



The Role of Curcumin in Neurogenesis and Neuroprotection in Alzheimer's disease: From Molecular Mechanisms to Clinical Evidence

Vishwa.S¹, Sarupruthiya.M², Jeevitha.D³, Saravan.V.S⁴, Metilda Stella Rani.G^{5*}

^{1,2,3,4,*5}Department of Pharmaceutical analysis, The Erode College of pharmacy, Erode, Tamil Nadu, India.

*Corresponding Author.

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Abstract: Alzheimer's disease (AD) is the most common form of senile dementia worldwide and is a progressive and irreversible neurodegenerative disorder, which represents a huge socioeconomic burden on modern healthcare systems. The neuropathology of AD is characterised by a very complex, interconnected cascade of cellular events including the extracellular accumulation of neurotoxic amyloid-beta (A β) peptides in senile plaques, the intracellular aggregation of hyperphosphorylated tau protein in neurofibrillary tangles (NFTs), chronic neuroinflammation, severe oxidative damage, cholinergic deficits and synaptic collapse. Standard FDA approved therapies provide modest symptomatic relief, leading to intensive research into multi-target disease modifying natural compounds. Curcumin is a natural hydrophobic diarylheptanoid polyphenol isolated from the rhizome of the turmeric plant (*Curcuma longa*) and has been proposed as a promising multi-target therapeutic candidate due to its strong antioxidant, anti-inflammatory, anti-protein-aggregating and neurogenic activities. Preclinical studies have demonstrated that curcumin can modulate a variety of pathological pathways. Curcumin down-regulates BACE1 expression and alters APP processing; it binds directly to A β monomers and fibrils to inhibit their aggregation and to promote the disaggregation of plaques. Curcumin blocks kinases (such as GSK-3 β) to prevent tau hyperphosphorylation, increases Nrf2-mediated antioxidant enzyme expression, chelates transition metals, inhibits NF- κ B-dependent chronic inflammatory cascades, and promotes adult hippocampal neurogenesis. However, the clinical translation of curcumin is severely hampered by the "bioavailability barrier" that is manifested by poor aqueous solubility, extensive first-pass metabolism in the intestine and liver, rapid systemic clearance and limited penetration across the blood-brain barrier (BBB). This review discusses multi-target neuroprotective mechanisms of curcumin, critically reviews the preclinical success and human clinical trial outcomes, and highlights advanced nano formulations (solid lipid nanoparticles, colloidal sub-micron dispersions, polymeric nanoparticles, multi-walled carbon nanotubes and exosomes) and synergistic combination regimens to maximise its CNS bioavailability and therapeutic efficacy in humans.

Keywords: Alzheimer's disease; Curcumin; Neuroprotection; Amyloid- β aggregation; Tau hyperphosphorylation; Bioavailability; Nanomedicine.

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease and the leading cause of dementia worldwide. It is characterised by progressive cognitive decline, short-term memory impairment and massive neuronal loss. The pathological landscape of AD is marked by classic histopathological features, such as extracellular senile plaques made of amyloid-beta ($A\beta$) peptides, intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein, chronic neuroinflammation, strong oxidative stress, and a progressive loss of synapses. Current drugs that are standard-of-care such as the AChE inhibitors and NMDA receptor antagonists are only symptomatic and do not affect the underlying rate of neuronal death [2, 6, 7]. Furthermore, the recently approved monoclonal antibodies for $A\beta$ clearance have limited efficacy in early-stage patients and are plagued with significant safety risks (e.g., amyloid-related imaging abnormalities, or ARIA), high costs and limited accessibility [2].

Because of the complex and multifactorial aetiology of AD, there has been a shift in the paradigm of drug discovery toward pleiotropic multi-target therapeutic agents that can modulate several pathological pathways at the same time [2, 7, 9]. Among these candidates, curcumin (diferuloylmethane), a hydrophobic natural polyphenol extracted from the rhizome of the turmeric plant (*Curcuma longa*), has attracted the interest of the scientific community. Turmeric has been used for centuries in traditional Ayurvedic and Chinese medicine for culinary and medicinal purposes due to its anti-inflammatory, antimicrobial, antiseptic and wound healing properties [3, 11, 14].

