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Plant-Derived Bioactive Compounds for Cognitive Enhancement: Formulation Strategies and Clinical Evidence on Memory and Attention

Mohammad Bagher Shahsavani, Mohammad Ali Nasiri Khalili*

Department of Cognitive Science, Malek Ashtar University of Technology, Tehran, Iran

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ABSTRACT

Plant-derived bioactive compounds (specifically polyphenols, terpenoids, and alkaloids) are increasingly studied for their potential to enhance memory and attention in populations ranging from healthy adults to patients with Alzheimer's disease (AD). However, the clinical utility of potentially potent agents (e.g., curcumin, resveratrol) is frequently compromised by a critical translational bottleneck: poor oral bioavailability, rapid metabolism, and limited blood-brain barrier permeability. This review integrates clinical evidence with recent advances in formulation science to evaluate the efficacy of key botanicals, including *Bacopa monnieri*, standardized *Ginkgo biloba* (EGb 761), saffron (*Crocus sativus*), cocoa flavanols, sage (*Salvia* spp.), and L-theanine combined with caffeine. We address how modern delivery systems (such as lipid-based nano emulsions, solid lipid nanoparticles, phytosomes, and cyclodextrin complexes) can overcome solubility limitations to improve systemic exposure and central nervous system delivery. By mapping the relationship between compound properties, formulation strategy, and cognitive endpoints, we highlight that while evidence supports the indication-specific use of these agents, reproducibility depends on overcoming pharmacokinetic variability. Future research must prioritize pharmacokinetic–pharmacodynamic (PK–PD) alignment, accurate standardization of chemo profiles, and the use of cognitively sensitive trial designs to validate these interventions.

Keywords: Cognition, Memory, Attention, Botanicals, Polyphenols.

INTRODUCTION

The preservation of cognitive function (particularly memory and attention) remains a paramount public health priority as the global population ages and the burden of age-associated cognitive impairment grows [1]. Cognitive decline is a hallmark not only of neurodegenerative diseases such as Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), but also of normative aging processes [2]. Conventional pharmacotherapies, including cholinesterase inhibitors and NMDA receptor antagonists, may provide symptomatic relief for some patients, yet their benefits are often modest and accompanied by adverse effects that limit long-term clinical utility [3]. Consequently, there is increasing scientific and commercial interest in plant-derived bioactive compounds as potentially safer, multi-target alternatives capable of modulating complex neurobiological systems [4–6]. Phytochemicals (including polyphenols, terpenoids, and alkaloids) are known to exert pleiotropic effects,

***Corresponding author. E-mail:** manasiri@ut.ac.ir

such as reducing oxidative stress, attenuating neuroinflammation, modulating vascular function, and influencing synaptic plasticity, all of which are implicated in cognitive aging and neurodegeneration [7–11]. However, clinical translation of these compounds is frequently hindered by significant challenges related to pharmacokinetics and standardization. Oral bioavailability is a critical issue for many candidate molecules; for example, lipophilic polyphenols like curcumin and resveratrol exhibit poor aqueous solubility, extensive first-pass metabolism, rapid glucuronidation and sulfation, and very low systemic exposure following standard oral dosing protocols, which constrain meaningful blood–brain barrier penetration and central nervous system (CNS) activity [12–14]. These limitations mean that cognitive efficacy in humans depends not only on intrinsic biological activity but also on how these compounds are formulated and delivered. Standard curcumin preparations frequently fail to achieve plasma concentrations associated with neurobiological activity observed *in vitro* [15–18]. Conversely, advanced delivery approaches designed to enhance systemic absorption and CNS exposure have produced encouraging results in carefully conducted randomized clinical studies. A prominent example is the 18-month double-blind, placebo-controlled trial of a highly bioavailable curcumin formulation (*Theracurmin*®) in non-demented adults, which demonstrated significant improvements in verbal and visual memory as well as attention relative to placebo, along with reductions in amyloid and tau tracer binding measured by positron emission tomography (PET) imaging [19]. Importantly, plant-derived bioactives differ substantially in whether they exert acute, state-dependent effects (e.g., caffeine–theanine) or require chronic administration to induce neuroplastic changes (e.g., Bacopa monnieri). These findings highlight the importance of formulation-aware research designs in evaluating the cognitive effects of botanical compounds. Therefore, this review aims to bridge the gap between mechanistic understandings from botanical science and accurate clinical outcomes. We combine human evidence on memory and attention within a framework that explicitly accounts for formulation quality and standardization strategies. Subsequent sections will integrate: (i) the mechanistic basis of key compound classes; (ii) an evaluation of high-quality randomized controlled trials and meta-analyses; and (iii) a critical analysis of delivery technologies (from standardized extracts to lipid-based nanosystems) that are essential for ensuring reproducible CNS exposure and demonstrable cognitive efficacy (Figure 1).

