 5 Hour (Post– IP Consumption)	0.0517$	0.0019$*	0.3277$

Notes: [b] p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. $Adjusted p-values were derived from an ANCOVA model with intervention as factor and baseline as a covariate, using Tukey's adjustment for multiple comparisons. *Statistical significance.
Abbreviations: SD, Standard deviation; n, Number of participants; IP, Investigational Product.

investigation was designed to evaluate whether *Alpinia galanga* extract, alone or in combination with caffeine, could enhance alertness, reduce fatigue, and improve cognitive performance, assessing both immediate (acute) and sustained (sub-acute) effects on cognitive parameters in healthy sleep-restricted adults.

In both stages, the combination group consistently demonstrated the most robust improvement in alertness at 1-hour post-dose, significantly outperforming placebo in both the acute (eg, Jin Fan Alertness Score: at 1 hour, +32.37 ± 23.43

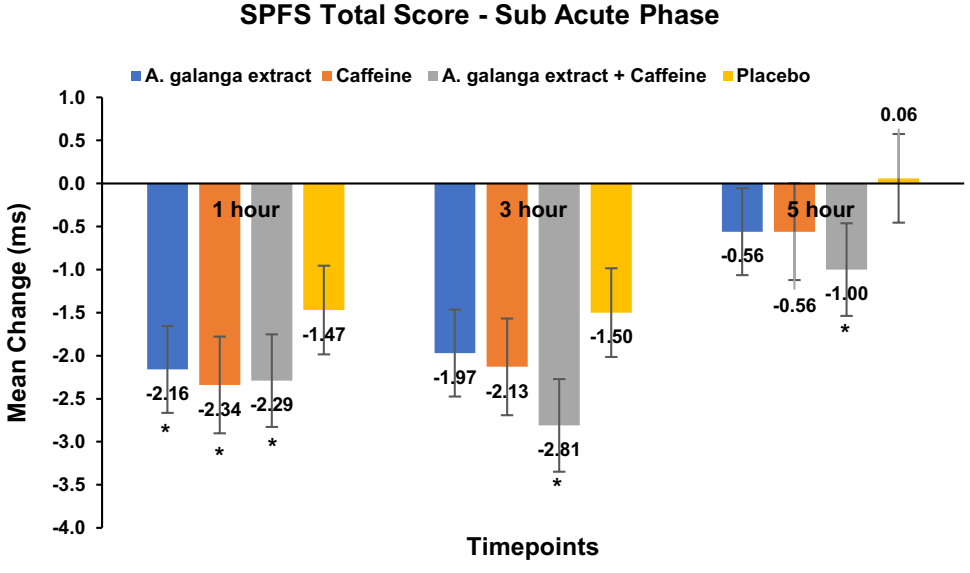

Figure 5 Mean change in Samn-Perelli Fatigue Score - Sub-acute Stage p-value was calculated using Tukey's HSD test (T) for pairwise comparisons. *p<0.05 significance over placebo.
Abbreviation: ms, milliseconds.

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ms versus placebo +22.13 ± 21.25 ms; p = 0.0031) and sub-acute stages (eg, Day 48 at 1h, +44.41 ± 36.48 ms versus placebo +10.72 ± 20.03 ms; p < 0.0001), while at 3 and 5 hours in sub-acute stages (p = 0.0142 and p = 0.0025, respectively) showed significant outperformance. The combination group performed significantly better than caffeine at 5 hours alone. Change at 5 hours for Caffeine was at (−4.51 ± 18.01 ms), showing a typical caffeine crash whereas the combination group was at (9.40 ± 23.21 ms), suggesting a more sustained alertness response compared with caffeine alone at later timepoints. (p = 0.0103). In the acute stage, the combination group also provided sustained improvements, especially at 3 and 5 hours, suggesting a potentially longer duration of alertness effects relative to caffeine alone. *Alpinia galanga* alone also demonstrated better results over placebo [(acute stage: p=0.0129 at 1 hour; p=0.0166 at 3 hour); (sub-acute stage: p =0.0263 at 1 hour; p=0.0341 at 5 hour)] and caffeine across timepoints and avoided the caffeine crash. These findings aligned with previous literature: caffeine is well-established for enhancing short-term alertness,[7,19] while *A. galanga* has shown efficacy in improving attention and alertness with a more stable profile.[12,20,21]

