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Research paper

Curcumin and Neurocognitive Health: Mechanistic Insights and Translational Clinical Evidence

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Abstract

Neurocognitive decline represents a growing public health concern, with limited disease-modifying therapeutic options currently available. Curcumin, a polyphenolic compound derived from Curcuma longa, has attracted interest due to its proposed neuroprotective properties, however, translating experimental findings into consistent clinical benefits remains uncertain. This narrative review synthesises mechanistic, preclinical, and clinical evidence examining the role of curcumin in neurocognitive health and highlights key translational challenges. Experimental studies demonstrate modulation of oxidative stress, neuroinflammatory signalling, amyloid aggregation, and neurotrophic pathways, supporting biological plausibility. Preclinical models frequently report improvements in learning and memory, though effects often occur at exposure levels not readily achievable in humans. Clinical evidence remains heterogeneous and influenced by formulation, bioavailability, dosage, intervention duration, and cognitive assessment methods. Conventional curcumin preparations generally show limited cognitive benefit, whereas selected trials using enhanced-bioavailability formulations report modest improvements, primarily in non-demented older adults. Curcumin supplementation is generally well tolerated, although long-term safety data remain limited. Overall, despite compelling mechanistic rationale, current clinical evidence is insufficient to support routine use of curcumin for neurocognitive enhancement or treatment of neurodegenerative disease, underscoring the need for rigorously designed trials using standardised formulations and robust cognitive and biomarker-based outcomes.

Keywords: *Curcumin; Neurocognition; Neuroinflammation; Polyphenols.*

1. Introduction

Neurocognitive decline represents a major global health challenge, with increasing prevalence driven by population ageing and the rising burden of neurodegenerative disorders. Conditions such as mild cognitive impairment and Alzheimer's disease are associated with progressive deterioration of memory, executive function, and quality of life, imposing substantial social and economic strain on healthcare systems worldwide [1], [2]. Despite advances in pharmacological research, current therapeutic options remain limited, offering modest symptomatic benefit without clearly altering disease progression [3].

Growing recognition of the multifactorial pathophysiology underlying cognitive ageing has shifted attention toward chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired synaptic plasticity as key contributors to neuronal vulnerability [4], [5]. Within this framework, nutritional and bioactive compounds have emerged as potential adjunctive strategies aimed at supporting neuroprotection rather than serving as disease-modifying therapies. Dietary polyphenols have received sustained interest due to their antioxidant, anti-inflammatory, and signalling-modulatory properties [6].

Curcumin, the principal bioactive polyphenol derived from Curcuma longa, has been extensively investigated for its biological activity. Literature indicates that curcumin may influence multiple molecular pathways relevant to neurodegeneration, including regulation of inflammatory mediators, attenuation of oxidative damage, modulation of amyloid aggregation, and enhancement of neurotrophic signalling [7 - 9]. These multimodal properties have positioned curcumin as one of the most widely studied nutraceuticals in relation to brain health. Despite more than two decades of investigation, translation of experimental findings into consistent clinical benefit has proven challenging. Human studies evaluating curcumin supplementation have reported heterogeneous results, influenced by variation in formulation, bioavailability, dosage, intervention duration, baseline cognitive status, and outcome assessment tools [10 - 12]. Curcumin's poor oral bioavailability has been identified as a major barrier to therapeutic efficacy, prompting the development of enhanced delivery systems [13].

Given the expanding but fragmented nature of literature, there is a need for an integrative synthesis that critically distinguishes mechanistic plausibility from clinically meaningful evidence. Interpretation of curcumin's neurocognitive effects, therefore, requires careful consideration of the hierarchy of evidence, recognising the differing inferential value of in vitro studies, animal models, and human intervention trials [14].

The objective of this narrative review is to synthesise current mechanistic, preclinical, and clinical evidence examining the effects of curcumin on neurocognitive function. The review evaluates proposed biological mechanisms, summarises findings from experimental and human studies, discusses limitations related to bioavailability and study design, and identifies key challenges and future research priorities relevant to translational application.

