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Nootropics for Cognitive Enhancement in Healthy Adults: What Does the Clinical Evidence Actually Show? A Narrative Review

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Abstract

Background: Nootropics are increasingly promoted to improve memory, attention, concentration, and intellectual performance in healthy individuals. However, their clinical evidence varies substantially, and statistically significant changes in cognitive tests do not necessarily indicate meaningful improvements in everyday functioning.

Objective: To provide clinicians with a practical and balanced overview of the efficacy, limitations, and safety of pharmacological, nutritional, and botanical interventions investigated for cognitive enhancement in healthy adults.

Methods: This narrative review examines selected randomized controlled trials, systematic reviews, and meta-analyses reporting objective cognitive outcomes in healthy adults. Evidence was interpreted according to the consistency of positive findings, cognitive domains affected, clinical applicability, and safety. Interventions were classified into three groups: more reproducible positive findings, preliminary or conflicting positive findings, and absence of demonstrated overall benefit or insufficient evidence.

Results: Caffeine produces reproducible but modest acute improvements in attention and reaction time. L-theanine, particularly combined with caffeine, may improve selected attentional outcomes. Methylphenidate and modafinil demonstrate small domain-specific effects under experimental conditions, without established benefits in everyday functioning. Creatine and *Bacopa monnieri* have shown favorable findings in memory and reasoning, although results remain heterogeneous. Positive findings have also been reported for Panax ginseng, *Salvia*, guarana, *Rhodiola rosea*, tyrosine, curcumin, and selected polyphenol-rich preparations, but the evidence is generally limited or population-dependent. Omega-3 supplementation has produced conflicting results, with several larger studies showing no overall benefit. Evidence does not support generalized cognitive enhancement from D-amphetamine or psychedelic microdosing.

Conclusions: Certain nootropics can improve performance in specific cognitive domains, but benefits are usually modest, context-dependent, and insufficiently validated in real-world settings. Clinicians should distinguish acute attention enhancement from sustained improvements in memory or executive function and consider reproducibility, safety, and functional relevance before interpreting claims of efficacy.

Keywords: Nootropics, Cognitive Enhancement, Healthy Adults, Attention, Memory, Executive Function, Caffeine, Creatine, Botanical Extracts, Narrative Review

1. Introduction

The growing interest in improving cognitive performance has encouraged the widespread use of substances collectively described as nootropics, including prescription medications, caffeine, amino acids, nutritional supplements, and botanical extracts. These products are frequently promoted as improving concentration, memory, learning, and productivity, although their supporting evidence varies considerably. Meta-analyses of pharmaceutical cognitive enhancers and caffeine demonstrate that some interventions can improve selected neuropsychological outcomes, but the magnitude of these effects is generally modest and their relevance to everyday intellectual performance remains uncertain [1, 2].

An important clinical distinction must be made between treating cognitive impairment and enhancing normal cognition. Findings obtained in patients with neurological or psychiatric disorders cannot automatically be extrapolated to healthy individuals. Moreover, cognition encompasses partially independent domains, including sustained attention, working memory, episodic memory, processing speed, and executive function. Improvement in a single cognitive test should therefore not be interpreted as generalized cognitive enhancement. This distinction is illustrated by recent evidence on tea-derived compounds, in which favorable effects were concentrated in specific attention-related tasks rather than uniformly distributed across cognitive domains [3]. Nutritional and botanical interventions introduce additional challenges because outcomes may depend on baseline characteristics, dietary patterns, extract standardization, treatment duration, and the cognitive instruments used. Creatine and *Bacopa monnieri*, for example, have demonstrated encouraging findings in selected trials, but subsequent studies have not consistently reproduced these benefits [4–8]. This narrative review provides a clinically oriented synthesis of representative evidence for nootropics in healthy adults, emphasizing which interventions have more reproducible positive findings, which remain promising but uncertain, and which lack convincing evidence of benefit.