Its neuroprotective potential was first suggested from epidemiological studies reporting a strikingly lower incidence of AD and better preservation of cognition in rural Indian populations whose diet is enriched with curry spices derived from turmeric [3, 15]. In the past two decades, extensive preclinical data have demonstrated that curcumin has multi-modal neuroprotective, anti-oxidative, anti-inflammatory and anti-amyloidogenic activities. But clinical trials of standard oral curcumin have yielded inconsistent and often inconclusive cognitive benefits, despite robust laboratory evidence, highlighting a significant translational gap. This story review includes the chemical structure-activity relationships of curcumin, its molecular mechanisms for neuroprotection and critically discusses the translational barriers that limit its clinical efficacy while emphasising advanced drug delivery mechanisms that have been engineered to overcome this gap [5, 12, 17, 21].

2. Sources and Chemistry of Curcumin

Curcumin is the principal polyphenolic compound obtained from the dried roots of the rhizome of *Curcuma longa* L. a tropical flowering plant of the ginger family Zingiberaceae of South Asia and the Indian subcontinent. Commercial standardised turmeric extracts typically contain a "curcuminoid complex" of three naturally occurring analogues, curcumin (curcumin I, ~80%), demethoxycurcumin (curcumin II, ~17%) and bisdemethoxycurcumin (curcumin III, ~3%), which are responsible for the intense yellow-orange pigment of turmeric [3, 5]. Curcumin (1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl) hepta-1, 6-diene-3, 5-dione, a symmetric lipophilic molecule with chemical formula $C_{21}H_{20}O_6$ and molecular weight 368.38 g/mol. It has a peculiar chemical architecture with three different functionalities: two aromatic ortho-methoxylated phenolic rings connected by a flexible unsaturated seven-carbon heptadiene chain with a central 1,3-diketone system.

Under physiological conditions, curcumin exists in keto-enol tautomerism. The keto form dominates at acidic and neutral pH (pH 3-7) while the enol tautomer is highly stabilised and favoured at alkaline pH (pH>8) or complexed to amyloid proteins. In solution the enol form is stabilised as the enol by an intramolecular hydrogen bond. Most importantly, biophysical and spectroscopic studies suggest that the active species interacting with the β -pleated sheet conformation of the misfolded $A\beta$ aggregates and fibrils is the stabilised enol tautomer, but not the keto form, which does not have this ability to bind [5, 6, 26]. The specific pharmacological and neuroprotective effects of curcumin are directly associated with a number of functional groups in the chemical structure:

Phenolic Hydroxyl and Ortho-Methoxy Groups: These groups are responsible for the antioxidant and free radical scavenging activity of curcumin. The ortho-methoxy group can form an intramolecular hydrogen bond with the neighbouring phenolic hydrogen, decreasing the activation energy for the hydrogen atom abstraction. Thus, curcumin is a very potent hydrogen or electron donor that directly scavenges reactive free radicals, thus preventing the chain reactions of lipid peroxidation [3, 7, 16].

Symmetrical hydrophobic phenol rings: These aromatic structures can form π - π stacking interactions and hydrophobic contacts with the nonpolar hydrophobic core recognition motif (KLVFF region) of $A\beta$ peptides, sterically blocking their self-assembly into oligomers and fibrils [3, 16, 20].

Conjugated Dienone Linker (Heptadiene Bridge): The anti-amyloidogenic activity of curcumin is mediated by conjugated double bonds of the heptadiene linker. The saturated metabolites like tetrahydrocurcumin (THC) that lack these double bonds still possess the lipid antioxidant and kinase-inhibiting functions, but are unable to bind $A\beta$ plaques or prevent amyloid deposition in vivo [16].