2. Methods

This narrative review synthesised mechanistic, preclinical, and clinical evidence examining the role of curcumin in neurocognitive health. A narrative approach was adopted due to substantial heterogeneity in study designs, curcumin formulations, populations, and cognitive outcome measures, which limited the feasibility of quantitative synthesis [15].

Literature searches were conducted in PubMed, Scopus, and Web of Science for articles published up to December 2025 using combinations of keywords including “curcumin,” “cognition,” “neuroprotection,” “neuroinflammation,” “Alzheimer’s disease,” “mild cognitive impairment,” “bioavailability,” and “clinical trials.” Reference lists of relevant articles were also screened to identify additional studies. Studies were included if they: (i) investigated curcumin or curcuminoids, (ii) reported outcomes related to neurocognitive function or relevant biological mechanisms, and (iii) were conducted as in vitro studies, animal experiments, clinical trials, or observational studies. Studies not available in English or not directly related to neurocognitive outcomes were excluded.

Although a formal risk-of-bias assessment was not performed due to the narrative design, consideration was given to study design, sample size, intervention duration, and methodological quality when interpreting clinical evidence. Greater emphasis was placed on randomised controlled trials and studies employing validated cognitive outcome measures.

3. Mechanisms of Action of Curcumin in Neurocognitive Function

Curcumin has been proposed to influence neurocognitive health through multiple biological pathways implicated in neuronal ageing and neurodegeneration. These mechanisms primarily involve modulation of oxidative stress, neuroinflammatory signalling, protein aggregation, and synaptic plasticity [16]. While experimental studies provide strong mechanistic plausibility, the clinical relevance of many of these pathways remains constrained by limited systemic and central nervous system exposure following oral administration.

3.1. Oxidative stress modulation

Oxidative stress is a central contributor to neuronal dysfunction and age-related cognitive decline. Curcumin demonstrates antioxidant activity through both direct free-radical scavenging and indirect activation of endogenous defence systems, including nuclear factor erythroid 2–related factor 2 (Nrf2) signalling. Experimental studies consistently demonstrate reductions in lipid peroxidation and upregulation of antioxidant enzymes following curcumin exposure [7], [9]. However, many of these effects are observed at concentrations substantially higher than those typically achieved in human plasma following oral supplementation. As a result, antioxidant actions may function as indirect modulatory mechanisms rather than primary drivers of clinical cognitive benefit.

3.2. Regulation of neuroinflammatory signalling

Chronic neuroinflammation, characterised by sustained microglial activation and elevated pro-inflammatory cytokine production, plays a key role in neurodegenerative progression. Curcumin has been shown to suppress inflammatory signalling through inhibition of nuclear factor kappa B (NF-κB) activation and downregulation of mediators such as tumour necrosis factor-α and interleukin-1β [7], [17]. Although these anti-inflammatory effects are among the most consistently reported in experimental models, translation to human neuroinflammation remains limited. The extent to which orally administered curcumin reaches the brain at concentrations sufficient to influence inflammatory pathways in vivo remains uncertain.

3.3. Effects on amyloid and tau pathology

Curcumin exhibits affinity for amyloid-β aggregates and has been shown to inhibit fibril formation and promote clearance in experimental systems.[8,18] In animal models of Alzheimer’s disease, curcumin administration has been associated with reduced amyloid plaque burden and attenuated microglial activation. In contrast, clinical studies have not consistently demonstrated corresponding reductions in amyloid burden, highlighting a translational gap between experimental efficacy and human outcomes. This discrepancy may reflect differences in dosing, disease stage, intervention timing, and the complexity of human neurodegenerative pathology, which is not fully captured by experimental models.

3.4. Neurotrophic signalling and synaptic plasticity

Curcumin has been reported to enhance brain-derived neurotrophic factor (BDNF) expression and activate signalling pathways involved in neuronal survival and synaptic plasticity.[19] In animal studies, these effects are associated with improvements in learning and memory performance. From a translational perspective, neurotrophic modulation represents a mechanism potentially relevant to early cognitive ageing rather than advanced neurodegeneration. However, evidence supporting clinically meaningful neurotrophic effects in humans remains limited and may be influenced by substantial interindividual variability in absorption and metabolism.