2. Clinical Interpretation of Cognitive Enhancement

This article is a narrative review based on selected randomized controlled trials, systematic reviews, and meta-analyses. The principal outcomes considered were objectively measured attention, working memory, verbal learning, delayed recall, processing speed, reasoning, and executive function. Studies involving clinical populations were discussed only when necessary to explain limitations in generalizability, and their results were not assumed to establish efficacy in healthy individuals.

The distinction between statistical significance and clinical relevance is particularly important. Small improvements in reaction time or accuracy may be reproducible under controlled laboratory conditions without translating into better academic achievement, occupational productivity, or everyday functioning. Acute changes in vigilance should also be distinguished from sustained improvements in learning or memory. Accordingly, the evidence was organized into three practical categories: interventions with more reproducible positive findings (Table 1), interventions with preliminary or conflicting positive findings (Table 2), and interventions without demonstrated overall benefit or with insufficient directly applicable evidence (Table 3). These categories are descriptive rather than formal evidence-certainty ratings.

Table 1: Nootropics with positive findings supported by meta-analyses

Author/year	Substance	Study design	Participants	Setting and duration	Main cognitive findings	Adverse events	Clinical interpretation
Roberts *et al*., 2020 [1]	Methylphenidate	Meta-analysis; 24 studies	Healthy, non-sleep-deprived adults; demographic characteristics varied across trials	Controlled experimental studies; acute administration	Overall cognition SMD 0.21; recall 0.43; sustained attention 0.42; inhibitory control 0.27	Adverse-event rates were not pooled; medication-related risks remain relevant	Small, domain-specific positive effects
Roberts *et al*., 2020 [1]	Modafinil	Meta-analysis; 14 studies	Healthy, non-sleep-deprived adults; demographic characteristics varied across trials	Controlled experimental studies; acute administration	Overall cognition SMD 0.12; memory updating 0.28	Adverse-event rates were not pooled; medication-related risks remain relevant	Small effects of uncertain functional significance
Kløve and Petersen, 2025 [2]	Caffeine	Meta-analysis; 31 RCTs	1,455 healthy, rested adults; age and sex varied across trials	Experimental attention assessments; acute exposure	Attention accuracy Hedges' g=0.27; reaction time g=0.28	Safety outcomes were not pooled; sleep disturbance and anxiety are recognized concerns	Reproducible, modest acute attentional benefit
Payne *et al*., 2025 [3]	L-theanine plus caffeine	Systematic review of 50 RCTs; 15 contributed to meta-analyses	Healthy participants; demographic characteristics varied across trials	Controlled experimental studies; assessments within two hours	Digit vigilance accuracy SMD 0.20 (95% CI 0.02–0.38); attention switching SMD 0.33 (0.13–0.54)	Adverse-event rates not established by the pooled cognitive analyses	Modest positive effects in selected attention tasks
Payne *et al*., 2025 [3]	L-theanine alone	Systematic review and meta-analysis	Healthy participants; demographic characteristics varied across trials	Controlled experimental studies; acute assessment	Choice reaction time SMD −0.35 (95% CI −0.61 to −0.10), indicating faster responses	Adverse-event rates not established by the pooled cognitive analyses	Possible acute benefit in reaction time

Note: Evidence of positive cognitive effects from higher-level syntheses. These effects are generally small and domain-specific. The participant characteristics and exposure protocols in meta-analyses vary across underlying studies; aggregated estimates should not be interpreted as individual-trial data. SMD, standardized mean difference; CI, confidence interval; RCT, randomized controlled trial.

3. Pharmaceutical Cognitive Enhancers

Methylphenidate and modafinil are among the most extensively investigated pharmaceutical cognitive enhancers. Roberts *et al*. conducted meta-analyses of these agents and D-amphetamine in healthy, non-sleep-deprived adults [1]. Methylphenidate demonstrated a small overall cognitive effect (standardized mean difference [SMD] 0.21), with larger effects in recall (SMD 0.43), sustained attention (SMD 0.42), and inhibitory control (SMD 0.27). Modafinil also demonstrated a small overall effect (SMD 0.12), including improvement in memory updating (SMD 0.28). In contrast, D-amphetamine did not demonstrate a significant overall cognitive benefit. These results illustrate that increased central nervous system stimulation does not necessarily translate into generalized cognitive enhancement.