In terms of attentional subdomains, the orienting effect at 3 hours and the conflict effect (executive control) at 1 hour during the acute stage did not show statistically significant differences between the intervention groups.In terms of attentional subdomains, active interventions non-significantly improved the orienting effect at 3 hours and reduced the conflict effect (executive control) at 1 hour during the acute stage. No statistically significant differences were observed between groups for orienting and conflict effects during the acute stage. Therefore, improvements in these specific attentional domains cannot be conclusively inferred from the present data. In the sub-acute stage, attentional network scores (JF-ANT) remained stable across 28 days, indicating no cognitive decline or tolerance development, a concern often associated with chronic caffeine use.[14] These results reinforced the neurocognitive stability and sustained ability of the extract's effects.

Fatigue reduction, assessed via the SPS, was greatest for the combination group during the acute stage (−2.20 ± 1.32) vs placebo at 1h; p = 0.0367), and these effects persisted through the sub-acute stage (p = 0.0334 at 1 hour). Notably, the combination group maintained alertness at 5 hours in both the acute (change +2.10 ± 20.36 ms) and sub-acute stages (change +9.40 ± 23.21 ms), suggesting a moderating role when combined with caffeine. This is consistent with existing evidence that caffeine's anti-fatigue effects are short-lived and may be followed by rebound fatigue.[14,16,17]

In terms of psychomotor function, the discrepancy may be attributed to high inter-individual variability and possible development of tolerance. Still, prior reports suggest caffeine can enhance fine motor skills acutely,[7,12] while the extract alone may require longer exposure or alternate measures to capture motor benefits.

Sustained attention, evaluated using the CPT and ANT, showed non-significant yet positive trends across both stages, especially in the *A. galanga extract* group. Notably, attentional network stability was preserved over 28 days, implying no habituation or performance decline, a key advantage over caffeine alone.

No serious adverse events were observed throughout the study, suggesting a favorable safety profile within the study duration of the extract alone, consistent with existing safety data on *A. galanga* and caffeine.

Some limitations should be acknowledged: subjective bias in fatigue assessments, the timing of sleep deprivation induction (which may have diluted cognitive impairment), and relatively short observation period in the acute stage. Additionally, the lack of long-term data limits conclusions about chronic efficacy and safety. The dip in alertness and fatigue scores observed across all groups at the 5-hour timepoint may be explained by the fact that this assessment coincided with lunchtime (dosing occurred around 7:30–8:00 a.m). Finally, diet variability could not be completely ruled out during the sub-acute phase, as participants continued this phase from their homes. Certain assessments, such as the NHPT and CPT, did not show statistically significant differences between groups, which could be attributed to the stringent inclusion and exclusion criteria applied in the trial.

Taken together, findings from both the acute and sub-acute stages supported the cognitive-enhancing properties of the intervention, both alone and when combined with caffeine. While the combination provided rapid and potent cognitive boosts, *A. galanga* extract alone offered sustained alertness and anti-fatigue benefits without the crash typically associated with caffeine. Taken together, the findings suggest that *A. galanga* extract, alone or in combination with caffeine, may have potential to support alertness and reduce subjective fatigue under sleep-restricted conditions. However, given the exploratory nature of some outcomes and the limited clinical evidence currently available for this

botanical extract, further well-powered and independently conducted studies are needed to confirm these effects and to better characterize their underlying mechanisms.

Conclusion

In this randomized, double-blind, placebo-controlled study, *A. galanga* extract demonstrated improvements in certain measures of alertness and subjective fatigue compared with placebo in sleep-restricted adults. When combined with caffeine, the extract was associated with improvements in early alertness responses and appeared to maintain performance at later time points compared with caffeine alone.

Although these findings suggest potential cognitive benefits, the results should be interpreted cautiously due to the study's sample size, short intervention duration, and exploratory analyses across multiple endpoints. Additional large-scale studies incorporating mechanistic assessments and longer follow-up periods are warranted to confirm these observations and better define the role of *A. galanga* extract in cognitive performance support.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

Abhijeet Ashok Morde is affiliated with OmniActive Health Technologies. The authors declare no other conflicts of interest in this work.

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