Review Article

Curcumin Nanoformulations For Neurological and Psychiatric Disorders: Delivery Strategies, Preclinical Evidence and Translational Prospects

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Abstract

Background: Curcumin has antioxidant, anti-inflammatory, and anti-aggregation properties relevant to neurological and psychiatric disorders. However, poor water solubility, instability, rapid metabolism, and low oral bioavailability limit its brain exposure. Nanoformulaitons and intranasal delivery offer potential ways to overcome these barriers.

Objective: To review how curcumin nanoformulations improve brain delivery, assess preclinical and clinical evidence in neurological and psychiatric disorders, and identify evidence relevant to adolescents.

Data Source: Targeted searches of PubMed, ScienceDirect, Google Scholar, and relevant journal archives using combined terms related to curcumin, nanoformulations, neurodegenerative diseases, Alzheimer's disease, epilepsy, cognition, and blood-brain barrier. Additional searches addressed children and adolescents. Relevant studies were synthesised narratively. Primary studies were classified according to brain curcumin measurement and inclusion of free-curcumin comparators and empty-carrier controls.

Data Synthesis: The review examines the delivery barriers and strategies involving liposomes, lipid and polymeric nanoparticles, protein-based carriers, nanoemulsions, exosomes, and intranasal administration. Selected preclinical studies demonstrated nanoformulations markedly increased curcumin brain exposure. Intranasal lactoferrin nanoparticles produced approximately 3.2-fold higher brain curcumin exposure than an intranasal suspension in rats. Intravenous nanostructured lipid carriers achieved measurable cerebral exposure when free curcumin was undetectable. However, many studies inferred brain delivery from behavioural or biochemical improvements rather than directly measuring unchanged curcumin. Some also lacked free-curcumin comparators or empty-carrier controls, limiting attribution of benefits to the formulation. Human findings remain limited and inconsistent, with insufficient evidence to establish adolescent-specific efficacy or safety.

Conclusion: Curcumin nanoformulations show preclinical promise, but clinical benefits remain unproven, particularly in adolescents. Priorities include measuring unchanged curcumin in brain tissue and cerebrospinal fluid, incorporating appropriate comparator and carrier controls, and conducting product-specific clinical trials with adequate safety monitoring. These steps are essential to determine whether improved delivery translates into meaningful patient benefit.

Keywords: Curcumin; Nanoparticles; Blood-Brain Barrier; Nervous System Diseases; Adolescent; Drug Delivery Systems.

Introduction

Neurological and psychiatric disorders impose a substantial global burden of illness and disability, underscoring the importance of effective prevention, treatment and rehabilitation.[1] Curcumin, the principal curcuminoid of turmeric (Curcuma longa), has attracted interest because of its antioxidant and anti-inflammatory properties.[2] This review critically examines curcumin nanoformulations and the preclinical and clinical evidence for their application in central nervous system disorders.

Curcumin acts on several pathways at once. It promotes nuclear translocation of Nrf2 and raises the activity of antioxidant enzymes such as haem oxygenase-1, superoxide dismutase and catalase, and it inhibits IKKβ and NF-κB signalling, which lowers the production of IL-1β, TNF-α, IL-6, COX-2 and iNOS and dampens microglial activation.[1] It is also reported to inhibit amyloid-β aggregation.[1] These activities have made curcumin a candidate for Alzheimer's disease, Parkinson's disease, stroke, epilepsy and depression.

The therapeutic use of curcumin is limited by its pharmacokinetics. Its aqueous solubility is about 11 ng/mL, its half-life in phosphate buffer at pH 7.4 is about 10 minutes, and its oral bioavailability is below 1%, with less than 0.1% of an oral dose estimated to reach brain tissue.[2] Even at 4 to 8 g/day, plasma concentrations in people reach only about 0.4 to 1.7 µmol/L.[1]

Nanotechnology offers a way to address these limits. Polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, micelles, protein-based carriers and exosomes have all

been loaded with curcumin and tested in models of central nervous system (CNS) disease.[3-5] Quantitative findings from open-access primary studies are reported wherever they are available, so that the strength of each claim can be judged.

Most of this literature is framed around ageing and adult disease. Adolescence, however, is the period in which many psychiatric disorders first appear and in which the brain is still maturing.[6,7] A compound that acts on oxidative stress and neuroinflammation, is sold as a food supplement, and is being reformulated for the brain is of obvious interest for young people, yet the evidence for that age group has not been gathered in one place. This review follows the path from formulation to brain, asks how strongly brain-delivery claims are supported, and then examines what is known, and not known, for adolescents.

1. Review approach

This narrative review does not follow a formal systematic-review protocol. Literature was identified through targeted searches of PubMed, ScienceDirect, Google Scholar, and the archives of relevant peer-reviewed journals. Searches used "curcumin" alone and in combination with "nanoformulations," "neurodegenerative diseases," "Alzheimer's disease," "epilepsy," "cognition," and "blood-brain barrier." Searches were conducted up to 10 October, 2026. Articles were selected for their relevance and substantive contribution to understanding curcumin nanoformulations, brain delivery, and neurological and psychiatric applications. The selected literature was synthesised narratively to discuss formulation strategies, pharmacokinetic and blood-brain barrier challenges, preclinical and clinical findings, safety considerations, and translational limitations. Numerical results are reported as stated in the cited papers. Each primary study was classified by whether curcumin was measured in brain, whether a free-curcumin comparator was used, and whether an empty-carrier control was included.