The Central Diketone System As a Potent Bidentate Chelator of Transition Metals: Curcumin chelates Cu^{2+} , Fe^{2+}/Fe^{3+} and Zn^{2+} to inhibit metal-induced cross-linking of $A\beta$ and to inhibit the Fenton-like and Haber-Weiss reactions for the generation of highly toxic hydroxyl radicals [3, 16].

3. Bioavailability and Pharmacokinetics of Curcumin

Curcumin is a BCS Class IV drug with poor systemic bioavailability (approximately 1% or less following oral versus

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systemic intravenous or intraperitoneal routes). Clinical pharmacokinetic studies show low plasma concentrations (generally 0.4–1.7 $\mu\text{mol/L}$; $\sim 0.051 \mu\text{g/mL}$) after high oral doses ($\sim 4\text{--}8 \text{ g/day}$ in humans) with a short elimination half-life (1–2 hours) [5, 21].

A number of biophysical and metabolic factors result in such severe pharmacokinetic attrition:

Severe Hydrophobicity: Curcumin is highly hydrophobic and essentially insoluble in water ($\sim 11 \text{ ng/mL}$ at neutral pH or $1.34 \mu\text{g/mL}$) but it is freely soluble in organic or hydrophobic solvents such as ethanol, methanol, acetonitrile and DMSO [21].

Rapid Phase II Metabolism: When ingested, curcumin undergoes extensive and rapid metabolism during the first-pass metabolism in the intestinal mucosa and liver. Curcumin is rapidly conjugated by UDP-glucuronosyltransferase (UGT) and phenol sulfotransferase enzymes to inactive metabolites, mainly curcumin glucuronides and curcumin sulphates, and excreted in urine and faeces [21].

Hepatic reduction: Curcumin is rapidly reduced to dihydrocurcumin, tetrahydrocurcumin (THC), hexahydrocurcumin and octahydrocurcumin by endogenous hepatic reductases [21].

Limited Blood-Brain Barrier (BBB) Permeability: Curcumin is lipophilic and crosses the BBB, however active efflux transporters (e.g. P-glycoprotein) on the brain microvascular endothelium actively pump free curcumin out of the brain parenchyma preventing therapeutic concentrations of curcumin from being achieved in the central nervous system (CNS) [21]. Interestingly, studies suggest that the systemic clearance of curcumin may be partially attenuated in the presence of inflammation. The inflamed brain tissue demonstrates a distinct increase in the local concentration of the lysosomal deconjugating enzyme, beta-glucuronidase. High amounts of beta-glucuronidase are secreted by glial cells, immune cells and gut microbiota, leading to the deconjugation of circulating curcumin glucuronide to the free active parent curcumin, thereby increasing local tissue concentrations at target inflammatory sites [11, 21].

4. Mechanisms of Neuroprotection

Curcumin may exert neuroprotection by modulating multiple interconnected pathophysiological processes in CNS [9, 16, 17].

4.1 Nrf2 Activation and the Antioxidant Defence

Curcumin diminishes oxidative damage by direct scavenging of free radicals and induction of endogenous antioxidant defences. Structurally curcumin acts as electron or hydrogen donor and directly scavenges free radicals like superoxide anions ($\text{O}_2^{\bullet-}$), hydroxyl radicals ($\bullet\text{OH}$), peroxynitrite (ONOO^-) and hydrogen peroxide (H_2O_2) [16].

Curcumin activates the cyto-protective signalling pathway nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE indirectly. Curcumin covalently modifies cysteine residues of Keap1 and causes Nrf2 dissociation, proteasomal degradation escape and translocation into the nucleus. Nrf2 binds to Antioxidant Response Elements (AREs) in the promoter regions of cytoprotective genes leading to the transcription of endogenous Phase II antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), and heme oxygenase-1 (HO-1). Curcumin also may induce the γ -glutamylcysteine ligase (γ -GCL) and activate the glutathione reductase (GR), restoring the depleted intracellular glutathione (GSH) pools and maintaining the mitochondrial membrane potential under oxidative stress [16, 17].