3.5. Emerging mechanisms

Additional mechanisms, including epigenetic modulation and regulation of gene expression, have been proposed, largely based on experimental observation [20]. While these pathways are mechanistically intriguing, current human data are insufficient to establish causal relevance for neurocognitive outcomes. At present, such mechanisms should be regarded as hypothesis-generating rather than clinically substantiated.

Collectively, curcumin exhibits pleiotropic biological activity across multiple pathways relevant to neurocognitive health. However, the majority of mechanistic evidence is derived from in vitro and animal studies conducted under exposure conditions that may not be readily achievable in humans, underscoring the need for cautious interpretation when inferring clinical efficacy.

4. Preclinical Evidence

Preclinical investigations have provided the foundational rationale for exploring curcumin as a neuroprotective compound. These studies include in vitro experiments and animal models designed to elucidate biological mechanisms, behavioural outcomes, and neuropathological changes. While such studies offer important mechanistic insight, their translational value must be interpreted cautiously, as experimental conditions often differ substantially from human physiology and exposure levels.

4.1. In vitro evidence

In vitro studies have demonstrated that curcumin can exert neuroprotective effects across multiple experimental systems. Neuronal cell culture models indicate that curcumin reduces oxidative injury, attenuates inflammatory mediator release, and protects against amyloid-β–induced cytotoxicity. These effects are commonly attributed to the modulation of redox-sensitive signalling pathways and the inhibition of pro-inflammatory transcription factors [7], [17]. Additional experimental work suggests that curcumin may interfere with amyloid fibril formation and destabilise pre-existing aggregates, supporting early hypotheses regarding its potential relevance to Alzheimer's disease pathology [8], [18]. However, the concentrations required to achieve these effects in vitro frequently exceed levels attainable through oral supplementation, limiting direct translational relevance.

4.2. Animal models of cognitive dysfunction

Animal studies have further explored curcumin's neurobiological effects using models of ageing, neuroinflammation, and amyloid pathology. In rodent models, curcumin supplementation has been associated with improvements in learning and memory performance, alongside reductions in oxidative stress markers and neuroinflammatory signalling [8], [19]. In transgenic mouse models of Alzheimer's disease, curcumin administration has been reported to reduce amyloid plaque burden and microglial activation, and improve behavioural outcomes [8], [18]. These findings support biological plausibility but are influenced by factors such as early intervention timing, high relative dosing, and species-specific metabolism.

4.3. Limitations of preclinical models

Despite consistent mechanistic findings, several limitations constrain the interpretation of preclinical data. Experimental studies often employ doses that are not physiologically achievable in humans, particularly given curcumin's limited oral bioavailability. Moreover, animal models capture only selected aspects of complex neurodegenerative diseases and may not accurately reflect human cognitive decline. Behavioural outcomes in rodents also vary across studies depending on testing paradigms, duration of exposure, and baseline pathology, contributing to heterogeneity in reported outcomes. Importantly, improvements in animal cognitive performance cannot be assumed to translate directly into clinically meaningful benefits in humans.
Overall, preclinical studies support the biological plausibility of curcumin's neuroprotective effects. However, limitations related to dose relevance, disease modelling, and species differences restrict direct extrapolation to clinical populations, underscoring the need for confirmation through rigorously designed human trials.

5. Clinical Evidence

Human studies examining the effects of curcumin on neurocognitive outcomes have produced heterogeneous results. Interpretation of clinical efficacy is complicated by wide variability in formulation, dosage, intervention duration, baseline cognitive status, and outcome assessment tools. Consequently, findings must be evaluated within a hierarchical framework that distinguishes disease stage and methodological quality.