2. Neuropharmacology of curcumin

The neuroprotective profile of curcumin rests on overlapping antioxidant, anti-inflammatory and anti-aggregation actions. Beyond the Nrf2 and NF-κB effects described above, curcumin binds amyloid-β oligomers directly.[1] In Parkinson's disease models it inhibits α-synuclein oligomerization and aggregation, protects the mitochondrial respiratory chain in rotenone-treated mice, reduces iron-positive cells in 6-hydroxydopamine models and modulates microglial JAK/STAT signalling. It has also been described as a positive allosteric modulator of α7 nicotinic receptors.[8] Whether neuroinflammation is a cause or a consequence of neuronal loss remains controversial.[8] Alzheimer's disease is increasingly viewed as a multi-hit disorder in which neuroinflammation links amyloid, tau and vascular factors, while mitochondrial and lysosomal dysfunction amplify proteotoxic stress. This is the kind of multi-target biology that curcumin is proposed to address.[9]

In epilepsy, proposed actions include modulation of cell-survival signalling, oxidative stress, apoptosis and inflammation, together with epigenetic effects on histone acetylation.[10] A meta-analysis of 23 rodent studies found that curcumin lengthened seizure latency (standardized mean difference 1.85, 95% CI 1.05 to 2.64; 11 studies), shortened Morris water maze escape latency, lowered malondialdehyde and raised glutathione and superoxide dismutase. Medium and high doses gave more consistent results, although publication bias was detected and many studies did not report blinding.[11] In depression, clinical studies have reported lower IL-1β, TNF-α and salivary cortisol and higher plasma BDNF with curcumin than with placebo.[12]

These mechanistic data need careful reading. Curcumin is a pan-assay interference compound, with metal chelation, redox reactivity and self-aggregation that can distort in vitro assays. Studies disagree on whether it promotes or inhibits amyloid fibril formation, and degradation products such as vanillin can contribute to observed effects, so activity cannot always be attributed to the parent compound.[13] Curcumin can also act as a pro-oxidant at high concentrations, and much of the mechanistic rationale comes from ageing biology (oxidative stress, mitochondrial dysfunction, impaired protein homeostasis and neuroinflammation).[14]

3. Pharmacokinetic and blood-brain barrier challenges

Curcumin delivery to the brain faces two main barriers: poor systemic availability and restricted passage across the blood-brain barrier (BBB). Its reported aqueous solubility is about 11 ng/mL, and its half-life in phosphate buffer at pH 7.4 is about 10 minutes;[2] although a solubility of about 0.4 µg/mL in water at gastric pH has also been reported.[15] After oral dosing, more than 90% of the dose fails to reach the circulation as unchanged curcumin, being excreted

or converted by glucuronidation and sulfation into inactive conjugates.[2] Absolute oral bioavailability is about 1% in rats. In volunteers, a 2 g dose produced plasma curcumin concentrations below 10 ng/mL at 1 hour, while co-administration of 20 mg piperine reportedly increased bioavailability by 2000%.[2] Curcumin undergoes more extensive metabolism in human than in rat intestinal preparations in vitro, which limits extrapolation of rodent findings to humans.[13,16] Moreover, most bioavailability estimates measure total curcumin, including inactive conjugates, which probably overstates active exposure.[2]

The second barrier is the blood-brain barrier. Passive brain entry is minimal, so a formulation that raises systemic exposure still needs a strategy to reach or cross it.[2] Nanoparticles below about 200 nm with a positive surface charge have been reported to cross the BBB more readily; animal CNS studies favour sizes of 50 to 100 nm, and PEG coating reduces opsonisation.[4] Other reports suggested that smaller, negatively charged particles cross more easily,[17] so surface charge alone is not a reliable design rule. Delivery can also be engineered through carrier-mediated pathways (GLUT1 and LAT1), receptor-mediated transcytosis (transferrin, lactoferrin, TET-1 and the B6 peptide), adsorptive-mediated transcytosis (TAT, penetratin and chitosan), intranasal delivery and exosomes. Of these, receptor-mediated transcytosis, 3D-prinitng and exosomes are considered the most promising approaches.[2]

Interpretation of brain-delivery claims is further complicated by assays that report total curcumin, whole-brain homogenates that obscure regional distribution, and comparisons that do not use free curcumin administered by the same route.

4. Nanoformulation strategies for brain delivery

4.1. Lipid-based carriers

Liposomes raise the apparent solubility of curcumin from about 11 ng/mL to roughly 1 to 10 mg/mL, with preclinical plasma AUC increases of 5- to 50-fold over unformulated curcumin depending on lipid composition and particle size. Their drawbacks include oxidation, leakage, reticuloendothelial clearance, a 2 to 8 °C cold chain, and a shelf life of 6 to 12 months.[2] A DPPC-cholesterol liposome of about 180 nm (encapsulation efficiency 68%) was tested in human microglial and astrocyte lines and in mouse cortical slices exposed to lipopolysaccharide. At high concentrations it was more cytotoxic than free curcumin (IC50 5.3 versus 19.6 µM in microglia and 2.1 versus 11.6 µM in astrocytes), but at 0.01 µM it reduced inflammatory gene expression and reversed the loss of slice viability at least as well as free curcumin, whereas empty liposomes were inactive; no in vivo data were reported.[18]A patented liposomal curcumin of about 120 nm improved motor function and reduced apoptosis in DJ-1 knockout rats, a genetic model of Parkinson's disease.[4]