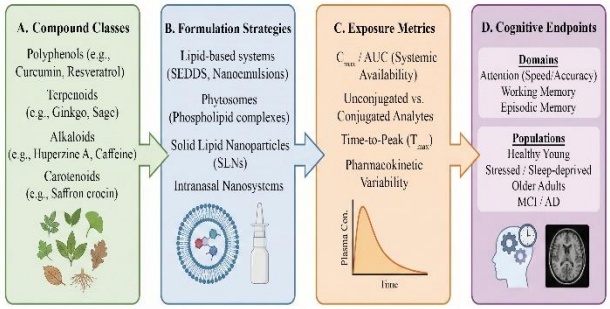


Figure 1. The "From Plant to Performance" Translational Framework. This figure visualizes the central argument of the review, illustrating the critical path from selecting a bioactive compound to achieving a measurable cognitive outcome. It maps directly to the framework proposed in the introduction and conclusion sections. A. Compound Classes: Identifies the key phytochemical categories reviewed in the paper. B. Formulation Strategies: Highlights the modern delivery systems that are essential for overcoming solubility and stability barriers. C. Exposure Metrics: Emphasizes the necessity of validating systemic availability and understanding the pharmacokinetics (PK) of the active compounds. D. Cognitive Endpoints: Shows the specific domains and populations where efficacy is evaluated, as detailed in the clinical evidence section.

Major Classes of Plant-Derived Bioactives and Cognitive Mechanisms

Plant bioactives rarely act through a single pathway; rather, they exert pleiotropic effects across multiple biological routes relevant to memory and attention. A mapping of these domain-specific biological mechanisms is provided in Table 1. These mechanisms generally converge on neurotransmitter regulation, reduction of oxidative stress, improvement of cerebrovascular function, and enhancement of synaptic plasticity (Figure 2).

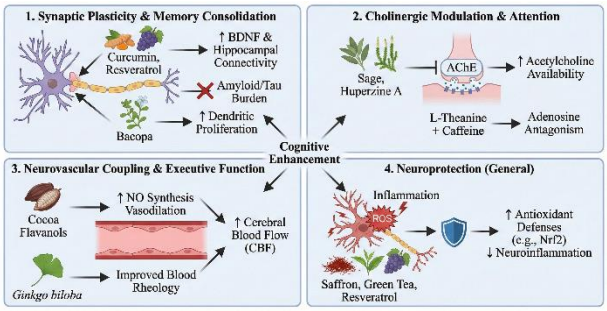


Figure 2. Multi-Target Mechanisms of Plant-Derived Bioactives. This figure provides a mechanistic view, by visually summarizing how different botanical modulators influence key biological pathways related to cognition. **Panel 1** (Synaptic Plasticity): Illustrates how curcumin, resveratrol, and Bacopa can enhance neural connectivity and reduce pathological markers like amyloid/tau, as. **Panel 2** (Cholinergic Modulation): Shows the specific action of Sage and Huperzine A in inhibiting acetylcholinesterase (AChE) to increase acetylcholine levels. It also includes the adenosine antagonism of L-Theanine + Caffeine. **Panel 3** (Neurovascular Coupling): Depicts the vascular mechanisms of cocoa flavanols and Ginkgo biloba, which improve cerebral blood flow through nitric oxide synthesis and blood rheology, respectively. **Panel 4** (Neuroprotection): Summarizes the general antioxidant and anti-inflammatory effects of polyphenols like saffron, green tea, and resveratrol, which combat oxidative stress (ROS) and neuroinflammation.

Table 1. Mechanistic Framework for Cognitive Enhancement. This table maps the plant compounds to the specific biological pathways.

Cognitive Domain	Biological Mechanism	Key Botanical Modulators
Memory Consolidation & Synaptic Plasticity	Upregulation of BDNF; Modulation of hippocampal functional connectivity; Reduction of amyloid/tau burden.	**Curcumin** (anti-amyloid/tau); **Resveratrol** (hippocampal connectivity); **Bacopa** (dendritic proliferation).
Attention & Processing Speed	Cholinergic modulation (AChE inhibition); Modulation of adenosine and dopamine receptors.	**Sage** (cholinergic); **Huperzine A** (cholinergic); **L-Theanine + Caffeine** (adenosine antagonism/alpha-wave promotion).
Executive Function & Vascular Health	Neurovascular coupling (NO-mediated vasodilation); Improvement of cerebral blood flow (CBF).	**Cocoa Flavanols** (endothelial function); **Ginkgo biloba** (blood rheology/microcirculation).
Neuroprotection (General)	Reduction of oxidative stress (ROS scavenging); Anti-inflammatory signaling (Nrf2 activation).	**Saffron** (antioxidant); **Green Tea** (catechins); **Resveratrol** (sirtuin activation).