4.2 Inhibition of Glial Activation and Chronic Neuroinflammation

Curcumin blocks the chronically activated neuroinflammatory state induced by activated microglia and reactive astrocytes at several critical check points. It inhibits the signalling pathways of Nuclear Factor kappa B (NF- κB) and Activator Protein-1 (AP-1). Curcumin also prevents the phosphorylation and degradation of I $\kappa\text{B}\alpha$, thereby blocking the nuclear translocation of NF- κB and the subsequent transcription of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6) and inducible enzymes such as iNOS and COX-2 (Figure 2) [16, 17].

Curcumin is also an agonist of the peroxisome proliferator-activated receptor-gamma (PPAR- γ). PPAR- γ activation directly suppresses the transcription of NF- κB , thus inhibiting the activation of microglia and astrocytes (as demonstrated by decreased GFAP and Iba-1 markers) and also promotes the polarisation of microglia from pro-inflammatory M1 to anti-inflammatory, phagocytic M2 that clears A β plaques [16].

4.3 Neurogenesis, Adult Induction Neurotrophic Factors

Curcumin significantly increases the levels of Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) in hippocampus and cerebral cortex. This neurotrophin upregulation is mediated by the activation of PI3K/Akt and ERK/MAPK pathways which phosphorylate and activate the transcription factor CREB, in turn leading to BDNF gene transcription. Increased BDNF levels maintain intact synaptic transmission and trigger the expression of synaptic proteins, including postsynaptic density protein 95 (PSD-95) and synaptophysin to maintain long-term potentiation (LTP) [1, 11, 16].

Curcumin also activates the canonical Wnt/ β -catenin pathway. Curcumin inhibits phosphorylation and degradation of β -catenin via inactivation of GSK-3 β . The stabilised β -catenin accumulates in the nucleus and promotes proliferation, survival and neuronal differentiation of adult neural stem/progenitor cells (NSCs) in the dentate gyrus [1, 11, 16].

4.4 Regulation of autophagy and mitophagy.

Curcumin modulates neuronal proteostasis via quality control autophagic/mitophagic pathways. It down-regulates the hyper-activated PI3K/Akt/mTOR signalling pathway, which negatively regulates autophagy. This results in a high conversion of LC3-I to LC3-II, upregulation of Beclin-1 and induction of formation of functional autophagosomes that aid in lysosomal degradation of toxic protein aggregates [16].

By contrast, curcumin can also inhibit hyperactivation of autophagy, which is excessive and pathogenic. Curcumin slightly downregulates Beclin-1 expression in primary cortical neurones or A β 1-42-treated HT-22 cells, suppressing excessive autophagic cell death and maintaining the cell viability [16].

4.5 Neurovascular Protection and Blood Brain Barrier (BBB) Integrity

Curcumin preserves and restores cerebrovascular and endothelial health. It restores endothelial nitric oxide synthase (eNOS) activity, normalises stimulus-induced cerebral blood flow, and protects the blood-brain barrier (BBB) by suppression of matrix metalloproteinase-9 (MMP-9). Curcumin inhibits MMP-9, downregulates tight junction proteins (claudin-5, occludin and ZO-1), and blocks the systemic A β influx, leukocyte infiltration and extravasation of neurotoxic plasma proteins into the brain parenchyma [16, 17].

5. Curcumin and Alzheimer's Disease

Curcumin targets the central diagnostic features of AD pathology by using multi-pronged biophysical and biochemical mechanisms [18, 26, 31].

5.1 Amyloid- β (A β) Pathogenesis and Clearance

The amyloid cascade is triggered by sequential cleavage of Amyloid Precursor Protein (APP) by β -secretase (BACE1) and the γ -secretase complex (containing presenilin-1, PS1). Curcumin affects this pathway at many levels:

Inhibition of BACE1 and APP cleavage: Curcumin decreases the expression and transcriptional activity of BACE1, and subsequently reduces the production of A β . Curcumin has also been shown to inhibit GSK-3 β , thus preventing GSK-3 β -mediated phosphorylation of PS1 and to reduce the catalytic activity of γ -secretase [26].