5.1. Curcumin in established neurodegenerative disease

Early randomised controlled trials conducted in patients with Alzheimer's disease predominantly utilised conventional curcumin preparations and generally failed to demonstrate significant cognitive benefit [11]. These null findings have been attributed to poor oral bioavailability, limited central nervous system exposure, and relatively short intervention durations [13]. In addition, several studies relied on global cognitive screening tools, which may lack sensitivity to detect incremental changes in progressive neurodegenerative disease [14]. Collectively, available evidence does not support curcumin as an effective therapeutic intervention for established Alzheimer's disease.

5.2. Mild cognitive impairment and early cognitive ageing

More recent studies have shifted focus toward individuals with mild cognitive impairment or age-associated cognitive decline. Trials employing enhanced-bioavailability formulations have reported modest improvements in selected cognitive domains, particularly memory and attention [10]. These benefits have primarily been observed in non-demented older adults and are generally domain-specific neuropsychological assessments rather than global screening instruments [10], [11]. Notably, studies reporting benefits have tended to employ longer intervention durations and more sensitive neuropsychological assessments. However, reported effect sizes remain small, and the clinical significance of observed improvements remains uncertain.

5.3. Neuroimaging and biomarker outcomes

Neuroimaging findings from selected trials have suggested potential reductions in amyloid and tau accumulation following supplementation with bioavailable curcumin formulations [10]. While these findings are of interest, they are limited by small sample sizes, short follow-up periods, and a lack of replication across independent cohorts. At present, biomarker evidence should be interpreted as preliminary and insufficient to establish disease-modifying activity.

5.4. Observational evidence

Observational studies examining habitual turmeric or curry consumption have reported associations with better cognitive performance, particularly within Asian populations [12]. While supportive of potential long-term dietary relevance, such associations cannot establish causality and may reflect broader dietary patterns, lifestyle behaviours, or cultural factors.

Overall, clinical evidence remains inconsistent and formulation-dependent. While curcumin does not appear effective as a treatment for established neurodegenerative disease, modest benefit in early cognitive ageing cannot be excluded. However, current findings remain insufficient to support routine clinical use.

Interpretation of clinical findings is further complicated by several methodological limitations. Many trials are characterised by relatively small sample sizes and short intervention durations, which may limit statistical power and the ability to detect clinically meaningful changes in cognitive outcomes. In addition, placebo effects and practice effects associated with repeated neuropsychological testing may contribute to observed improvements, particularly in studies involving non-demented populations. Variability in baseline cognitive status, outcome measures, and study design further contributes to heterogeneity across findings.

Recent clinical investigations continue to report mixed outcomes. For example, trials using enhanced-bioavailability formulations have demonstrated modest improvements in specific cognitive domains, whereas others have reported no significant effects, reinforcing the influence of formulation and study design on outcomes [21], [22]. Furthermore, the clinical relevance of observed changes remains uncertain, as effect sizes are often small and not consistently associated with functional improvements. These limitations highlight the need for larger, longer-duration trials with standardised methodologies and robust cognitive and biomarker-based endpoints.

Table 1: Summary of Key Clinical Studies Evaluating Curcumin and Neurocognitive Outcomes

Study (APA style)	Population	Sample Size	Formulation	Dose	Duration	Key Findings
Small et al. (2018)[10]	Non-demented older adults	40	Bioavailable curcumin (Theracurmin)	90 mg twice daily	18 months	Improved memory and attention; reduced amyloid and tau binding (FDDNP-PET)
Rainey-Smith et al. (2016)[11]	Community-dwelling healthy older adults	96	Standard curcumin (Biocurcumax)	1500 mg/day	12 months	No consistent cognitive improvement; results were mixed with limited clinical significance
Cox et al. (2015)[21]	Healthy older adults	60	Solid lipid curcumin	400 mg (≈80 mg curcumin)	4 weeks	Improved working memory and sustained attention; reduced fatigue and improved mood
Wang et al. (2025)[22]	Meta-analysis (RCTs)	501 (pooled)	Various formulations	~0.8 g/day optimal	≥24 weeks	Significant improvement in global cognition; effects influenced by dose, duration, age, and population characteristics

6. Bioavailability of Curcumin

Curcumin's clinical application is substantially constrained by its limited oral bioavailability. Native curcumin exhibits low aqueous solubility, limited intestinal absorption, rapid metabolism, and fast systemic elimination, resulting in very low circulating concentrations following conventional oral intake [13], [23], [24].