Note: BDNF = Brain-Derived Neurotrophic Factor; AChE = Acetylcholinesterase; NO = Nitric Oxide; ROS = Reactive Oxygen Species.

Cholinergic Modulation and Acetylcholinesterase (AChE) Inhibition

The cholinergic hypothesis of geriatric cognitive decline suggests that maintaining acetylcholine levels is critical for attention and memory.

Sage (*Salvia* spp.): Extracts of sage have demonstrated consistent cholinesterase-inhibiting properties in vitro. These mechanistic effects appear to translate clinically; randomized controlled trials (RCTs) indicate that standardized *Salvia officinalis* and *Salvia lavandulaefolia* extracts can improve secondary memory and attention accuracy in healthy older adults, likely by prolonging the availability of acetylcholine at the synapse [20].

Huperzine A (*Huperzia serrata*): This alkaloid is a potent, reversible, and selective AChE inhibitor. Its safety and efficacy were thoroughly evaluated in a large, multicenter Phase II trial involving patients with mild-to-moderate Alzheimer's disease. While the 200 µg twice-daily (BID) dose showed no significant benefit, the 400 µg BID dose demonstrated cognitive improvement on the Alzheimer's disease assessment scale-cognitive Subscale (ADAS-Cog), providing pivotal context for its dose-dependent therapeutic window [21].

Antioxidant and Anti-Inflammatory Signaling

Chronic neuroinflammation and oxidative stress are key drivers of cognitive aging. Polyphenols (including curcumin, resveratrol, and cocoa flavanols) modulate these pathways via mechanisms such as Nrf2 activation and cytokine downregulation. However, clinical success is often dictated by pharmacokinetics.

Curcumin: The efficacy of curcumin is heavily dependent on overcoming its poor oral bioavailability. This was demonstrated in an 18-month trial where a lipidated curcumin formulation (Theracurmin®), designed to increase absorption, resulted in significant improvements in memory and attention in non-demented adults, directly linking formulation strategy to clinical outcome [19].

Cerebrovascular Effects and Neurovascular Coupling

Adequate cerebral blood flow is a prerequisite for sustained cognitive performance. Cocoa Flavanols: These compounds enhance the bioavailability of nitric oxide (NO), leading to improved endothelial function. A key controlled study demonstrated that daily consumption of cocoa flavanols reduced insulin resistance and improved cognitive performance (specifically executive function and processing speed) in elderly individuals with Mild Cognitive Impairment (MCI), suggesting a vascular mechanism of action [22].

Synaptic Plasticity and Network-Level Effects

Beyond vascular and antioxidant effects, some bioactives may directly influence neural connectivity. Resveratrol: In a seminal 26-week randomized trial, supplementation with resveratrol significantly improved word retention in older adults. Neuroimaging revealed that these behavioral gains were accompanied by increased functional connectivity between the hippocampus and the medial prefrontal cortex, providing evidence of network-level modulation in the aging brain [23].

To provide a structured overview of these distinct classes and their primary cognitive targets, we have summarized the evidence landscape in Table 2.

Table 2. Overview of Plant-Derived Bioactives and Cognitive Potential.

Compound / Class	Primary Plant Source	Dominant Cognitive/Biological Targets	Level of Clinical Evidence
Bacosides	*Bacopa monnieri*	Synaptic plasticity, dendrite proliferation, antioxidant defense.	**Strong:** Chronic memory acquisition and retention (typically >12 weeks).
Flavanols	*Theobroma cacao* (Cocoa)	Endothelial function (NO synthesis), neurovascular coupling.	**Moderate-Strong:** Executive function/processing speed in elderly/MCI.
Curcuminoids	*Curcuma longa* (Turmeric)	Anti-inflammatory (amyloid/tau modulation), oxidative stress reduction.	**Conditional:** Efficacy is strictly dependent on enhanced bioavailability formulations.
Stilbenes	*Vitis vinifera* (Grape), *Polygonum cuspidatum*	Hippocampal functional connectivity, glucose metabolism, SIRT1 activation.	**Moderate:** Memory performance in older adults (requires adequate dose/duration).
Crocins & Safranal	*Crocus sativus* (Saffron)	Neurotransmitter modulation (serotonergic/cholinergic), neuroprotection.	**Strong:** Symptomatic improvement in mild-to-moderate AD (comparable to donepezil).
Alkaloids (AChE Inhibitors)	*Salvia* spp. (Sage); *Huperzia serrata*	Acetylcholinesterase (AChE) inhibition; cholinergic transmission.	**Variable:** Sage shows acute attention benefits; Huperzine A requires high doses (400 µg BID) in AD.
Amino Acid + Methylxanthine	*Camellia sinensis* (L-Theanine + Caffeine)	Alpha-wave activity, antagonism of adenosine receptors.	**Strong:** Acute synergy for sustained attention and vigilance (antagonizing caffeine jitters).