Inhibition of APP Maturation: Curcumin specifically affects the secretory pathway of APP. It inhibits post-translational processing of APP, keeping immature APP in the endoplasmic reticulum and decreasing its trafficking to the cell surface, thus directly decreasing its availability for endocytosis-dependent amyloidogenic cleavage [26].

Epigenetic Regulation: Curcumin upregulates the key microRNAs miR-15b-5p and miR-101. These miRNAs are directed to the 3'-untranslated region (3'-UTR) of APP mRNA, thereby silencing APP translation at the post-transcriptional level [13].

Curcumin is unique among these agents in that its planar, methoxylated phenolic structure enables it to serve as a direct biophysical inhibitor of A β self-assembly. It directly binds the hydrophobic β -pleated sheet conformation of A β monomers and soluble oligomers, interacting specifically with the core-recognition motif KLVFF. This impairs hydrogen bonding and hydrophobic interactions and hence they are unable to assemble into neurotoxic soluble oligomers and fibrils [3, 26].

Curcumin, rather than simply inhibiting aggregation, alters the biophysical aggregation pathway by changing the manner in which A β assembles into stable, non-toxic, pre-fibrillar, "off-pathway" soluble oligomers that do not interact destructively with the neuronal membranes [26].

Disassembly of Plaques: Curcumin directly disassembles preformed A β fibrils and dense senile plaques into smaller, soluble, non-toxic fragments [26].

Phagocytic and Enzymatic Clearance: Curcumin enhances the enzymatic clearance of A β by upregulating neprilysin (NEP), the rate limiting enzyme for A β degradation. Moreover, it enhances the clearance of A β across the blood-brain barrier (BBB) by downregulating the Receptor for Advanced Glycation End-products (RAGE) that mediates the toxic influx of A β , and upregulating low-density lipoprotein receptor-related protein-1 (LRP1)-mediated efflux into the systemic circulation. Importantly, curcumin can recruit microglial cells to amyloid plaques and directly stimulate microglial phagocytosis and lysosomal clearance of preformed plaques [26].

5.2 Hyperphosphorylation of Tau and Neurofibrillary Tangles

In AD, tau protein is hyperphosphorylated, dissociates from microtubules (microtubule instability and axonal collapse) and self-assembles into toxic soluble tau dimers, oligomers and insoluble paired helical filaments (PHFs) that form NFTs. This tau pathology is inhibited by curcumin in a biophysical and biochemical fashion:

Inhibition of Kinase: Curcumin inhibits GSK-3 β , the major tau kinase. It promotes Akt-mediated phosphorylation of GSK-3 β at the inhibitory Ser9 residue, thus inactivating the enzyme and reducing tau hyperphosphorylation. It also inhibits other pathogenic tau kinases like stress-activated JNK, p38 MAPK, and cyclin-dependent kinase 5 (CDK5) [26].

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Direct interaction with tau: Curcumin directly interacts with tau monomers and soluble tau dimers/oligomers inhibiting conformational transition to β -sheet structures and disintegrating preformed tau filaments in vitro [26].

Molecular Chaperones Induction: Curcumin induces the expression of molecular chaperones like heat shock protein 70 (HSP70), heat shock cognate 70 (HSC70) and heat shock protein 90 (HSP90). Such chaperones may stabilise misfolded tau, assist in refolding structurally or target hyperphosphorylated tau species for proteasomal degradation [26].

6. Animal study data

The therapeutic efficacy of curcumin has been confirmed in several animal models of AD with significant reduction in pathology and improvement in cognition [5, 12, 17].

6.1 Mouse models of transgenic Alzheimer's disease.

APP/PS1 Mouse Model: Male APP/PS1 transgenic mice were given curcumin by daily oral gavage at 50 or 200 mg/kg/day for 3 months (Sun et al. 2020). The treatment significantly improved spatial learning and memory and significantly decreased the density of A β plaques in the hippocampus. These beneficial effects were closely correlated with alterations in the gut microbiota composition (up-regulation of beneficial Lactobacillaceae and down-regulation of pro-inflammatory Bacteroidaceae) and the biotransformation of curcumin into active, highly bioavailable neuroprotective metabolites by gut bacteria [11].