Despite the positive findings for methylphenidate and modafinil, their clinical relevance remains uncertain. Improvements were generally small, varied across cognitive domains, and were obtained under experimental conditions that do not adequately reproduce the complexity of everyday intellectual activities. Moreover, potential cardiovascular, psychiatric, sleep-related, and other medication-associated

adverse effects must be considered when evaluating interventions intended for otherwise healthy individuals. Thus, evidence of measurable laboratory effects should not be interpreted as justification for routine pharmacological enhancement of normal cognition.

4. Caffeine and L-Theanine

Caffeine has one of the clearest bodies of evidence supporting acute improvement in attention. Kløve and Petersen conducted a meta-analysis of 31 randomized, double-blind, placebo-controlled trials involving 1,455 healthy, rested adults [2]. Significant improvements were observed in attention accuracy (Hedges' g=0.27) and reaction time (g=0.28). These results support a reproducible but modest attentional effect. Nevertheless, better performance in an experimental attention task does not establish improved intelligence, long-term learning, or generalized cognitive capacity. Furthermore, sleep disturbance, anxiety, and individual differences in sensitivity may influence the overall balance between benefit and harm.

L-theanine, an amino acid naturally present in tea, has been investigated independently and in combination with caffeine. Payne *et al*. reviewed 50 randomized controlled trials involving healthy participants, with 15 contributing to at least one meta-analysis [3]. The combination improved digit vigilance accuracy during the second hour of assessment (SMD 0.20; 95% confidence interval [CI] 0.02–0.38) and attention-switching accuracy (SMD 0.33; 95% CI 0.13–0.54). L-theanine alone was associated with faster choice reaction time during the first hour (SMD −0.35; 95% CI −0.61 to −0.10). However, several outcomes remained uncertain, and the findings cannot automatically be extrapolated from standardized experimental preparations to ordinary tea consumption. Overall, these interventions have evidence of modest, domain-specific attentional benefits rather than generalized cognitive enhancement.

5. Creatine and Cerebral Energy Metabolism

Creatine participates in cerebral energy homeostasis through the creatine kinase–phosphocreatine system, providing a plausible biological basis for investigating its cognitive effects. Rae *et al*. conducted a randomized, double-blind crossover trial involving 45 healthy young vegetarian adults and reported significant improvements in backward digit span and Raven's Advanced Progressive Matrices after six weeks (both $p<0.0001$) [4]. These findings suggested potential benefits in working memory and reasoning, although the selected dietary characteristics of the participants limit generalizability.

Avgerinos *et al*. subsequently reviewed six randomized trials involving 281 healthy individuals and identified favorable findings in short-term memory and reasoning, but inconsistent results in attention, executive function, and reaction time [5]. A later meta-analysis by Xu *et al*., including 16 trials and 492 participants, reported a positive pooled effect on memory but no statistically significant overall cognitive benefit; importantly, this synthesis included both healthy and clinical populations [9]. A separate review also questioned whether existing evidence supports cognitive enhancement in otherwise unstressed individuals [10]. Taken together, these findings suggest that creatine may benefit selected populations or cognitive domains, but generalized enhancement in healthy adults remains unproven.

6. Botanical Nootropics

6.1. *Bacopa monnieri*

Bacopa monnieri is among the botanical preparations most frequently investigated for memory enhancement. Roodenrys *et al*. conducted a randomized trial involving 76 adults aged 40–65 years and reported improved retention of newly acquired information after three months, without significant improvements in attention or short-term memory [6]. Calabrese *et al*. subsequently evaluated a standardized extract in 54 healthy older adults and observed favorable effects on delayed verbal recall and selected Stroop task outcomes after 12 weeks [7]. These findings suggested possible benefits in memory retention rather than a uniform improvement across cognitive domains.