Formulation Strategies that Matter for Cognition Trials

In clinical cognitive neuroscience, the "active intervention" is never just the molecule; it is the specific formulation delivered to the participant. For hydrophobic polyphenols, the bioavailability barrier is often so high that raw extracts fail to reach the brain in therapeutic concentrations. Consequently, cognitive outcomes are highly formulation-sensitive.

Standardized Extracts and Chemoprofiling

Accurate standardization is the prerequisite for reproducibility. It ensures that the specific ratio of bioactive constituents remains constant across batches and studies. The Case of EGb 761: The importance of specific extract identity is best exemplified by *Ginkgo biloba*. The specific extract EGb 761 has demonstrated

efficacy in stabilizing cognitive function in patients with dementia [24]. However, meta-analytic evidence for *Ginkgo* in healthy individuals is far less consistent, highlighting that results from high-dose, pharmaceutical-grade extracts in impaired populations cannot be automatically extrapolated to healthy populations using generic supplements [25].

Oral Lipid-Based Delivery (SEDDS and Nano emulsions)

Many candidates' cognitive enhancers (e.g., curcumin, resveratrol) are Class II or IV compounds in the Biopharmaceutics Classification System (BCS), characterized by poor solubility.

Strategy: Lipid-based delivery systems, such as Self-Emulsifying Drug Delivery Systems (SEDDS) and nano emulsions, encapsulate lipophilic bioactives to enhance solubilization in the gastrointestinal tract.

Implication for Trials: This has profound implications for evidence synthesis. A negative trial utilizing a raw, unformulated powder should be interpreted as a failure of delivery, not necessarily a failure of the molecule's mechanism. Advanced lipid formulations are essential to distinguish between lack of efficacy and lack of exposure [26].

The relationship between physicochemical barriers and the necessary formulation strategies to overcome them is detailed in Table 3, highlighting why raw extracts often fail to achieve therapeutic thresholds.

Table 3. Major Translational Barriers and Formulation Strategies.

Compound Class	Physicochemical Barrier	Translational Consequence	Formulation Strategy Examples
Curcuminoids & Resveratrol	High lipophilicity (BCS Class II/IV); Rapid glucuronidation.	Negligible plasma levels with raw powder; "failed" trials due to lack of exposure.	**Lipid-based Systems:** Solid Lipid Nanoparticles (SLNs), Nanoemulsions, Phytosomes (phospholipid complexes).
Ginkgo & Bacopa	Complex mixture of actives; Batch-to-batch variability.	Inconsistent results across studies; difficulty replicating effect sizes.	**Standardization:** Setting strict chemoprofiles (e.g., EGb 761: 24% flavone glycosides, 6% terpene lactones).
Essential Oils (Sage/Rosemary)	Volatility; Poor oxidative stability.	Loss of active terpenes during storage; variable dosing.	**Encapsulation:** Soft-gel technologies; Microencapsulation to prevent oxidative degradation.
Green Tea Catechins (EGCG)	Poor stability in GI pH; Low membrane permeability.	Low systemic bioavailability; rapid elimination.	**Structural Modification:** Structural analogues; Co-administration with absorption enhancers (e.g., piperine, Vitamin C).

Note: BCS = Biopharmaceutics Classification System; GI = Gastrointestinal.

Phospholipid Complexes (Phytosomes)

Phospholipid complexation involves binding a polyphenol to a phospholipid (e.g., phosphatidylcholine) to create a phytosome.

Mechanism: This amphiphilic structure improves the compound's ability to cross lipid-rich biological membranes, enhancing both stability and absorption.

Relevance to Cognition: By reducing inter-individual variability in plasma concentrations, these formulations increase the statistical power of clinical trials, making it easier to detect subtle changes in sensitive cognitive endpoints.

Combination Formulations for Synergy

Polypharmacy is a core concept in traditional herbal medicine, but modern combinations require rigorous validation.

Clinical Evidence: Some synergistic effects have been confirmed in controlled conditions. For instance, a seminal trial demonstrated that a combination of *Ginkgo biloba* and *Panax ginseng* significantly improved the "Quality of Memory" index in healthy middle-aged adults over a 12-week period, an effect not fully replicated by either treatment alone [27].

The Caveat: Combination products must be evaluated with the accurate of fixed-dose drug combinations. This requires a clear pharmacological rationale, standardized dosing for all components, and trial designs capable of attributing efficacy to the combination rather than a single dominant ingredient.

Clinical Evidence on Memory and Attention

This section synthesizes human clinical data, distinguishing between acute effects (hours) and chronic adaptation (weeks/months), and

differentiating efficacy in healthy adults versus those with cognitive impairment.