SLNs and NLCs provide the strongest quantitative brain pharmacokinetic data. After intravenous dosing at 4 mg/kg in amyloid-β-treated rats, cerebral AUC_{0-t} was 505.76 ± 38.4 ng/g-1h for curcumin NLCs and 116.31 ng/g-1h for SLNs, whereas curcumin was undetectable in brain after free curcumin.[2, 19, 20] Plasma AUC_{0-t} followed the same order: 513 ± 90.79, 266.41 ± 45.65 and 91.99 ± 3.85 ng/mL^{-1}h for NLCs, SLNs and solution respectively.[20]

In rats given amyloid-β, curcumin NLCs raised brain curcumin (505.76 ± 38.4 ng/g^{-1}h), lowered oxidative-stress markers and improved spatial memory.[19] In four-month-old TgCRND8 transgenic mice and wild-type littermates, blank SLNs (176.0 nm) or curcumin SLNs (153.3 nm; 150 mg/kg intraperitoneally, three times weekly for 3 weeks; n = 5 per group) were both well tolerated, and the curcumin SLNs modulated tissue transglutaminase isoforms differently in wild-type and transgenic mice.[21] The unloaded-particle control makes this study particularly informative.

4.2. Polymeric nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles of 76 to 264 nm with encapsulation efficiencies above 78% release curcumin over days to weeks.[2] Surface modification with PEG and brain-targeting ligands, such as the B6 peptide in PLGA-PEG-B6 particles of about 150 nm, reduced hippocampal β-amyloid and tau hyperphosphorylation in Alzheimer's models.[4] A nanoparticle formulation of curcumin gave a six-fold higher brain AUC and a longer mean residence time than free curcumin in mice.[8] In a recent MPTP mouse model of Parkinson's disease, intravenous mPEG-PLGA curcumin nanoparticles (149.4 ± 87.6 nm, zeta potential -30.8 mV, 200 mg/kg/day for 7 days raised the ratio of phosphorylated to total Akt more than free curcumin ($P < 0.05$) and shifted the gut microbiota towards that of control animals, although brain curcumin was not measured.[22]

PLGA-PEG-B6 particles loaded with curcumin improved Morris water maze performance in APP/PS1 mice (n = 8 per group, 25 mg/kg/day) more than native curcumin, reduced hippocampal β-amyloid and tau phosphorylation and

showed good blood compatibility in vitro.[23] PLGA particles conjugated with the transferrin-receptor peptide CRT and co-loaded with curcumin and the β-secretase-site peptide S1 (139.8 ± 15.2 nm) improved Y-maze and object-recognition performance in transgenic mice and lowered β-amyloid, reactive oxygen species, TNF-α and IL-6, but curcumin encapsulation efficiency was only 21.4 ± 6.9%, far below the figure quoted above, and brain delivery was shown with a fluorescent dye rather than by measuring curcumin.[24] In primary hippocampal cultures, g7-modified PLGA nanoparticles carrying curcumin showed no apparent toxicity and decreased β-amyloid aggregates.[25]
Spherical 200 nm PLGA-PEG-lipid nano-constructs were taken up by 99.6% of macrophages within 24 hours, versus 14.4% for 1000 nm discoidal particles, and curcumin-loaded 200 nm particles lowered IL-1β, IL-6 and TNF-α production up to 6.5-fold in macrophages stimulated with amyloid-β fibers, although the authors note that BBB permeability studies are still needed.[26] An intramuscular PLGA-PEG-PLGA thermosensitive curcumin hydrogel improved water maze performance and reduced amyloid-β deposition without toxicity in aluminium-chloride-induced Alzheimer rats, but as sustained release depot it addresses adherence and steady blood levels more than BBB crossing.[27] PEG-functionalized carbon nanotubes loaded with curcumin (310 ± 7.92 nm, entrapment efficiency 91.4 ± 0.8%) gave higher brain curcumin 4 hours after administration,[28] although carbon-based carriers need particularly careful long-term safety assessment.

4.3. Protein-based and ligand-targeted carriers

Lactoferrin exploits receptor-mediated uptake. self-assembled curcumin-lactoferrin nanoparticles (84.8 ± 6.5 nm, PDI 0.078, zeta potential +22.8 mV, encapsulation efficiency 91.2%) raised apparent permeability across an MDCK monolayer approximately 48-fold over a curcumin suspension and protected PC12 cells from amyloid-β25-35 toxicity (viability 91.0% at 10 μM versus 68.4% in the model group and 87.2% with free curcumin). After intranasal dosing at 10 mg/kg in rats, brain $AUC_{0\text{-}8h}$ was 352.91ng/mL^{-1}h versus 108.90 ng/mL^{-1}h for an intranasal suspension (about 3.2-fold), brain C_{max} was 161.18 versus 44.99 ng/mL, and brain-targeting efficiency was 248.1%. Intravenous nanoparticles gave a lower brain AUC (167.00 ng/mL h) than the intranasal route, so route and carrier act together.[29]
Gelatin nanoparticles (141.27 ± 32.93 nm) decorated with the RVG29 peptide were given intravenously at 20 mg/kg for 7 days in rats with middle cerebral artery occlusion. Morris water maze landing time was 53 ± 8.89 s in treated rats and 28 ± 7.55 s in normal rats, while untreated model rats failed to land within 120 s. Brain curcumin was not quantified and no free-curcumin group was included.[30] Transferrin and TET-1 functionalization of PLGA systems have also been reported to improve brain targeting.[2] H-ferritin nanocages carrying curcumin showed improved water dispersibility, were non-toxic and crossed an in vitro BBB model. In 5xFAD mice (1 mg/kg twice weekly from 2 to 4 months of age) they produced mild cognitive benefits and reduced microgliosis and astrogliosis, and they lowered RAGE-mediated stress in blood cells from patients with Alzheimer's disease.[31]