However, more recent evidence has challenged the consistency of these results. Lopresti and Smith evaluated 101 adults aged 40–70 years with subjective memory or attention complaints in a 12-week randomized, double-blind, placebo-controlled trial [8]. No significant between-group improvements were observed in verbal learning (p=0.391), attention (p=0.713), working memory (p=0.610), or information-processing speed (p=0.528). Although supplementation was associated with reductions in self-reported stress reactivity (p=0.030) and fatigue, these secondary effects did not translate into measurable improvements in objective cognitive performance. Importantly, treatment-related adverse events were significantly more frequent in the *Bacopa monnieri* group than in the placebo group (30.0% vs. 11.8%; p=0.024), predominantly comprising gastrointestinal complaints and headaches, although no serious adverse events were reported. Differences in extract composition, baseline cognitive characteristics, and outcome selection may partly explain the conflicting findings. Taken together, the available evidence suggests that *Bacopa monnieri* may have selective effects on certain memory outcomes, but consistent enhancement of cognition in healthy adults has not been established. Larger, adequately powered, independently replicated randomized trials with standardized cognitive outcomes and systematic safety monitoring are needed [6–8].

6.2. *Ginkgo biloba* and Panax Ginseng

Ginkgo biloba is widely marketed for cognitive health, although its clinical findings remain inconsistent. Solomon *et al*. conducted a randomized controlled trial involving 230 cognitively healthy older adults and found no significant improvement in learning, memory, attention, concentration, naming, or verbal fluency after six weeks [11]. In contrast, smaller experimental studies have reported favorable results for selected cognitive outcomes following *Ginkgo biloba*, Panax ginseng, or their combination [12]. These findings illustrate why isolated positive results should be interpreted alongside larger negative trials rather than considered independently.

Panax ginseng has also demonstrated favorable effects in selected experimental tasks. In a controlled crossover study involving 30 healthy young adults, Reay *et al*. observed improved performance during sustained mental activity, particularly in a serial subtraction task, together with reduced subjective mental fatigue [13]. Nevertheless, a Cochrane review concluded that convincing evidence of cognitive enhancement in healthy participants was lacking because of small samples, heterogeneity, and limited comparability between trials [14]. Thus, both *Ginkgo biloba* and Panax

ginseng should be regarded as interventions with inconsistent or preliminary evidence rather than established cognitive enhancers.

6.3. Salvia, Guarana, and *Rhodiola rosea*

Several other botanical preparations have produced positive findings in small experimental studies. Tildesley *et al*. evaluated *Salvia lavandulifolia* in 24 healthy volunteers and reported improvements in selected measures of memory speed and secondary memory [15]. Kennedy *et al*. investigated guarana, Panax ginseng, and their combination in 28 healthy young adults and observed improvements in certain attention and memory-related tasks, although some outcomes suggested a trade-off between speed and accuracy [16]. A subsequent trial involving 129 young adults reported favorable cognitive findings with a multivitamin–mineral formulation containing guarana; however, the combined formulation prevents attribution of the effect to guarana alone [17].

Rhodiola rosea has been investigated particularly under conditions of fatigue and occupational stress. Darbinyan *et al*. studied 56 healthy physicians working night duty and reported improvements in a composite measure of mental performance after a short intervention [18]. Although these findings suggest possible benefits during stress-related cognitive demands, they do not establish enhancement in healthy, rested individuals. A systematic review subsequently emphasized the heterogeneity and methodological limitations of the available trials [19]. Collectively, evidence for *Salvia*, guarana, and *Rhodiola rosea* remains preliminary, with positive results that require confirmation in larger, independently replicated studies.

7. Other Nutritional and Metabolic Compounds

Tyrosine, a precursor of catecholamine neurotransmitters, has been investigated for its potential to attenuate cognitive deterioration under stressful conditions. A rapid evidence assessment by Attipoe *et al*. identified 10 randomized and four controlled clinical trials and suggested possible benefits during cognitive stress, while concluding that the overall evidence was insufficient for confident recommendations [20]. This distinction is clinically relevant because maintaining performance under sleep deprivation or stress is not equivalent to enhancing cognition in healthy, rested individuals.