Bacopa monnieri

Bacopa monnieri has emerged as one of the most consistent herbal interventions for chronic memory support. A comprehensive meta-analysis of randomized controlled trials (RCTs) indicates that standardized extracts can significantly improve attention speed (e.g., reduced choice reaction time) and delayed recall. Crucially, these effects are rarely acute; benefits typically manifest only after approximately 12 weeks of sustained supplementation, suggesting a mechanism involving synaptic remodeling rather than immediate neurotransmitter modulation [28].

Clinical Takeaway: *Bacopa* is a leading candidate for chronic cognitive enhancement, provided the extract is standardized to bacosides and the treatment duration exceeds three months.

***Ginkgo biloba* (EGb 761 and General Extracts)**

The clinical utility of *Ginkgo biloba* is heavily stratified by population health status.

In Healthy Adults: Evidence for cognitive enhancement in healthy cohorts is weak. A meta-analysis examining memory, executive function, and attention found no ascertainable positive effects for *Ginkgo* in cognitively intact individuals, cautioning against its use as a "nootropic" for the general population [25].

In Cognitive Impairment/Dementia: Conversely, the extract EGb 761 has a robust history of clinical efficacy in pathologic states. Large-scale, controlled trials, such as those by the North American EGb Study Group, have demonstrated that standardized *Ginkgo* can stabilize cognitive performance and social functioning in patients with dementia, likely due to rheological and neuroprotective properties [29].

Cocoa Flavanols

Cocoa flavanols represent a plausible dietary intervention for vascular-mediated cognitive support. The Cocoa, Cognition, and Aging (CoCoA) study demonstrated that controlled dosing of flavanols in elderly subjects with Mild Cognitive Impairment (MCI) improved executive function and processing speed. These cognitive gains occurred alongside improvements in insulin resistance and blood pressure, reinforcing the hypothesis that cocoa bioactives enhance cognition via neurovascular coupling [22].

L-Theanine + Green Tea Catechins (EGCG)

While green tea is epidemiologically associated with neuroprotection, clinical trial results for specific extracts are mixed. A randomized, double-blind, placebo-controlled trial (the LGNC-07 study) evaluated a combination of L-theanine and green tea extract in patients with MCI. While the study found marginal signals of improvement at intermediate time points, there was no significant difference in memory or attention at the end of the trial [30]. This suggests that efficacy may be highly sensitive to dose formulation and the timing of cognitive assessments.

L-Theanine + Caffeine

In contrast to the chronic effects of other botanicals, the combination of L-theanine and caffeine provides consistent, acute synergistic benefits. Research indicates that this pairing significantly enhances attention, vigilance, and reaction time (particularly under conditions of fatigue) more effectively than either compound alone. The addition of L-theanine serves to attenuate the vasoconstrictive and anxiogenic side effects often associated with caffeine monotherapy [31].

Panax ginseng

Panax ginseng is characterized by acute, demand-specific cognitive modulation.

Acute Effects: A placebo-controlled crossover study using the standardized G115 extract reported significant improvements in working memory and calmness in healthy young adults following single doses [32].

Synergy: When combined with *Ginkgo biloba*, *Panax ginseng* has been shown to improve an index of "Quality of Memory" in healthy middle-aged adults over 12 weeks, suggesting potential synergy between the adaptogenic properties of ginseng and the vascular effects of ginkgo [27].

***Salvia* Species (Sage) and Rosemary**

Volatile terpene-rich herbs show promise for acute cholinergic modulation.

Sage (*Salvia officinalis*): In healthy older volunteers, standardized sage extracts have demonstrated acute improvements in memory and attention [20]. Furthermore, a double-blind, randomized trial in patients with mild-to-moderate AD found that *S. officinalis* extract produced significant cognitive benefits comparable to pharmaceutical cholinesterase inhibitors [35].

Rosemary (*Rosmarinus officinalis*): Similarly, acute administration of rosemary powder in elderly populations has been linked to speed-of-processing benefits, likely mediated by 1,8-cineole content [36].

Curcumin (Formulation-Critical)

Curcumin serves as the definitive case study for the "formulation-exposure-response" framework. In a landmark 18-month, double-blind, placebo-controlled trial, non-demented adults supplemented with a highly bioavailable solid lipid curcumin formulation (Theracurmin®; 90 mg BID) showed significant improvements in memory and attention. This trial provides some of the strongest clinical evidence linking enhanced bioavailability to tangible cognitive preservation [19].

Resveratrol

Similar to curcumin, resveratrol requires adequate exposure to impact brain function. A 26-week randomized controlled trial in older adults (200 mg/day) reported not only improved word retention but also structural changes, specifically increased functional connectivity in the hippocampus. This suggests that resveratrol may exert network-level neuroplastic effects in the aging brain [23].

