Caffeine and Enhancement of Cognitive Performance

General Information:

- **Active component[s]:** Caffeine, 1,3,7-trimethylxanthine.
- **Source material:** Isolate, synthetic.
- **Dosage route:** Oral.
- **Directions of use:** Insufficient evidence available.
- **Duration of use:** For occasional use only.
- **Target Population:** Adults.
- **Risk Information:**
  - **Consult a health care practitioner** prior to use if you have high blood pressure, glaucoma, and/or detrusor instability [overactive bladder syndrome], are consuming doses >300 mg per day, consuming lithium, and if you are of childbearing age, pregnant or breastfeeding (NHPD, 2008).
  - Consumption with natural health products [e.g. bitter orange extract, synephrine, octopamine, ephedra], or other drugs [e.g. ephedrine] which increase blood pressure is not recommended (NHPD, 2008).
  - Consumption with other caffeine-containing products [e.g. medications, coffee, tea, colas, cocoa, guarana, and mate] is not recommended (NHPD, 2008).
  - This product is not intended as a substitute for sleep aid (NHPD, 2008).
  - **Avoid if you have a known allergy** to caffeine as hypersensitivity/allergy is known to occur; in which case, discontinue use (NHPD, 2008).
  - T**he following have been reported with caffeine** intake at doses > 600 mg per day: anxiety, tachycardia [rapid heart rate], palpitations, insomnia, restlessness, nervousness, tremor and headache (NHPD, 2008).

Human Health Indications:

Recommended Use or Purpose	Dosage Range
General	100-200 mg, every 3-4 hours, as needed, without exceeding 1 000mg every 24 hours
Helps (temporarily) to promote alertness and wakefulness, and to enhance cognitive performance (Health Canada, 2010)	

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CAFFEINE AND ENHANCEMENT OF COGNITIVE PERFORMANCE

Caffeine is among the most popular behaviourally active substance consumed worldwide; ingested in the diet in the form of coffee or tea (Fredholm et al., 1999). Caffeine has been described as a central nervous system [CNS] stimulates reported to improve 'alertness', sustained attention and reaction time when taken within effective doses (Haskell et al., 2008; Holmgren et al., 2004). However, when taken outside of recommended dosages caffeine consumption can result in serious adverse CNS and cardiac events (Holmgren et al., 2004).

The Natural Health Product Directorate [NHPD] of Health Canada formally recognizes the efficacy of caffeine consumption to temporarily promote alertness and wakefulness, and to enhance cognitive performance. The NHPD-issued monograph for caffeine specifies an efficacious daily dose of 100-200 mg, every 3-4 hours, as needed, without exceeding 1 000 mg every 24 hours (NHPD, 2007).

In addition, a number of recent clinical studies [2008 and more recent] demonstrate variable findings with respect to dose and efficacy of caffeine for improving cognitive performance during various experimental circumstances.

A single-blind, 2 by 2, randomized, placebo-controlled trial was conducted to examine the effect of pre-existent expectancy on the relationship between caffeine, cognitive performance and mood. To test this relationship, 25 caffeine-deprived undergraduate students were divided into four treatment arms; two of which received a caffeinated beverage containing 200 mg caffeine while the remaining two received a decaffeinated beverage [placebo]. Each test beverage was comprised of 170 ml water and 30 ml milk without sugar or artificial sweeteners. Of the two caffeinated treatment arms, one was accurately informed of the caffeine content in the test beverage, while the other was falsely informed that the beverage was decaffeinated. The same procedure applied to the two decaffeinated treatment arms, where one was accurately informed and the other was not. Each subject consumed the test beverage the day after a caffeine "fast" in which subjects abstained from consuming caffeinated coffee after 10p.m. the night before testing. On the day of testing, subjects consumed the test beverage and rested for 20 minutes before performing a 30-item Profile of Mood States [POMS] form and a Bakan vigilance task to access mood and cognitive performance, respectively. The Bakan vigilance task required subjects to identify a series of odd or even numerical patterns presented on a visual display monitor as soon as a pattern was recognized. Performance was assessed by the number of correct repossesses over the course of the task. Subjects in the caffeinated group whom were accurately informed of the caffeine content scored significantly higher than any of the respective groups [$p < 0.001$]. Moreover, the information given to subjects [whether truthful or false] had a significant effect on performance whereby subjects who were informed accurately performed significantly better than those who were falsely informed. Adverse events were not addressed in this study. Overall, the caffeinated beverage significantly improved performance compared to the decaffeinated beverage (Elliman et al., 2010).