Omega-3 fatty acids have also been extensively studied, with conflicting findings. A randomized trial involving 310 healthy adults aged 25–49 years reported favorable effects of an EPA-rich preparation on selected global cognitive performance measures [21]. However, another six-month randomized trial involving 193 cognitively healthy adults aged 20–80 years found no significant overall improvement in primary or secondary cognitive outcomes [22]. A larger systematic review involving 38 randomized trials and approximately 49,757 participants found little or no effect of increased omega-3 intake on new cognitive impairment or global cognitive outcomes [23]. Although the populations and endpoints differ, these results indicate that omega-3 supplementation should not be considered an established general cognitive enhancer.

Polyphenol-rich interventions have generated additional interest. Small *et al*. conducted an 18-month randomized trial of a bioavailable curcumin preparation in nondemented adults and reported improvements in selected memory and attention outcomes [24]. Krikorian *et al*. also observed favorable memory findings following blueberry supplementation in older adults with early memory complaints [25]. However, the latter population is not equivalent to asymptomatic healthy adults, and the findings should not be directly generalized. These studies suggest potential cognitive effects of certain polyphenol-rich preparations but remain insufficient to establish reproducible enhancement of normal cognition.

8. Experimental Compounds and Unsupported Claims

Several synthetic compounds and alternative preparations are promoted as nootropics despite limited directly applicable clinical evidence. Studies involving neurological disorders, animal models, or mechanistic outcomes cannot establish efficacy in healthy individuals. For compounds such as Noopept and certain racetams, the available evidence considered in this review does not establish reliable generalized cognitive enhancement. Similarly, homeopathic preparations promoted for memory or concentration lack convincing, reproducible clinical evidence demonstrating objective cognitive benefits in healthy adults.

Psychedelic microdosing provides a particularly relevant example of the discrepancy between popular expectations and controlled cognitive outcomes. Pinhas *et al*. conducted a systematic review and meta-analysis of 14 studies involving 1,614 participants and found no overall cognitive benefit, while cognitive control showed a negative pooled effect [26]. These findings emphasize the importance of distinguishing subjective perceptions of improved creativity, concentration, or mental clarity from objectively demonstrated enhancement. They also reinforce the need to differentiate absence of demonstrated benefit from absence of studies, since these represent distinct forms of uncertainty.

9. Safety and Implications for Clinical Practice

The interpretation of nootropic evidence should integrate the magnitude of cognitive benefit with the potential for adverse effects. Prescription medications may produce measurable experimental effects while introducing clinically relevant cardiovascular, psychiatric, sleep-related, and interaction risks. Botanical and nutritional preparations may appear safer, but their composition, standardization, tolerability, and interaction potential can vary considerably. Moreover, adverse-event reporting is frequently incomplete, especially in small or short-duration trials, and failure to report adverse events should never be interpreted as evidence that none occurred.

For clinicians, the most useful distinction is between reproducible but modest benefits in specific cognitive domains, preliminary findings that have not been consistently replicated, and interventions without convincing evidence of objective benefit. A systematic review of dietary supplements in healthy young adults and military personnel identified substantial methodological limitations in much of the literature, reinforcing the need for caution when translating experimental findings into practical claims [27]. Persistent cognitive complaints should also prompt consideration of sleep quality, psychological factors, medication effects, and underlying medical conditions rather than immediate attribution to a need for cognitive enhancement.

10. Limitations

This review is narrative and does not claim exhaustive identification of all published studies or formal grading of evidence certainty. Differences in study populations, cognitive instruments, intervention formulations, and follow-up duration limit direct comparisons. Several published syntheses include both healthy individuals and clinical populations, requiring caution when interpreting pooled findings. Furthermore, short-term laboratory effects cannot reliably predict sustained improvements in academic, occupational, or everyday cognitive functioning. Furthermore, improvements in subjective stress, fatigue, or mood should not be interpreted as evidence of enhanced objective cognitive performance. Interpretation should therefore prioritize reproducibility, effect magnitude, population characteristics, functional relevance, and safety, including adverse-event frequency and tolerability, rather than isolated positive findings or commercial claims. Larger, independently replicated randomized controlled trials using standardized cognitive outcomes and systematic safety assessments are needed before generalized cognitive-enhancement claims can be supported.