4.4. Nanoemulsions, micelles and exosomes

Nanoemulsions and self-nanoemulsifying systems (droplets of 20 to 200 nm) have improved oral bioavailability and neuroprotection in cerebral ischaemia and Alzheimer's models, although the outcomes are mostly qualitative.[2] A self-nanomicellizing solid dispersion raised oral curcumin bioavailability 117-fold and, in aged APPSwe/PS1dE9 mice, prevented cognitive decline and returned performance towards that of younger animals without evident toxicity.[32]
Pache et al. (2026) reports that curcumin nanoemulsions suppress pro-inflammatory cytokines and oxidative stress more than free curcumin in preclinical anti-inflammatory models, and calls for large clinical evaluations, standardised formulation protocols and clear regulatory frameworks.[33] Curcumin-loaded exosomes (extracellular vesicles of 30 to 150 nm) distributed across brain regions after intranasal dosing in ischaemic mice and improved neurological scores at 3 days. Active loading can raise cargo up to 11-fold over passive loading but may damage exosome's native structure and targeting.[4]

4.5. Intranasal delivery

Intranasal administration uses olfactory and trigeminal pathways to bypass the BBB. In a murine haemorrhage model, intranasal curcumin exceeded intravenous brain levels at 12 hours, and transgenic mice showed reduced amyloid plaque burden after six months of intranasal treatment.[13] Practical limits include passive deposition of less than 10% of inspired air in the olfactory region, possible local metabolism of curcumin by olfactory cytochrome P450, and the need for an encapsulation efficiency above 80%.[13] A recent review of nanocarrier-based intranasal systems for epilepsy credit them with rapid onset, better bioavailability and patient compliance, but notes that comparisons with other platforms are lacking and that scalability, stability, mucosal safety and regulatory pathways remain

unresolved.[34] Table 1 summarises the platforms.

Table 1: Carrier platforms for curcumin delivery to the CNS.

Platform	Representative evidence	Main limitations
Liposomes	Plasma AUC 5- to 50-fold higher than unformulated curcumin in preclinical work[2]; anti-inflammatory effect in glia and brain slices at 0.01 μM[18]	Oxidation, leakage, cold chain, shelf life of 6 to 12 months[2]
SLNs and NLCs	Cerebral AUC_{0-t} in rates after 4mg/kg intravenously: 505.76ng/g·h (NLCs), 116.31 ng/g·h (SLNs) and undetectable (free curcumin)[2]; brain accumulation of 505.76 ng/g·h with NLCs in an amyloid model[19]	Aggregation and limited drug loading[3]
PLGA and PLGA-PEG	Lower hippocampal β-amyloid and tau phosporylation in Alzheimer's models[4,23]; stronger Akt signalling than free curcumin in MPTP mice[22]	Efficacy data mainly from transgenic or toxin models; encapsulation efficiency ranges from about 21% to above 78%.[2,24]
Protein-based (lactoferrin, gelatin, albumin, ferritin)	Intranasal brain AUC about 3.2-fold and Cmax about 3.6-fold higher than suspension[29]; RVG29-gelatin improved water maze performance after stroke[30]; ferritin nanocages crossed an in vitro BBB model[31]	Whole-brain homogenate only; n = 3 per time point[29]; no free-curcumin group in vivo[30]
Nanoemulsions, SNEDDS, and micelles	Better oral bioavailability and neuroprotection in ischaemia and Alzheimer's models[2]; 117-fold higher oral bioavailability with a nanomicellar dispersion[32]	Outcomes mostly qualitative[2,33]
Exosomes	Distribution across brain regions and better neurological scores after intranasal dosing[4]	Possible damage to exosome structure with active loading[4]
Intranasal route (any carrier)	Brain levels above intravenous at 12 hours in a haemorrhage model[13]	Less than 10% passive olfactory deposition; olfactory CYP450 metabolism[13]; few comparisons between platforms[34]

5. Preclinical evidence by disorder

5.1. Alzheimer's disease

Alzheimer's disease is the most frequently modelled condition. In a rat model of sporadic Alzheimer-type disease (intracerebroventricular streptozotocin), oral curcumin in poly(ε-caprolactone) nanocapsules (254 ± 2 nm, given at 6 mg/kg for 14 days) restored object-recognition performance (P = 0.0251 versus the model group) and inhibitory-avoidance performance (P = 0.0312), normalised hippocampal catalase activity and prefrontal non-protein thiols, and reduced GFAP. Free curcumin at the same dose lowered prefrontal acetylcholinesterase activity but had no significant effect on the memory tests. Lipid peroxidation markers did not differ between groups, and brain curcumin was not measured.[35] In a second streptozotocin model, oral curcumin nanoparticles (6 days before and 8 days after the injection) improved Morris water maze performance and most neurochemical and histopathological changes in male Wistar rats.[36]

Other nanosystems reported to reduce amyloid burden or improve memory in animal models include selenium-PLGA nanospheres, which showed higher antioxidant capacity than free curcumin,[37] a lactoferrin-modified LDL-

mimic nanocarrier that crossed the BBB and reduced neuronal damage in amyloid-β-injected rats,[4] and curcumin NLCs, with significantly higher brain curcumin than free curcumin.[37] Piperine combinations have been studied extensively. A systematic review of about 20 preclinical studies in neurodegenerative models found better outcomes than with monotherapy, often with nanoformulations performing better. Nine studies were rated at high risk of bias and seven at moderate risk, mainly because of unclear blinding, and data could not be pooled because models and doses varied (curcumin 10 to 400 mg/kg, piperine 2.5 to 60 mg/kg).[38]