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In contrast to the aforementioned results, 200 mg of caffeine did not elicit a significant efficacious response with respect to cognitive performance in a recent double-blind, placebo-controlled, with-in subjects trial. The study was conducted to examine the effect of 100 mg caffeine; 200 mg caffeine, 440-calorie macronutrient breakfast; or placebo on cognitive performance and mood perception on energy and fatigue in of 18 male subjects. The experimental protocol involved the administration of the Bakan vigilance test to measure changes in cognition, POMS forms to measure changes in mood intensity, a Visual Analogue Scale [VAS] to assess the effects of treatment on mental energy and mental fatigue, and State-Trait Energy and Fatigue Scales [STEF] to assess the intensity of mental energy and fatigue. Each subject was oriented with testing procedures prior to treatment and preformed four active trails within this experiment [one of each treatment arm], with seventy-five percent [75%] of subjects completing each trial on non-consecutive days. All subjects fasted for 8-hours the night prior to testing, and answered baseline mood questionnaires as well as preformed the Bakan cognitive test before treatment administration of caffeine [100mg or 200 mg in capsule form], breakfast or placebo. After a 20 minute resting period, subjects repeated the mood and cognitive performance tests 4 consecutive times until the end of testing at 135 minutes in duration. After subjects completed all 4 treatment arms, results showed that only 100 mg caffeine significantly improved POMS and VANS scores; however, other treatments did not significantly improve mood. Moreover, 100 mg of caffeine *tended* to reduce omission errors, false alarms and reaction times; however these results were not statistically significant. In line with these findings, consumption of 200 mg of caffeine also *tended* to decrease omission errors and reaction times while breakfast *tended* to reduce false alarms and reaction times; however, results did not reach statistical significance. Adverse events were not addressed in this study. Overall, caffeine at 100 mg and 200 mg and 440-calorie breakfast tended to improve cognition [i.e. reduced omission errors, false alarms and reaction times] while 100 mg caffeine significantly improved mood [perception of energy]. Therefore, these results provide further insight into the efficacious dosage range of 100–200 mg recommended on the NHPD caffeine monograph [2007] (Maridakis et al., 2009).

In comparison to doses mentioned above [100 mg and 200 mg], a randomized, double-blind, placebo-controlled, crossover trial was conducted to determine the effect of *150 mg* caffeine on cognition through the administration of four different treatment arms: 150 mg caffeine; 250 mg L-theanine; a combination of 150 mg caffeine and 250 mg L-theanine; or placebo in 250 ml of decaffeinated Ice Tea. Twenty-four [24] undergraduate subjects were randomized to receive one of each treatment arm and performance was measured at baseline, 30 and 90 minutes after consumption. Tests were performed on five separate occasions with a washout period of 7 days in duration. The first day familiarized subjects with testing procedures while the remaining four occasions contributed as active study periods. A battery of CDR [computerized cognitive tests] – consisting of 6 subtests - as well as sentence verification and serial seven subtractions tasks were used to assess changes in cognition, while Bond-Lader and Caffeine Research VAS were performed to assess changes in mood. The CDR test examined simple reaction time; digit vigilance