Saffron (*Crocus sativus*)

Saffron has accrued a remarkably coherent evidence base in the context of Alzheimer's disease.

Efficacy: Multiple double-blind, randomized trials have shown that saffron extract is superior to placebo [37] and non-inferior to donepezil (10 mg/day) in treating mild-to-moderate AD [38].

Adjunctive Use: Recent trials have also evaluated saffron as an adjunct to standard therapy, noting improvements in clinical outcomes and inflammatory markers [39]. Current systematic reviews continue to validate saffron as a potent therapeutic candidate, although evidence for cognitive enhancement in healthy, non-demented adults remains less established. Given the heterogeneity in trial designs, a consolidated summary of key randomized controlled trials (detailed by dose, duration, and primary cognitive findings) is presented in Table 4.

Table 4. Summary of Key Clinical Trials on Memory and Attention.

Intervention	Study Design & Population	Dose / Regimen	Primary Cognitive Findings
Bacopa monnieri	Meta-analysis of 9 RCTs (Healthy Adults)	Various (Standardized extracts); >12 weeks	Improved attention speed and delayed memory recall; effects are chronic, not acute.
Ginkgo biloba	Meta-analysis of 13 RCTs (Healthy Adults)	Various; acute and chronic	No robust statistical benefit found for memory, executive function, or attention in healthy cohorts.
Ginkgo biloba (EGb 761)	RCT, Placebo-controlled (Dementia)	120 mg/day; 52 weeks	Significant stabilization of cognitive performance (ADAS-Cog) and social functioning compared to placebo.
Cocoa Flavanols	RCT, Double-blind (MCI/Elderly)	990 mg vs 520 mg vs 45 mg flavanols; 8 weeks	Dose-dependent improvement in verbal fluency and Processing Speed Test; correlated with insulin resistance.
Theracurmin® (Curcumin)	RCT, Double-blind (Non-demented Adults)	90 mg BID (bioavailable form); 18 months	Significant improvement in verbal memory (Buschke SRT) and attention (sustained attention task); reduced amyloid signals.
Resveratrol	RCT, Double-blind (Older Adults)	200 mg/day; 26 weeks	Significant improvement in word retention; increased hippocampal functional connectivity (fMRI).
Saffron	RCT, Double-blind (Mild-Mod AD)	30 mg/day; 16 weeks	Cognitive outcomes significantly superior to placebo; comparable to standard care in related trials.
Sage (*Salvia officinalis*)	RCT, Crossover (Healthy Elderly)	333 mg, 666 mg, 1332 mg; Acute	Significant enhancement of secondary memory performance and attention accuracy (dose-dependent).
Ginkgo + Ginseng	RCT, Double-blind (Middle-aged Adults)	Combination (Standardized); 12 weeks	Significant improvement in "Quality of Memory" index compared to placebo or single agents.
Huperzine A	Phase II Multicenter RCT (Mild-Mod AD)	200 µg vs 400 µg BID; 16 weeks	400 µg BID showed cognitive benefit (ADAS-Cog); 200 µg BID did not differ from placebo.

Interpreting the Combined Evidence

The landscape of plant-derived cognitive enhancers is defined by a dichotomy between mechanistic plausibility and clinical reproducibility. While preclinical models consistently demonstrate neuroprotective potential, human translation is often complicated by methodological heterogeneity. By filtering the evidence through the lens of formulation science and trial design, distinct patterns of efficacy and sources of heterogeneity emerge (Figure 3).

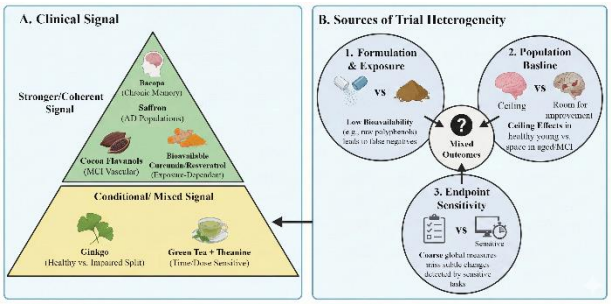


Figure 3. Clinical Evidence and Drivers of Trial Heterogeneity. This figure visually summarizes the key findings from the "Clinical Evidence" and "Discussion" of the manuscript. **A)** Clinical Signal: This panel provides a tiered view of the strength of clinical evidence for different botanical interventions. It visually separates compounds with a Stronger / Coherent Signal (top green section) in specific contexts (e.g., Bacopa for chronic memory, Saffron for AD) from those with a more Conditional / Mixed Signal (bottom yellow section) (e.g., Ginkgo in healthy adults). This reflects the nuanced conclusions drawn in the text regarding the importance of population and specific extract identity. **B)** Sources of Trial Heterogeneity: This panel illustrates the primary reasons why clinical trials for these compounds often yield conflicting results, as detailed in the discussion section. It highlights three key factors contributing to Mixed Outcomes: 1. Formulation & Exposure: Shows how low bioavailability (e.g., raw powder vs. advanced formulation) can lead to false negatives. 2. Population Baseline: Illustrates the "ceiling effect" in healthy young adults versus the potential for improvement in aged or impaired populations. 3. Endpoint Sensitivity: Demonstrates how coarse measurement tools can miss subtle cognitive changes that more sensitive, domain-specific tasks might detect.