After ingestion, curcumin undergoes extensive first-pass metabolism in the intestinal epithelium and liver, producing glucuronide and sulphate conjugates that demonstrate reduced biological activity relative to the parent compound [23]. Consequently, plasma concentrations of unconjugated curcumin following standard supplementation are often low or undetectable, even at high oral doses [13].

To improve systemic exposure, multiple formulation strategies have been developed, including co-administration with bioenhancers such as piperine, lipid-based carriers, phospholipid complexes, nanoparticles, and micellar systems [24-26]. These approaches have demonstrated significant increases in curcumin absorption and circulating levels compared with unformulated preparations, although the magnitude of enhancement varies across formulation and study design [24], [25].

Evidence regarding curcumin's distribution to central nervous system tissues in humans remains limited. While experimental studies suggest potential blood-brain barrier permeability, human data are sparse, and most pharmacokinetic studies focus primarily on plasma concentrations rather than direct tissue exposure [27].

Variation in formulation represents an important source of heterogeneity across clinical trials. Studies reporting cognitive benefits have predominantly utilised enhanced-bioavailability preparations, whereas trials employing conventional curcumin powders have more frequently reported null findings [10], [11], [24]. This variability limits cross-study comparability and complicates the interpretation of efficacy.

Interindividual differences in gastrointestinal physiology, metabolic capacity, gut microbiota composition, and dietary context may further contribute to variability in absorption and responsiveness [28]. Together, these factors highlight bioavailability as a central determinant of translational potential.

Different formulation strategies have demonstrated variable improvements in curcumin bioavailability, with important implications for clinical efficacy. Co-administration with piperine enhances bioavailability primarily through inhibition of hepatic and intestinal glucuronidation, leading to increased systemic exposure. Lipid-based and nanoparticle formulations improve aqueous solubility and facilitate intestinal absorption, while phospholipid complexes (e.g., curcumin–phosphatidylcholine) and micellar systems further enhance bioavailability and may improve tissue distribution. Notably, clinical studies reporting cognitive benefits have predominantly utilised enhanced-bioavailability formulations such as Theracurmin or solid lipid curcumin, whereas trials employing conventional curcumin preparations have more frequently reported null findings [21], [23]. Recent systematic reviews and meta-analyses also indicate that formulation type is a critical

determinant of therapeutic response, with bioavailable formulations demonstrating more consistent, though modest, cognitive benefits [22], [30]. These findings highlight the importance of formulation-specific considerations in both research and clinical applications of curcumin.

7. Safety and Tolerability

Curcumin has a long history of dietary exposure and has been extensively evaluated in human studies, contributing to its reputation as a compound with a favourable safety profile. Early phase clinical trials and subsequent intervention studies consistently report low toxicity, even at relatively high oral doses [30-32].

Dose-escalation studies indicate that curcumin is well tolerated at doses ranging from 2 to 8 g/day, with no dose-limiting toxicity observed [30], [31]. Reported adverse effects were predominantly mild gastrointestinal symptoms, including nausea, bloating, and diarrhoea, and were reversible upon discontinuation. Serious adverse events attributable to curcumin have not been consistently documented in controlled human studies [32-34].

Subsequent clinical investigations across diverse populations have reinforced these findings, supporting the overall tolerability of curcumin when administered orally over short to moderate durations [33], [35]. Importantly, safety profiles appear broadly comparable across conventional and enhanced-bioavailability formulations, although increased systemic exposure underscores the need for formulation-specific evaluation [23-26], [36].

Despite reassuring short-term data, limitations remain. Most clinical trials have been of limited duration and sample size, restricting the detection of rare or long-term adverse effects. Potential interactions with anticoagulant therapy and effects in populations with chronic illness or polypharmacy remain insufficiently characterised [33], [34]. These gaps are particularly relevant given the increasing commercial availability of high-dose curcumin supplements.