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reaction time; rapid visual information processing [RVIP]; spatial memory accuracy; numeric working memory reaction time and delayed work recognition time. Results showed that when comparing both caffeine bearing beverages to placebo, only the caffeine plus L-theanine drink reached significance [$p<0.05$] for simple reaction time and numeric working memory reaction time. In contrast, the caffeine beverage alone produced significantly faster reaction times in the digit vigilance reaction time test when both caffeine groups were compared to placebo [$p<0.05$]. Interestingly, both caffeine bearing beverages had a significant effect on rapid visual information processing. However, due to significant baseline differences, no treatment had a significant effect on special memory accuracy. Only a main effect of caffeine was noted in the delayed word recognition reaction time test with a trend toward significance in the caffeine plus L-theanine group. Further analysis within these results also showed a positive caffeine x L-theanine interaction [$p<0.05$]. With respect to the other two cognitive tests [sentence verification and serial seven subtractions tasks], caffeine plus L-theanine significantly improved sentence verification, while L-theanine alone improved serial seven subtractions [$p<0.05$]. Caffeine plus L-theanine significantly increased 'alert' ratings in the Bond-Lader 'alert' VAS test, and reduced 'tired' [$p<0.005$], 'headache' [$p<0.05$] and 'mental fatigue' [$p<0.05$] ratings in the Caffeine Research VAS test. Caffeine alone also significantly reduced 'mental fatigue' ratings in the Caffeine Research VAS test; however, L-theanine increased 'headache' ratings [$p<0.05$]. Overall, caffeine alone improved 2 of the 6 parameters of the CDR test [digit vigilance reaction time, and RVIP accuracy] and reduced 'mental fatigue' while the combination of caffeine plus L-theanine significantly improved 3 of the 6 measures of the CDR test [simple reaction time, RVIP accuracy, numeric working memory] with a trend toward improving delayed word recognition reaction time. Caffeine plus L-theanine also significantly improved accuracy of sentence verification and 'alert', 'tired', 'headache', and 'mental fatigue' ratings. Lastly, L-theanine significantly impaired serial seven subtractions and also increased 'headache' ratings. No adverse events were reported. Although 150 mg caffeine effectively improved cognition and mood, the combination of caffeine plus L-theanine demonstrated a greater improvement of cognition and mood (Haskell et al., 2008).

A similar study to the one mentioned previously examined the effects of 35 mg caffeine; 35 mg caffeine with 100 mg L-theanine in a beverage containing 15 mg caffeine and placebo on cognitive performance. Twenty-seven subjects were randomized to one of each treatment arm with a washout period of 7 days before crossing over to a new treatment. Similar testing procedures as seen in the Haskell et al., [2008] experiment were employed in this study. Word recognition test, RVIP, Critical flicker fusion [CFF] test [a test used to distinguish light flicker from fusion] and an Attention switching task were used to assess changes in cognition. The Bond–Lader mood questionnaire was also used to measure changes in mood. Performance was evaluated at baseline, 60 minutes and 90 minutes after each treatment. Results showed that all treatments improved word recognition time at 60 and 90 minutes but only the caffeine and L-theanine combination group noted significant improvements in the number of correctly identified words. No significant effects of treatment on cognition were noted in the RVIP test. Similarly, no treatment effects were noted in CFF testing despite a significant decrease in arousal reported across all treatment groups 60 and 90 minutes into testing. Moreover, no treatment effects were reported in the

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attention switching task; however, upon further analysis, a significant treatment by time interaction was noted for the number of correct responses when comparing the caffeine and caffeine with L-theanine group. Researchers reported a significant increase in correct responses in the caffeine with L-theanine group 60 minutes post-consumption compared to caffeine group, and 90 minutes in the caffeine group compared to the combination group. A decrease in calmness was noted between 60 and 90 minutes, however this was common among all treatments. Lastly, caffeine significantly improved 'alertness' at 60 minutes while the combination of caffeine with L-theanine merely tended to improve subjective measures of 'alertness'. Overall, caffeine improved attention-switching and 'alertness' at 90 minutes while caffeine with L-theanine improved word recognition time at 60 and 90 minutes and attention-switching at 60 minutes. Therefore, based on results of this study, caffeine at 50 mg can significantly improve cognition 90 minutes post-consumption (Haskell et al., 2008; Owen et al., 2008).