Stronger vs. Conditional Evidence Patterns

When evaluating accuracy, consistency, and effect size, the evidence base stratifies into two distinct categories:

1: Coherent Clinical Signals

Several interventions show a consistent "signal-to-noise" ratio in specific contexts:

Chronic Memory Support: *Bacopa monnieri* is supported by meta-analytic evidence for improving memory retention and attention speed, provided administration is chronic (typically >12 weeks) [28].

Vascular-Mediated Enhancement: Cocoa flavanols demonstrate robust effects in elderly populations with mild cognitive impairment (MCI), likely due to a clear mechanism of action involving endothelial function and neurovascular coupling [22].

Bioavailability-Dependent Efficacy: The efficacy of curcumin and resveratrol is strongly tied to exposure. The success of lipidated curcumin (Theracurmin®) in preserving memory over 18 months [19] and resveratrol's ability to enhance hippocampal connectivity [23] highlights that positive outcomes are achievable when formulation barriers are overcome.

Pathology-Specific Benefits: Saffron (*Crocus sativus*) has accrued a persuasive evidence base specifically for AD, with multiple trials suggesting efficacy comparable to conventional pharmacotherapy [37,38]. Similarly, *Salvia* (Sage) species show replicable acute benefits for memory and attention in older adults [34].

2: Mixed or Conditional Evidence

Other popular interventions show divergence between public perception and clinical reality:

***Ginkgo biloba*:** A clear divide exists based on baseline cognitive status. While effective for symptomatic management in dementia, meta-analyses consistently fail to find robust benefits for standardized extracts (EGb 761) in healthy, cognitively intact individuals [25].

Green Tea Combinations: The combination of L-theanine and green tea extract (e.g., in the LGNC-07 trial) has yielded mixed results in MCI, with no significant end-of-trial effects on memory, suggesting that dosing regimens or the timing of assessments relative to ingestion may obscure potential benefits [30].

Why Trials Disagree: Sources of Heterogeneity

Inconsistencies across literature should not be dismissed as mere noise; rather, they often reflect three critical methodological variables:

Formulation and Exposure Variance: This is the most significant confounder for hydrophobic polyphenols. Trials utilizing raw, unmodified curcumin or resveratrol often fail to achieve therapeutic plasma concentrations, leading to false negatives. The positive outcomes seen in trials utilizing solid lipid nanoparticles or phytosomes confirm that "negative" results in earlier studies may have been failures of delivery rather than mechanism.

Population and Ceiling Effects: The "baseline dependency" phenomenon is pervasive. Healthy, young adults often perform near the physiological ceiling on standard memory tasks, leaving little room for improvement. Significant effects are more frequently observed in populations with cognitive headroom (e.g., older adults, fatigue states, or MCI).

Endpoint Sensitivity: Global screening tools (e.g., MMSE) are often too coarse to detect subtle enhancements in healthy brains. Trials that employ sensitive, domain-specific measures (such as reaction time, rapid visual information processing (RVIP), or delayed word recall) are more likely to capture the nuanced effects of botanical interventions.

The Role of Network Meta-Analysis

To address these disparities, recent network meta-analyses (NMA) have begun to provide a structured comparative framework for natural extracts in healthy adults. By statistically linking direct and indirect comparisons, these analyses help rank interventions by efficacy. However, the validity of such rankings remains strictly dependent on the comparability of the underlying "nodes" specifically, the assumption that different formulations of the same botanical (e.g., crude powder vs. nanoemulsion) are pharmacologically equivalent, which this review suggests is often incorrect.

FUTURE DIRECTIONS

The integration of botanical pharmacology, formulation science, and clinical neuropsychology offers a promising frontier for cognitive enhancement. However, moving this field from "promising signals" to "standard of care" requires a paradigm shift in how research is conducted. Future investigations must prioritize accuracy, specificity, and mechanistic clarity; a proposed roadmap for this formulation-aware research framework is outlined in Figure 4.