11. Conclusions

The available evidence indicates that certain nootropics produce measurable improvements in selected cognitive domains among healthy adults, but benefits are generally modest, heterogeneous, and context-dependent. Caffeine has reproducible acute effects on attention, while L-theanine-containing interventions may improve specific attentional outcomes. Methylphenidate and modafinil demonstrate small experimental cognitive effects without establishing meaningful generalized enhancement. Creatine has produced promising but inconsistent findings, whereas the evidence for *Bacopa monnieri* remains conflicting, with earlier positive trials not consistently replicated in more recent investigations. Evidence for several other botanical and nutritional interventions remains preliminary or inconclusive. The central clinical conclusion is that statistically significant improvement in a cognitive test does not necessarily represent clinically meaningful cognitive enhancement.

Declarations

Ethics approval and consent to participate: Not applicable. This study is a narrative review of previously published literature and involved no new human or animal research.

Consent for publication: Not applicable.

Availability of data and materials: No original datasets were generated. The evidence discussed was obtained from previously published scientific literature.

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Table 2: Nutritional and botanical nootropics with preliminary, selective, or inconsistent cognitive benefits in healthy adults

Study / intervention	Country	Design and sample	Demographics	Setting and follow-up	Cognitive assessments	Main results	Clinical interpretation	Adverse events
Rae *et al*., 2003 [4] — Creatine	Australia	Double-blind, placebo-controlled crossover RCT; 45 participants	Healthy vegetarians; 12 men, 33 women	Experimental setting; 6 weeks	Backward Digit Span; Raven's Advanced Progressive Matrices	Significant improvements in working memory and reasoning (both reported $p<0.0001$)	Positive findings in a selected vegetarian population; generalizability uncertain	Event frequencies not established from the available extraction
Avgerinos *et al*., 2018 [5] — Creatine	Japan, Australia, UK, USA	Systematic review of 6 RCTs; 281 participants	Heterogeneous age groups; individual studies enrolled 22–121 participants; one trial enrolled only women	Controlled studies lasting 5 days to 6 weeks	Working memory, reasoning, attention, reaction time, executive function	Some favorable results for short-term memory and reasoning; inconsistent effects in other domains	Suggestive but heterogeneous evidence; participants overlap with Rae *et al.*	No pooled adverse-event estimate
Roodenrys *et al*., 2002 [6] — *Bacopa monnieri*	Australia	Placebo-controlled RCT; 76 participants	Healthy adults aged 40–65 years; exact sex distribution not verified	Community-based study; 12 weeks	Retention of newly acquired information; short-term memory; attention	Improved retention of newly learned information; inconsistent effects on other outcomes	Possible selective memory benefit	Event frequencies not verified
Calabrese *et al*., 2008 [7] — *Bacopa monnieri*	USA	Double-blind placebo-controlled RCT; 54 participants	Older adults; mean age approximately 73.5 years; exact sex distribution not verified	Community-based study; 12 weeks	Delayed verbal recall; Stroop; other neuropsychological tests	Improvements in selected delayed-recall and interference-control measures	Small positive trial in older adults; findings require replication	Gastrointestinal complaints reported; frequencies not verified
Reay *et al*., 2005 [13] — Panax ginseng	UK	Double-blind crossover RCT; 30 participants	Healthy young adults; 16 women, 14 men; mean age 22.6 years	Laboratory study; acute testing over repeated assessments	Serial Threes, Serial Sevens, Rapid Visual Information Processing; mental-fatigue ratings	Significant improvement in Serial Sevens at five assessment points (reported p values 0.041, 0.002, 0.006, 0.035 and 0.038); no consistent benefit across all tasks	Selective improvement in demanding arithmetic tasks; not generalized enhancement	Blood-glucose reductions reported; adverse-event incidence not reliably quantified
Tildesley *et al*., 2005 [15] — *Salvia lavandulifolia*	UK	Double-blind crossover RCT; 24 participants	16 women, 8 men; mean age 23.21 years, range 18–37	Laboratory study; assessments at 1, 2.5, 4 and 6 hours	Cognitive Drug Research battery; word recall and recognition; working memory; vigilance; reaction time	Improvements in selected memory-speed and secondary-memory outcomes	Preliminary acute, domain-specific findings	No reliable adverse-event frequency established