A randomized, double-blind, placebo-controlled trial was conducted to examine the effects of caffeine, L-theanine, caffeine plus L-theanine and placebo on cognitive function in 48 healthy adults. Test beverages were comprised of 250 mg caffeine; 200 mg L-theanine; a combination of 250 mg caffeine plus 200 mg L-theanine; or placebo, in a 200 ml decaffeinated tea beverage. Both the State-Trait Anxiety Inventory [STAI] and the Depression, Anxiety and Stress Scales [DASS] were used to measure state and trait anxiety, and 'trait' depression, anxiety and stress, respectively. A Mood, Alertness and Physical Symptoms [MAPS] questionnaire was also used to subjectively measure 'headache', 'heart pounding', 'jittery/shaky', 'light-headed/feeling faint/dizzy', 'hands trembling', 'scared', and 'feeling hot' ratings. Changes resulting from treatment in blood pressure [systolic and diastolic] and heart rate were also recorded. Finally, a visual probe task was employed to measure attention and reaction time to visual stimuli. Results showed that caffeine consumption significantly increased 'jitteriness' and 'alertness' with a trend toward increasing 'heart pounding' [$p=0.064$] as well as significantly increased systolic and diastolic blood pressure, greater than the respective treatment arms [$p<0.05$]. Caffeine alone also tended to increase reaction time in the visual probe test by ~ 7 ms, although this affect did not achieve statistical significance. Only L-theanine significantly reduced reaction time in the visual probe test and 'antagonized' caffeine's effects on systolic and diastolic blood pressure when taken concurrently with caffeine. L-theanine did not significantly increase blood pressure. Overall, 250 mg caffeine proved to be ineffective for the improvement of reaction times during visual probe testing. However, caffeine improved subjective measures of 'alertness' further supporting the use or purpose of caffeine reported in the NHPD monograph [2007]. Adverse events were not reported in this study (Rogers et al., 2008).

Finally, a double-blind randomized placebo-controlled trial was carried out to determine the effect of caffeine, glucose, caffeine plus glucose and placebo on cognitive performance. Seventy-two [72] healthy males and females were randomized to receive; 75 mg caffeine; 75 g glucose; a combination of 75 mg caffeine plus 75 g glucose; or placebo, in 150 ml water. A battery of tests were administered to evaluate treatment effects on attention, learning, memory and mood. Tests included the following: Rey Auditory Verbal Learning Memory Test [RAVLT] to assess verbal memory; Purdue-Pegboard [Pegboard] to assess

fine motor skills, dexterity and manipulation speed; Benton Judgement of Line Orientation Test [Benton] to assess visuo-spatial function; Digit Span of WAIS [WAIS] to assess general attention and verbal working memory; Wisconsin Card Sorting Test [WCST] to assess cognitive processing speed, concept formation, and cognitive flexibility; California Computerized Assessment Package [Cal-CAP] to assess sustained attention, reaction time and visual scanning speed; and 8 unipolar VAS tests to measure subjective effects of treatment on mood. Cognitive performance testing was measured at 30 minutes post-treatment consumption and subjective testing [VAS] at 30 and 60 minutes after consumption. Statistical analysis of the RAVLT test results showed that that the mean number of words remembered was significantly greater in the caffeine plus glucose group compared to caffeine, glucose or placebo. A post *hoc* analysis revealed that the *total* number of words remembered and memory consolidation in this group [caffeine plus glucose] superseded that of the placebo and glucose groups. Analysis of Pegboard testing showed significant differences between groups, where further analysis revealed that subjects who consumed glucose significantly outperformed those consuming caffeine and placebo. Statistical evaluation of the Benton performance testing showed a shorter execution time in the caffeine plus glucose [$p=0.017$] and glucose [$p=0.009$] treatment groups compared to the caffeine group alone. None of the 4 test beverages had a significant effect on working memory, or showed improvements in prefrontal cognitive functions as measured by WAIS and WCST**,** respectively. In contrast, initial Cal-CAP results showed a main effect of beverage on simple reaction time, mean response time. Further statistical analysis revealed that the placebo group performed poorest in comparison to respective test beverage groups [$0.006>p<0.044$]. When analysing the results of the subtests within the Cal-CAP procedure, no significant effect of any beverage on choice reaction time or sequential reaction time was noted in the two tasks performed. In contrast to these findings, a post-hoc analysis revealed discrepancies in execution times between groups. With respect to sequential task 1 within the Cal-CAP test procedure, placebo treatment had a greater mean reaction time than glucose [$p=0.042$] or caffeine plus glucose [$p=0.028$], whereas caffeine plus glucose significantly outperformed placebo in sequential task 2 [$p=0.016$]. Lastly, analysis of mood using VAS showed an increase in subjective activation from baseline to finish; however, no significant differences in mood were noted between beverage groups. Overall, this study demonstrates that 75 mg of encapsulated caffeine in isolation had a significant effect on simple reaction time [Cal-CAP] compared to placebo in low-to-moderate caffeine consumers; however, caffeine plus glucose showed improvements in learning [RAVLT], verbal memory [RAVLT] and simple and sequential reaction time [Cal-CAP], whereas glucose improved manual dexterity [Pegboard] as well as simple reaction time [Cal-CAP] compared to placebo. Interesting to note, is the caffeine dosage administered by Adan et al., [2010] falls short [by 25 mg] of the efficacious dosage range [100 mg -200 mg] recommended by the NHPD [2007]; yet, this study highlights the significant effect of 75 mg caffeine on simple reaction time. Moreover, a potential synergistic effect of caffeine and glucose was noted by the authors as this combination treatment was shown to vastly improve cognition in comparison to placebo. Adverse events were not reported in this study (Adan et al., 2010).