Overall, current human evidence supports curcumin as a generally safe and well-tolerated nutraceutical when consumed at doses commonly investigated in clinical research. However, the expanding use of high-dose and bioavailable formulations highlights the importance of continued pharmacovigilance and long-term safety evaluation to ensure responsible translational application.

8. Limitations of the Current Evidence

Several limitations constrain the interpretation of the current evidence regarding curcumin and neurocognitive outcomes. A major concern is the heavy reliance on in vitro and animal studies, which are frequently conducted using concentrations and exposure conditions that are not physiologically achievable in humans. While such models provide valuable mechanistic insight, they may overestimate therapeutic potential when extrapolated to clinical settings.

Human intervention studies are characterised by substantial heterogeneity in formulation, dosage, duration, and outcome assessment. This variability limits cross-study comparability and complicates the synthesis of findings. Differences in bioavailability between formulations represent a critical confounding factor, as studies employing conventional preparations and those using enhanced-delivery systems are not pharmacokinetically equivalent. Many clinical trials are further limited by small sample sizes and short intervention periods. Given the slow and progressive nature of cognitive decline and neurodegenerative disease, such study designs may be insufficient to detect meaningful or sustained cognitive change. Consequently, null findings may reflect inadequate study duration or statistical power rather than true biological inefficacy.

Outcome assessment also represents a significant limitation. Several studies rely on global cognitive screening tools with limited sensitivity to subtle domain-specific changes, particularly in non-demented populations. In addition, repeated cognitive testing may introduce practice effects, potentially inflating apparent benefit in short-term trials. The limited incorporation of biomarker-based endpoints further restricts the mechanistic interpretation of observed cognitive outcomes. These methodological limitations contribute to uncertainty regarding the magnitude, consistency, and clinical relevance of curcumin's neurocognitive effects.

Overall, while existing evidence supports biological plausibility, the current literature remains insufficient to establish definitive clinical efficacy. These limitations highlight the need for adequately powered, longer-duration trials employing standardised bioavailable formulations and sensitive cognitive and biomarker-based outcome measures.

9. Future directions

Future research should prioritise well-designed randomised controlled trials using standardised, bioavailable curcumin formulations with clearly characterised pharmacokinetic profiles. Studies conducted in populations at early stages of cognitive decline may offer greater sensitivity than trials in established neurodegenerative diseases. Incorporation of biomarker-based outcomes, including neuroimaging and inflammatory or oxidative stress markers, would strengthen mechanistic interpretation. In addition, investigation of interindividual variability related to metabolism and gut microbiota may help identify subgroups most likely to benefit from supplementation. Long-term safety and effectiveness should remain key considerations as curcumin use continues to expand.

10. Clinical and Public Health Implications

From a clinical and public health perspective, curcumin cannot currently be recommended as a therapeutic intervention for established neurodegenerative diseases such as Alzheimer's disease. However, its potential role as an adjunctive strategy in early cognitive ageing or in populations at risk of cognitive decline warrants further investigation. The use of standardised, bioavailable formulations and appropriate dosing regimens remains critical for achieving potential benefits. Clinicians and researchers should interpret existing evidence cautiously, recognising the influence of formulation, study design, and population characteristics on observed outcomes.

11. Conclusion

Curcumin demonstrates strong mechanistic plausibility for neuroprotection through antioxidant, anti-inflammatory, and neurotrophic pathways. However, translation of these experimental findings into consistent clinical benefit remains limited. Human evidence is heterogeneous and strongly influenced by formulation, bioavailability, duration, and outcome assessment. Trials using conventional curcumin

preparations have generally reported null findings, whereas modest cognitive effects have been observed in selected studies employing enhanced-bioavailability formulations, primarily in non-demented populations. At present, available evidence does not support curcumin as a therapeutic intervention for established neurodegenerative disease. Further well-designed randomised trials using standardised bioavailable formulations, longer intervention periods, and sensitive cognitive and biomarker-based outcomes are required to clarify its potential role in cognitive ageing.

12. Declarations

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None

Conflict of Interest

None declared

Ethical Approval

Not required

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