Study / intervention	Country	Design and sample	Demographics	Setting and follow-up	Cognitive assessments	Main results	Clinical interpretation	Adverse events
Kennedy *et al*., 2004 [16] — Guarana	UK	Double-blind crossover RCT; 28 participants	Healthy young adults; exact age and sex distribution not verified	Acute laboratory assessment	Attention, memory and information-processing tasks	Selected favorable cognitive outcomes, varying across tasks	Exploratory evidence; no demonstrated generalized enhancement	Frequencies not verified
Darbinyan *et al*., 2000 [18] — *Rhodiola rosea*	Armenia	Double-blind crossover study; 56 participants	Healthy physicians on night duty; age and sex counts not verified	Occupational night-shift setting; two-week treatment periods	Composite mental-performance assessments under fatigue	Improved selected performance measures during night duty	Potential fatigue-related effects; not directly generalizable to rested adults	No adverse effects reported in the study summary
Attipoe *et al*., 2015 [20] — Tyrosine	Multiple countries	Rapid evidence assessment of 10 RCTs and 4 controlled trials	Healthy adults exposed to physical or cognitive stress; pooled demographics unavailable	Laboratory and operational stress settings; variable follow-up	Working memory, vigilance, attention and other stress-sensitive outcomes	Some positive findings under stress, with substantial inconsistency	Potential context-dependent effects; insufficient evidence for routine enhancement	No pooled safety estimate
Patan *et al*., 2021 [21] — EPA-rich omega-3	UK	Randomized controlled trials; 310 participants overall	Healthy adults aged 25–49 years; sex distribution not verified	Controlled supplementation studies; approximately 26 weeks	Global cognitive performance, processing speed and accuracy	Selected positive findings with EPA-rich supplementation	Individual positive evidence within a conflicting broader literature	Detailed frequencies not verified
Small *et al*., 2018 [24] — Curcumin	USA	Double-blind placebo-controlled RCT	Nondemented middle-aged and older adults; exact N and sex counts not verified in this extraction	Clinical trial; 18 months	Verbal and visual memory; attention	Improvements in selected memory and attention outcomes	Promising but formulation-specific findings	Gastrointestinal complaints reported; frequencies not verified

***Abbreviations**:* RCT, randomized controlled trial; EPA, eicosapentaenoic acid; UK, United Kingdom. Systematic-review participants must not be added to the totals of individual trials included in those reviews. Country indicates study location rather than ethnicity. "Not verified" denotes a field for which a precise value cannot be established from the source material examined; it does not imply that the original study failed to report it.

Table 3: Interventions with negative or insufficient evidence for generalized cognitive enhancement