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In conclusion, the majority of the results collected from the aforementioned studies support the efficacy of caffeine for improving cognitive performance. Interestingly, recent literature highlights the efficacy of caffeine outside the NHPD-monograph dosage range of 100 mg/day to 200 mg/day (NHPD, 2008). For example, caffeine administered at 50 mg in beverage form showed significant improvements in attention switching at 90 minutes post consumption in comparison to the caffeine and L-theanine group, and 'alertness' at 60 minutes compared to placebo (Owen et al., 2008). Adan et al., [2010] noted improvements in simple reaction time compared to placebo, upon consumption of 75 mg caffeine (Adan et al., 2010]. Both studies administered dosages below the NHPD recommended range [50 mg and 75 mg, respectively] yet still elicited significant results with respect to cognition and 'alertness' (Adan et al., 2010; Owen et al., 2008]. Rogers et al., [2008] also noted a significant effect on 'alertness' in subjects consuming caffeine above the NHPD-recommended range [250 mg caffeine]; however, researches also reported increased 'jitteriness' which could be interpreted as a mild side effect not formally addressed by authors (Adan et al., 2010). With respect to the remaining 3 studies, only 1 [Maridakis et al., (2009)] failed to report significant effects of caffeine on cognition within the NHPD-recommended dose of 100 mg to 200 mg; however, 100mg did improve mood (Elliman et al., 2010; Haskell et al., 2008; and Maridakis et al., 2009). Moreover, caffeine may have synergistic effects on cognition when combined with glucose or L-theanine as outcomes on performance were greater in combination than with caffeine alone. However, further dose-ranging studies are required in order to test for the degree of synergistic relationships. In all, caffeine improves cognition without causing serious adverse events.

SAFETY AND TOXICITY:

A range of adverse events have been reported with caffeine intake in humans. Chronic intake of caffeine ingested at a mean dose of 410 mg/day can significantly increase systolic and diastolic blood pressure compared to coffee consumed at a mean intake of 725 mg/day (Noordzij et al., 2004). However, acute intake of caffeine has been shown to 'cause death by intoxication' in four case studies presented by Holmgren et al., [2004] (Holmgren et al., 2004). Within these case reports all subjects had blood caffeine levels between 150 µg/g and 200 µg/g (Holmgren et al., 2004). In three of the four reported case studies other drug substances were found in the blood; however, authors state that it was unlikely that any of these substances interacted with caffeine (Holmgren et al., 2004).

Substance abuse with caffeine as an ergogenic aid has also been noted in athletes. A 28 year old body builder looking to enhance performance reportedly consumed in excess of 3.5 grams in one day and 7.5 grams over the course of the previous three days. The patient's blood level of caffeine was 12.3 mg/L, slightly below the toxic level of caffeine [15 mg/L]. Symptoms of nausea, anxiety, dizziness, head ache, fast heart rate, palpitations, insomnia and aching in both thighs were reported. On the day of emergency admission, the patient was witnessed to have a grand mal seizure. Symptoms subsided after three days of caffeine abstinence and care (FitzSimmons et al., 1998). Moreover, a meta-anaylsis examining the effect of ephedra or ephedrine and caffeine on weight loss and athletic performance reported an

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association with increased risk of psychiatric, autonomic, or gastrointestinal symptoms, and heart palpitations upon concurrent intake (Shekelle et al., 2003).