5.2. Parkinson's disease and other neurodegenerative disorders

Parkinson's disease nanoformulations have been tested mainly in toxin-induced rodents and in Drosophila. Lactoferrin-curcumin nanoparticles protected SH-SY5Y cells against rotenone better than free curcumin.[4] Glyceryl monooleate nanoparticles carrying curcumin and piperine inhibited α-synuclein aggregation in vitro and improved motor function in rotenone-treated mice, and polysorbate 80-modified cerasomes combined with ultrasound-targeted microbubble destruction reduced symptoms in MPTP mice, although one review caution that prolonged ultrasound use could cause serious harm.[5] In the mPEG-PLGA study described above, nanoparticles restored tyrosine hydroxylase protein and serum antioxidant enzymes in MPTP mice and enriched Lactobacillus in the gut, but the acute MPTP model does not reflect chronic disease and the gut-brain link was not tested causally.[22]

In Huntington's disease, solid lipid nanoparticles restored superoxide dismutase and glutathione and reduced motor impairment in 3-nitropropionic acid rats.[5] In multiple sclerosis, randomised placebo-controlled trials of nano-curcumin in 50 patients with relapsing-remitting disease over six months reported lower inflammatory markers and EDSS scores. In an amyotrophic lateral sclerosis pilot trial, nano-curcumin added to riluzole improved survival probability but not ALSFRS-R, muscle strength or compound muscle action potential.[3]

A cuprizone model of demyelination shows why carrier controls matter. Male mice (n = 15 per group up to week 5) received an intraperitoneal self-nanoemulsifying oil formulation of curcumin (10 mg/kg), curcumin with piperine (3 mg/kg), or the blank formulation. Curcumin with piperine gave better memory performance and less neuroinflammation than curcumin alone, but the blank formulation was itself active: at week 5 superoxide dismutase in the blank group (16.54 ± 1.08 U/mg) matched the control group (16.38 ± 1.16) and exceeded the cuprizone group (9.98 ± 0.75), and myelin basic protein was partly restored (27.48 ± 1.26 versus 21.10 ± 1.74 pg/mg protein). The authors suggested that the oil carrier itself may be protective. Brain curcumin was not measured.[39]

5.3. Other CNS disorders

5.3.1. Stroke

The RVG29-decorated gelatin nanoparticles described above are the clearest recent example in cerebral ischaemia.[30] Curcumin-loaded exosomes given intranasally reduced infarct volume, oedema and vascular damage in type 1 diabetic mice with stroke, and in mouse cerebral ischaemia they lowered TNF-α, IL-1β and IL-6 and reduced apoptosis.[4]

5.3.2. Epilepsy

Unformulated curcumin has anticonvulsant and antioxidant effects in rodent models.[10,11] Nanoformulations have been tested in fewer studies; liposomal curcumin at 25 and 50 mg/kg was examined in seizure models.[3] In mice, oral curcumin loaded into bovine serum albumin nanoparticles (about 140 nm) at 50 and 100 mg/kg raised the pentylenetetrazole (PTZ) seizure threshold. The 100 mg/kg nanoparticle dose was better than free curcumin at the same dose ($P < 0.0001$), and natural curcumin at 50 mg/kg had no effect. Hippocampal phospho-JNK was increased by the convulsant and was not reduced by the nanoparticles, so JNK restoration did not explain the effect. Brain curcumin was not measured and no empty-albumin control was reported.[40]

5.3.3. Depression and anxiety

Early meta-analyses of curcumin as an add-on treatment in depression pooled 6 studies in 377 patients and 10 studies in 531 patients and reported moderate to large effects. Doses above and below 500 mg/day did not differ, and curcumin was well tolerated at up to 12 g/day.[12] A 2025 systematic review of 15 randomised trials in 1,123 adults with depression or anxiety associated with chronic diseases found lower depressive symptoms (standardised mean difference -0.65, 95% CI –1.16 to –0.13, $I^2 = 93\%$) and lower anxiety symptoms (–0.22, 95% CI –0.40 to –0.05;
7 trials, 494 patients, $I^2 = 0\%$). The effect was larger in the nanocurcumin subgroup (–1.30, 95% CI –2.31 to –0.30) than with standard curcumin (–0.40, 95% CI –1.04 to 0.24, not significant), although the nanocurcumin subgroup was small and highly heterogeneous.[41] Table 2 summarises the primary preclinical studies discussed in Sections 4

and 5, including their design and whether brain curcumin was measured.

Table 2: Primary studies of curcumin nanoformulations in CNS models discussed in this review.