Study / intervention	Country	Design and sample	Demographics	Setting and follow-up	Cognitive assessments	Main results	Clinical interpretation	Adverse events
Roberts *et al*., 2020 [1] — D-amphetamine	Multiple countries	Meta-analysis of 10 experimental studies	Predominantly healthy young adults; no consolidated age, sex or ethnicity distribution	Placebo-controlled experimental studies; acute assessments	Stroop, Flanker, working memory, response inhibition, attention and processing-speed tasks	No statistically significant overall cognitive benefit; selected individual findings varied	No demonstrated generalized enhancement	No pooled adverse-event estimate
Lopresti and Smith, 2025 [8] — *Bacopa monnieri*	Australia	12-week, double-blind, parallel-group RCT; 101 randomized (*Bacopa* 50; placebo 51); 87 completed (40 and 47, respectively)	Bacopa: mean age 60.36 years (SE 1.18), 37 women/13 men. Placebo: mean age 58.86 years (SE 1.20), 36 women/15 men. Overall: 73 women/28 men. Eligibility specified ages 40–70 years; baseline table also reports a 70–75-year category. Ethnicity not reported in the baseline table	Community recruitment and research-center assessment; cognitive testing at baseline and week 12; questionnaires additionally at weeks 4 and 8	RAVLT for verbal learning; Digit Vigilance and Choice Reaction Time for attention; Corsi Blocks and Numeric Working Memory; information-processing speed; secondary PSRS, VAMS, VAS and EMQ	No between-group cognitive benefit: RAVLT p=0.391; attention accuracy p=0.713; working memory p=0.610; processing speed p=0.528. RAVLT improved within both groups (*Bacopa* 13.98%, placebo 11.82%), without significant between-group difference. Stress reactivity improved (PSRS interaction p=0.030; reductions 20.3% vs 6.0%). No between-group improvement in everyday memory (EMQ, p=0.538)	Negative trial for cognitive enhancement. Secondary reductions in perceived stress and fatigue should not be interpreted as improved objective cognition	Treatment-related AEs: 15/50 (30.0%) vs 6/51 (11.8%), p=0.024. GI complaints: 9/50 (18%) vs 5/51 (9.8%); headache 3/50 (6%) vs 1/51 (2%); sleep disturbance 2/50 (4%) vs 1/51 (2%). Four *Bacopa* and two placebo participants discontinued owing to suspected treatment-related AEs. No serious AEs
Solomon *et al*., 2002 [11] — *Ginkgo biloba*	USA	Placebo-controlled RCT; 230 participants	Cognitively healthy older adults aged 60–82 years; 98 men, 132 women	Community-based study; 6 weeks	Learning, memory, attention, naming and verbal fluency	No significant improvement in the principal cognitive outcomes	Negative evidence for generalized memory enhancement in healthy older adults	Detailed event frequencies not verified

Study / intervention	Country	Design and sample	Demographics	Setting and follow-up	Cognitive assessments	Main results	Clinical interpretation	Adverse events
Maltais *et al*., 2022 [22] — Omega-3 fatty acids	Canada	Double-blind RCT; 243 randomized, 236 eligible and 193 analyzed (96 intervention; 97 placebo)	Healthy adults aged 20–80 years; mean age 49.4 ± 16.4 intervention and 50.5 ± 16.6 placebo; sex distribution not verified	Community-based study; 6 months	Cued Letter task, Brown–Peterson working-memory task, Delayed Cued Recall and Trail Making Test B	No significant improvement in visuospatial ability (p=0.639), working memory (p=0.251), episodic memory (p=0.483) or executive function (p=0.967). Exploratory finding in participants with poorer baseline episodic memory (p=0.043)	Negative overall trial; exploratory subgroup finding is hypothesis-generating	10 discontinuations associated with suspected treatment-related AEs: 4 intervention, 6 placebo; predominantly gastrointestinal symptoms
Brainard *et al*., 2020 [23] — Omega-3 and other PUFAs	Multiple countries	Systematic review/meta-analysis of 38 RCTs, approximately 49,757 participants	Heterogeneous populations, including many older adults; not exclusively healthy young adults	Multiple settings; interventions lasting at least 24 weeks	Global cognition, cognitive impairment and domain-specific outcomes	Little or no overall cognitive benefit	Broad negative or neutral evidence; applicability depends on population	No pooled adverse-event estimate established here
Pinhas *et al*., 2026 [26] — Psychedelic microdosing	Multiple countries	Systematic review/meta-analysis of 14 studies; 1,614 participants	Adult research populations; detailed demographics not verified	Heterogeneous experimental protocols	Cognitive control and other neuropsychological outcomes	No demonstrated overall cognitive benefit	Experimental evidence does not establish efficacy or long-term safety	Long-term adverse-event incidence not established

***Abbreviations**:* AE, adverse event; EMQ, Everyday Memory Questionnaire; GI, gastrointestinal; PSRS, Perceived Stress Reactivity Scale; PUFA, polyunsaturated fatty acid; RAVLT, Rey Auditory Verbal Learning Test; RCT, randomized controlled trial; SE, standard error; VAMS, Visual Analogue Mood Scale; VAS, Visual Analogue Scale. Lopresti and Smith's values were extracted directly from Tables 1, 2, 4 and 6 and the trial flow diagram.

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