General toxic effects of caffeine have been reported which induce vomiting, abdominal pain, effects on the central nervous system such as changes in conscious state, supraventricular, and ventricular tachyarrhythmias (Holmgren et al., 2004).

Prospective cohort studies have shown associations between caffeine intake and other adverse events as well. One study examining the association between maternal caffeine consumption during pregnancy and the risk of miscarriage noted an increased risk of miscarriage for women consuming more than 200 mg caffeine per day (Weng et al., 2008). Another prospective cohort study on postmenopausal women reported a 35% increased risk of wrist fracture in women consuming more than 500 mg/day (Hansen et al., 2000). Although, these two prospective studies do not prove causation they provide insight into potential safety risks associated with caffeine.

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Cautions, Warnings, Contraindications and Interactions

Consult a health care practitioner prior to use if you have a pre-existing medical condition, are taking prescription medications, or are pregnant or breastfeeding.

For additional information from the clinical literature regarding interactions, please refer to the following tables:

Drug	Interaction with Caffeine
Alcohol	Consumption of caffeine with alcohol has been reported in a double-blind, placebo-controlled study to negatively influence cognitive performance (Curry et al., 2009).
Clozapine	An open label, randomized, crossover study noted an increase in oral clearance of clozapine during concurrent intake with caffeine compared to clozapine alone (Hagg et al., 2000).
Diazepam	Four placebo-controlled, double-blind trials with parallel treatment groups noted an improvement in diapepam-induced cognitive decline upon consumption of caffeine (Mattila and Nuotto, 1983).
Disulfiram	Consumption of disulfiram concurrently with caffeine has been reported to inhibit caffeine elimination (Beach et al., 1986).
Ephedrine	A synergistic relationship has been reported between ephedrine and caffeine on thermogensis in humans (Astrup et al., 1991).
Ibuprofen	A randomized, double-blind, parallel, multicenter, single-dose, placebo- and active-controlled study reported that subjects diagnosed with tension-type headaches taking Ibuprofen in conjunction with caffeine noted significantly greater analgesic activity than those administered ibuprofen alone, caffeine alone, or placebo (Diamond et al., 2000).
Lorazepam	Caffeine citrate significantly reduced lorazepam-induced decrements in learning and performance (File et al., 1982).
Mexiletine	It has been reported that mexiletine inhibits caffeine elimination (Joeres et al., 1987).
Midazolam	The effects of midazolam have been reported to be moderately counteracted by caffeine (Mattila et al., 2000).
Oral Contraceptives	Oral contraceptives taken concurrently with caffeine has been reported to extend half-life of caffeine clearance (Abentethy and Tod, 1985).
Phenytoin	Phenytoin taken concurrently with caffeine has been reported to increase caffeine clearence (Wietholtz et al., 1989).
Pipemidic acid	Pipemidic acid taken concurrently with caffeine has been reported to increase elimination half-life of caffeine (Carbó et al., 1989).
Triazolam	It has been reported that caffeine and trizolam are antagonists (Mattila et al., 1992).
Zopiclone	It has been reported that caffeine and zipicole are antagonists (Mattila et al., 1992).

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Natural Health Products [NHP] Substances	Interaction with Caffeine
L-thenaine	L-theanine may antagonize caffeine's effects on systolic and diastolic blood pressure (Rogers, 2008). Caffeine in combination with L-theanine has been reported to synergistically improve cognitive function (Haskell et al., 2008; Owen et al., 2008).

Nutrient	Interaction with Caffeine
β-glucan	A clinical literature search did not yield results with respect to interactions between other nutrients and β-glucan.

Foods	Interaction with Caffeine
	A clinical literature search did not yield any results with regards to caffeine and interactions with food ingredients.

You might also be interested in our reports on:

- ✓ Alpha-lactalbumin and Improved Cognitive Performance
- ✓ Fish Oil and Cognitive Function
- ✓ L-Theanine and Attention and Cognitive Performance
- ✓ L-Tyrosine and Cognitive Performance
- ✓ Panax Ginseng and Cognitive Function and Mental Fatigue

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