Study	Carrier and route	Model and dose	Brain curcumin measured?	Main finding
Li et al. 2023 [29]	Lactoferrin nanoparticles, 84.8 nm; intranasal	Rats, 10 mg/kg; PC12 cells with amyloid-β25-35	Yes (UPLC-MS/MS, whole brain)	Brain AUC0-8h about 3.2-fold higher than suspension; cell viability 91.0% versus 68.4% in model
Sadegh Malvajerd et al. 2019 [19]	Nanostructured lipid carriers	Rat amyloid-β model	Yes (brain accumulation 505.76 ng/g·h)	Higher brain and serum curcumin; less oxidative stress; better spatial memory
Savall et al. 2024 [35]	Poly(ε-caprolactone) nanocapsules, 254 nm; oral	Streptozotocin rats, 6 mg/kg for 14 days	No	Memory deficits reversed (P = 0.0251 and 0.0312); free curcumin not significant on memory tests
Fan et al. 2018 [23]	PLGA-PEG-B6 nanoparticles	APP/PS1 mice, n = 8, 25 mg/kg/day	Not reported	Better water maze performance than native curcumin; less hippocampal β-amyloid and tau phosphorylation
Huang et al. 2017 [24]	CRT-PLGA nanoparticles with S1 peptide, 139.8 nm	Transgenic Alzheimer mice	No (dye imaging of labelled particles only)	Better memory tests; lower β-amyloid, TNF-α and IL-6; curcumin encapsulation efficiency 21.4%
Campisi et al. 2022 [21]	Solid lipid nanoparticles, 153 nm; intraperitoneal	TgCRND8 and wild-type mice, 150 mg/kg, 3 weeks, n = 5 per group	Not reported	Well tolerated; blank-particle group included; transglutaminase isoforms modulated differently by genotype
Morasso et al. 2024 [31]	H-ferritin nanocages	5xFAD mice, 1 mg/kg twice weekly; in vitro BBB model	In vitro BBB transport only	Mild cognitive benefit; less microgliosis and astrogliosis
Moezi et al. 2021 [40]	Albumin nanoparticles, about 140 nm; oral	Mice, pentylenetetrazole, 50 and 100 mg/kg	No	Seizure threshold raised at both doses; better than free curcumin at 100 mg/kg (P < 0.0001)
Yang et al. 2024 [30]	RVG29-gelatin nanoparticles, 141 nm; intravenous	Rats, middle cerebral artery occlusion, 20 mg/kg for 7 days	No	Water maze landing time 53 s versus failure at 120 s in model
Mu et al. 2026 [22]	mPEG-PLGA nanoparticles, 149 nm; intravenous	MPTP mice, 200 mg/kg/day for 7 days	No	Higher p-Akt/Akt than free curcumin (P < 0.05); gut microbiota shifted towards control
Alam et al. 2025 [39]	Self-nanoemulsifying oil formulation; intraperitoneal	Male mice, cuprizone demyelination, curcumin 10 mg/kg with or	No	Curcumin with piperine better than curcumin alone on memory and neuroinflammation; blank formulation also raised

Study	Carrier and route	Model and dose	Brain curcumin measured?	Main finding
		without piperine 3 mg/kg		superoxide dismutase to control level
Schmitt et al. 2020 [18]	DPPC-cholesterol liposomes, about 180 nm	Microglia, astrocytes and brain slices, 0.01 µM	Not applicable (cell uptake imaged)	Anti-inflammatory effect at least equal to free curcumin; empty liposomes inactive

6. Clinical evidence in adults

Clinical evidence for curcumin in cognitive disorders is inconsistent. In a 336-day trial in mild to moderate Alzheimer's disease (n = 36), 2 or 4 g/day of Curcumin C3 Complex did not change amyloid or tau biomarkers and showed a non-significant trend towards worse cognition. A 180-day trial (n = 34) of 1 or 4 g/day gave mixed serum amyloid results with low circulating curcumin metabolites. In healthy older adults, a bioavailable formulation (Longvida) gave no cognitive benefit at 400 mg/day for 84 days (n = 89) or 800 mg/day for 112 days (n = 152).[13] An 18-month placebo-controlled trial of Theracurmin in non-demented adults reported better memory and attention and a lower FDDNP-PET signal in some brain regions, but the sample was small and the imaging analysis exploratory.[42]

Trials of nanoformulated or otherwise formulated curcumin are fewer and smaller. A pilot study of 10 nm curcumin nanomicelles (80 mg on alternate days for 2 months) in Alzheimer's disease found no significant change in MMSE, antioxidant enzymes or cholinesterase activity.[42] In a six-month randomised trial in 48 adults with moderate Alzheimer-type dementia (16 per arm, recruited through the Cochin chapter of the Alzheimer's and Related Disorders Society of India), a curcumin-galactomannan complex (400 mg twice a day) raised the MMSE score from 16.07 ± 1.81 to 19.27 ± 1.67, whereas the placebo group fell from 16.09 ± 1.86 to 13.81 ± 1.72 and unformulated curcumin produced no significant change (15.69 ± 1.70 versus 16.15 ± 1.14). Serum tau, amyloid-β42 and inflammatory markers also fell with the formulation, but plasma curcumin was not measured.[43] Nano-curcumin has been tested in randomised trials in multiple sclerosis, and in a pilot trial in ALS.[3] Pooled data for depression and anxiety are described in Section 5.3.3.[41]

Two gaps stand out. No clinical study has shown conclusively that oral curcumin reaches the cerebrospinal fluid at therapeutic concentrations, and no completed human trial of intranasal curcumin in Alzheimer's disease has been identified.[13]

7. Curcumin Nanoformulations And Adolescent Health

7.1. Why adolescence needs its own evidence

Adolescence is a period of risk for new-onset mental disorders. In a meta-analysis of 192 studies with 708,561 participants, 34.6% of people with any mental disorder had onset before 14 years, 48.4% before 18 and 62.5% before 25, and the peak age at onset was 14.5 years. Neurodevelopmental and anxiety disorders peaked at about 5.5 years, whereas mood disorders, schizophrenia-spectrum disorders and substance use disorders peaked at 19.5 to 20.5 years, so the teenage years are the lead-in to their highest-risk period.[6] The brain is still maturing during this time, with changes in cortical thickness and white-matter volume whose cellular basis, such as synaptic pruning and myelination, is still being resolved.[7]

Two features of the curcumin literature limit its transfer to this age group. First, the mechanistic rationale (oxidative stress, mitochondrial dysfunction, impaired protein homeostasis and neuroinflammation) was developed largely from ageing biology.[14] Whether it applies to a developing brain is untested. Second, developmental data on curcumin nanocarriers come from neonatal injury, where PLGA-PEG nanoparticles reached injured regions of the neonatal rat brain after hypoxic-ischaemic injury.[44] A neonatal brain with an injured barrier is not an adolescent brain, and in the sources screened for this review no study measured curcumin nanoparticle brain exposure in adolescent animals.