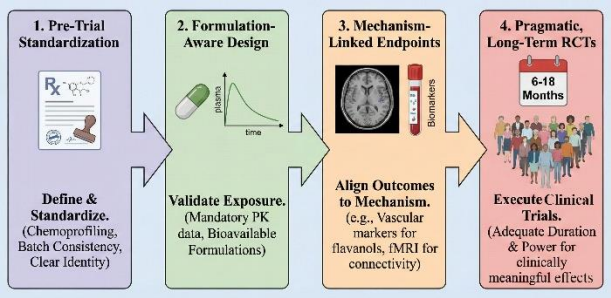


Figure 4. Proposed Roadmap for Future Formulation-Aware Cognitive Trials. This figure provides a forward-looking visual summary of the recommendations made in the "Future Directions" and "Conclusion" of the manuscript. It outlines a four-stage framework for conducting more accurate and reproducible research in this field. **1. Pre-Trial Standardization:** Emphasizes the necessity of defining and standardizing the botanical intervention (chemoprofiling, batch consistency) before a trial begins to ensure reproducibility. **2. Formulation-Aware Design:** Highlights the critical need to validate systemic exposure through mandatory pharmacokinetic (PK) data, ensuring that the active compounds are actually reaching the target. **3. Mechanism-Linked Endpoints:** Encourages for selecting cognitive and biological endpoints that are specifically aligned with the compound's hypothesized mechanism of action (e.g., using vascular markers for flavanols or neuroimaging for connectivity), rather than relying on generic tools. **4. Pragmatic, Long-Term RCTs:** Calls for the execution of strong, adequately powered, long-duration randomized controlled trials (e.g., 6-18 months) to detect clinically meaningful changes in cognitive trajectories, particularly in aging or impaired populations.

Formulation-Aware Trial Design

The era of treating complex extracts as "black boxes" must end. Future trials should adopt a "formulation-aware" design philosophy. This entails explicitly validating exposure metrics before assessing cognitive outcomes. For instance, trials involving hydrophobic polyphenols should mandate pharmacokinetic confirmation of systemic absorption. Furthermore, endpoint selection must align with the compound's hypothesized mechanism of action utilizing vascular markers (e.g., flow-mediated dilation) for cocoa flavanols, or specific attention-switching tasks for cholinergic agents like sage, rather than relying solely on generic screening tools.

Standardization and Reporting Transparency

Reproducibility is the bedrock of clinical evidence. Researchers must adopt higher standards of transparency regarding the "identity" of the intervention. Minimum reporting standards should include detailed chemoprofiles, batch-to-batch consistency data, and precise extraction ratios (e.g., Drug Extract Ratio). Without this granular detail, distinguishing between the failure of a compound and the failure of a specific low-quality preparation remains impossible.

Prioritizing Long-Term and Pragmatic RCTs

While acute studies provide valuable mechanistic insight, the true public health potential of these interventions lies in modifying the trajectory of cognitive aging. There is an urgent need for adequately powered, long-duration RCTs (spanning 6 to 18 months) particularly in populations with Mild Cognitive Impairment (MCI). Detecting clinically meaningful divergence in cognitive decline requires time, and short-term studies risk underestimating the potential of neuroprotective agents.

Mechanism-Linked Outcomes

Finally, to bridge the gap between subjective behavior and objective biology, future research should integrate biomarker analysis. Where feasible, trials should incorporate neuroimaging modalities (e.g., fMRI to assess functional connectivity, as seen in resveratrol research) or blood-based biomarker panels (e.g., BDNF, inflammatory cytokines). This "triangulation" of evidence (linking bioavailability, biological mechanism, and cognitive behavior) is essential

for validating the therapeutic utility of plant-derived bioactives.

CONCLUSION

The therapeutic landscape for cognitive enhancement is evolving. The synthesized evidence indicates that plant-derived bioactive compounds are no longer merely "alternative" remedies but are plausible, and in some cases clinically meaningful, modulators of human memory and attention. However, the translation of this potential into reliable outcomes is strictly governed by three variables: population baseline, endpoint sensitivity, and (most critically) formulation quality. Our review identifies a "layer of consistency" among the candidate agents. Bacopa monnieri, cocoa flavanols, and sage demonstrate the most coherent signals across well-controlled human studies. Similarly, saffron has established a robust profile specifically within Alzheimer's disease pathology. Perhaps most notably, the efficacy of curcumin and resveratrol serves as a proof-of-concept for the role of modern delivery systems; their clinical success is inextricably linked to technologies that overcome their native poor bioavailability. Conversely, the widely used Ginkgo biloba (EGb 761) displays a divergent profile, offering reliable symptomatic support in dementia but lacking consistent "nootropic" efficacy in healthy, younger adults. Ultimately, the future of this field does not lie in discovering new compounds, but in better understanding the ones we have. Moving forward, "statistically significant" results must be weighed against "pharmacokinetic reality." Progress will depend on a shift toward formulation-aware trial designs that align pharmacokinetic–pharmacodynamic (PK–PD) data with rigorous cognitive testing. Only by bridging the gap between chemical standardization and clinical observation can we unlock the full neuroprotective potential of the botanical pharmacopeia.

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