7.2. Clinical evidence in young people

Clinical evidence is very limited (Table 3). In an open-label, 8-week pilot trial in six youths with treatment-resistant bipolar depression, adjunctive curcumin was started at 500 mg once daily and raised to 1000 mg twice daily. Clinician-rated depression and illness severity fell significantly, and greater falls in depression scores were associated

with greater falls in a lipid peroxidation marker (8-iso-prostaglandin F2α, r = 0.89, P = 0.02 at week 4). The most common side effects were in the CNS and gastrointestinal systems.[45] With six participants, no control group and no stated nanoformulation, this is a hypothesis-generating signal and not evidence of efficacy.

In children with intractable epilepsy, a randomised, double-blind crossover trial of nanomicelle curcumin as add-on therapy in 22 children reported a reduction in seizure frequency. The reported mean age was 4.28 years, so the trial speaks to young children and not to adolescents, and it did not measure curcumin in the CNS.[46] Cognitive comorbidities complicate childhood epilepsy, and drug-resistant epilepsy is estimated to affect 30 to 40% of patients, which explains the interest in add-on treatments.[34] To our knowledge, no trial of a defined curcumin nanoformulation has been restricted to adolescents with a neurological or psychiatric disorder.

7.3. Route and acceptability

A non-invasive route is attractive for young patients, and the nasal route already has a clinical precedent in this age group: intranasal midazolam is approved in the United States for people aged 12 years or older and intranasal diazepam for those aged 2 years or older,[47] both for seizure clusters.[48] These are small-molecule rescue drugs with rapid systemic absorption. They show that nasal products can be used by adolescents, but they say nothing about nose-to-brain transport of curcumin nanocarriers, for which even adult human data are missing (Section 6).

7.4. Dose, liver safety and interactions

Safety data for curcumin come mainly from adults and from food-additive assessment. The European acceptable daily intake for curcumin as a food additive is 3 mg/kg body weight per day.[49] This is not a therapeutic ceiling, but it shows the gap: for an illustrative adolescent of 50 kg it equals 150 mg/day, whereas the youth trial reached 2000 mg/day, or about 40 mg/kg/day. Therapeutic doses therefore lie well outside the range for which food-safety data exist, and weight-based dosing and exposure measurement are needed in young people.

Turmeric supplements have also been linked to liver injury. In ten cases from a United States drug-induced liver injury registry, most patients were women in their mid-50s, injury was mainly hepatocellular and appeared 1 to 4 months after exposure. Five patients were hospitalised and one died of acute liver failure, seven carried HLA-B*35:01, and some products also contained black pepper.[50] No adolescent data are available, so liver monitoring should be built into any adolescent trial. Piperine, used to raise curcumin exposure, inhibits drug-metabolising enzymes and may alter exposure to other medicines,[13] which matters for young people taking antiseizure or psychotropic drugs. Finally, long-term safety data are scarce for curcumin and even scarcer for its nanoformulations,[14] and the consequences of repeated carrier exposure during ongoing brain development are unknown.

Table 3: Evidence relevant to adolescent health and its limits.

Evidence	What was found	Limitation for adolescents
Epidemiology of onset[6]	62.5% of mental disorders begin before 25 years; peak onset at 14.5 years	Not specific to curcumin; shows where the need lies
Youths with bipolar depression, open-label, 8 weeks, n = 6 [43,45]	Curcumin 500 mg daily raised to 1000 mg twice daily; clinician ratings improved; symptom change tracked a lipid peroxidation marker	No control group; formulation not stated as nano; six participants
Children with intractable epilepsy, randomised crossover, n = 22 [46]	Nanomicelle curcumin add-on reduced seizure frequency	Mean age 4.28 years; no CNS pharmacokinetics; short treatment periods
Neonatal rats with hypoxic-ischaemic injury[44]	PLGA-PEG curcumin nanoparticles reached injured brain regions	Neonatal age and injured barrier; no adolescent animal data identified
Intranasal rescue drugs for seizure clusters[48]	Midazolam approved from 12 years, diazepam from 2 years	Small molecules with systemic effect; not curcumin nanocarriers
Turmeric liver injury, adult registry cases[50]	Hepatocellular injury, one death, HLA-B*35:01 in 7 of 10 patients	Adult cases; adolescent risk unknown

Table 3 summarises the position. The adolescent case for curcumin nanoformulations currently rests on a plausible mechanism, a clear clinical need and two small trials that do not test a nanoformulation in adolescents.

8. Safety and regulatory considerations

Curcumin itself is generally well tolerated. Single oral doses of up to 12 g were safe in healthy volunteers, although long-term safety data are limited.[2] Nanoformulations introduce the additional safety profile of the carrier. Toxicity depends on particle size, surface charge, ion dissolution and shape.[17] Reported risks of nanoparticles include neuroinflammation, excitotoxicity, DNA damage and allergic responses, and toxicity varies with the methods of preparation and purification.[3] Long-term exposure to polymeric nanomaterials may also cause adverse effects, and no regulatory framework yet exists specifically for nanotechnology-enabled health products.[4] The gut microbiome metabolises curcumin, and how nanocarriers change the mix of metabolites is not understood.[14]

The primary studies give both reassurance and cautions. RVG29-gelatin nanoparticles caused 0.59% haemolysis at 100 µg/mL, below the 5% threshold usually applied.[30] Empty liposomes had no effect on brain slices at the doses tested, but they were cytotoxic at higher concentrations (IC50 86.4 µg/mL in microglia and 36.4 µg/mL in astrocytes), and the curcumin liposome itself was more cytotoxic than free curcumin at high concentrations.[18] Taken together, these data support a case-by-case safety evaluation of each carrier, dose range and route, with repeated-dose studies where chronic use is intended and age-appropriate studies where use in adolescents is planned.

9. Challenges and future perspectives

The central challenge is the gap between animal findings and human benefit. Most positive animal findings for curcumin have not been reproduced in humans, formulations are often incompletely characterised, and few clinical trials include biomarkers of CNS exposure.[2] The primary studies reviewed here show the same pattern at the preclinical level. Of the twelve in vivo animal studies in Table 2, only two reported quantified curcumin in brain tissue.[19,29] One tracked fluorescently labelled particles and not curcumin,[24] and the others inferred delivery from behavioural or biochemical effects.[18,21-23,30,31,35,39,40] A free-curcumin comparator was not used in the stroke study,[30] and no empty-carrier control was reported in the albumin and mPEG-PLGA studies.[22,40] Some studies did include carrier controls, such as unloaded SLNs[21] and a blank formulation, and the blank formulation was active.[39] Without these elements, an effect cannot be assigned to improved brain delivery, to the carrier itself, or to a higher dose of curcumin. A review of ageing-related disease has made the same point about the lack of side-by-side free-curcumin comparisons, and has also cautioned that nanoformulation may limit passage across the BBB in some designs.[14]

Model choice adds uncertainty. The acute MPTP model does not reflect chronic Parkinson's disease,[22] no published curcumin study has used humanised or knock-in Alzheimer models, and rodent metabolism of curcumin differs from human metabolism.[13] Piperine combinations rarely include formal synergy analysis, so the literature speaks of combined or complementary effects, not synergy.[38] Manufacturing is a further hurdle: liposomes need a cold chain and have a shelf life of 6 to 12 months, and batch-to-batch variability is a recognised problem.[2] Table 4 pairs the main challenges with practical responses, including those specific to adolescents.

Table 4: Challenges and suggested responses

Challenge	Why it matters	Suggested response
Brain exposure rarely quantified	Delivery is inferred from effect	Measure parent curcumin in brain, ideally by region, in the same animals used for efficacy testing[2,29]
Total curcumin measured	Overstates active exposure	Measure aglycone-specific pharmacokinetics[2]
Missing or active controls	Benefit of the carrier cannot be isolated	Include free curcumin by the same route and an empty-carrier arm[22,30,39,40]
Model and species limits	Acute toxin models and rodent metabolism may not predict human disease	Chronic or genetic models and humanised models where available[13,22]

Challenge	Why it matters	Suggested response
Piperine combinations	Synergy rarely tested formally; interaction risk	Factorial designs with formal synergy analysis[38]
Manufacturing and stability	Cold chain, short shelf life, batch variability	Defined critical quality attributes and stability data for each product[2]
Clinical evidence	Small, sponsor-linked trials with inconsistent endpoints	Phase II and III trials with CSF exposure biomarkers and adaptive designs[2,43]
No adolescent pharmacokinetic or safety data	Adult and neonatal findings may not transfer; dose by body weight is untested	Juvenile animal studies of brain exposure and toxicity, then weight-based dose-finding in adolescents after adult safety is established[14,45]
Liver safety and interactions	Turmeric liver injury reported in adults; piperine alters drug metabolism	Liver tests and medicine review in every adolescent trial[13,50]
Adolescent efficacy unknown	Existing trials are tiny, uncontrolled or in younger children	Randomised, placebo-controlled trials of a defined product in adolescents, with age-appropriate outcomes and exposure measures[45,46]

Several directions look promising. Receptor-mediated transcytosis and exosome carriers are regarded as the most promising strategies for crossing the BBB.[2] The intranasal route deserves head-to-head comparison with oral and intravenous dosing, because the only measured data show that route and carrier act together,[29] and because it is the route with the clearest acceptability for young patients.[48] Tetrahydrocurcumin, a colourless metabolite with better solubility and stability than curcumin, has been proposed as a more bioavailable alternative, particularly for intranasal use.[13] Whatever the approach, product-specific evidence will be needed, because the result for one carrier cannot be assumed to hold for another, and adolescents should enter trials only when adult safety data and adequate preclinical safety data support it.

10. Conclusion

Curcumin has a broad and plausible pharmacology for neurological and psychiatric disorders, and nanoformulations address its poor solubility, instability and limited brain exposure through lipid, polymeric, protein-based and exosome carriers and through intranasal delivery. Quantitative data show that carriers can change brain exposure substantially, as with intranasal lactoferrin nanoparticles and NLCs, and many formulations improve behaviour or biochemical markers in animal models of Alzheimer's disease, Parkinson's disease, stroke and epilepsy. Human evidence is limited to small and inconsistent trials. Evidence for use in adolescents remains scarce: two small trials in youth and young children, no adolescent pharmacokinetic data and no adolescent safety data for nanoformulated products. The next stage of development should quantify parent curcumin in brain and cerebrospinal fluid, use free-curcumin and empty-carrier controls, study juvenile animals, and test each product in adequately powered, age-appropriate trials with attention to liver safety, interactions and long-term carrier exposure.

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