Wang et al. (2014) examined the effects of curcumin in APP/PS1 double-transgenic mice fed on a diet containing low (160 ppm) and high (1000 ppm) doses of curcumin for 6 months. Both doses were effective in reducing cognitive deficits and A β 42 levels, the higher dose showing greater cognitive improvement. Curcumin induced autophagy in hippocampal CA1 region, as evidenced by significant decrease in p-Akt and p-mTOR, significant increase in Beclin-1 expression and increased ratio of LC3-II/LC3-I, thus stimulating autophagic clearance of A β [16].

Sun et al. (2017) [16] found that oral administration of curcumin at 0.16 g/kg or 1.0 g/kg per day for 6 months significantly reduced tau hyperphosphorylation in the hippocampus and cerebral cortex of APP/PS1 mice by downregulating the Caveolin-1/GSK-3 β signalling pathway.

APPSw (Tg2576) Mice: Lim et al. (2001) fed Tg2576 mice low-dose (160 ppm) and high-dose (5000 ppm) curcumin diet for 6 months starting at a late stage of plaque pathology. Low dose curcumin significantly reduced soluble A β levels, reduced insoluble A β plaque burden by 43–50% and significantly reduced oxidative damage and glial inflammatory markers (IL-1 β , GFAP) without any systemic side effects [15]. Cheng et al. (2013) orally administered highly stabilised curcumin nanoparticles by gavage weekly at a dose of 100 mg/kg for 3 months in Tg2576 mice. Treatment resulted in a significant improvement of cue memory in the fear conditioning test compared to unformulated curcumin, decreased A β plaque load and high brain tissue concentrations of curcumin [21].

Transgenic hTau Mice: Aged hTau transgenic mice (15–16 months old) were fed solid lipid nanocurcumin (Longvida) in the diet at 500 ppm for 4–5 months (Ma et al. 2013). Lipidated curcumin crossed the BBB, significantly reduced levels of toxic soluble tau dimers, corrected molecular chaperone deficits (increased synaptic HSP90 and HSC70) and fully restored synaptophysin and post synaptic density markers correcting behavioural and memory deficits [5].

McClure et al. (2016) treated 5XFAD mice with aerosolised curcumin (5 mg/kg) by inhalation for 18 weeks. [21] This treatment resulted in large brain delivery, strong reduction of hippocampal and subicular A β plaques, prevention of neuritic dystrophy, and enhancement of spatial memory, without any systemic toxicity.

6.2 Induction of Sporadic and Toxin AD Models

A β 1-42-Induced Mice: Lou et al. (2024) [1] infused A β 1-42 mice with curcumin i.g. (100 mg/kg/day) in 0.1% CMC-Na for 14 days. BrdU+ and BrdU+/NeuN+ newborn neurones in dentate gyrus of A β 1-42 mice exhibited a significant loss of 40% that was fully rescued and restored with curcumin treatment suggesting active adult hippocampal neurogenesis. Curcumin significantly reduced MWM escape latency and increased swimming time in target platform quadrant. Importantly, co-administration of either the conventional Wnt inhibitor MSAB (0.6 nmol/mouse, i.c.v.) or the BDNF-scavenging TrkB/Fc chimera (Fc, 10 ng/mouse, i.c.v.) abolished the neurogenic and cognitive-improving effects of curcumin, indicating that in vivo beneficial effects of curcumin are mediated via Wnt/ β -catenin and BDNF pathways activated by the PI3K/Akt cascade.

A β 1-40 treated rats: Wang et al. (2013) treated A β 1-40-induced AD rats with daily i.p. 7 days 300 mg/kg curcumin injections. Treatment with curcumin markedly enhanced spatial learning and memory performance with a significant down-regulation of GFAP mRNA and protein expression in the hippocampus, indicating a direct suppression of reactive astrogliosis and neuroinflammation [16].

ELBini-Dhouib et al. (2021) investigated the effects of oral curcumin (100 mg/kg) as a co-treatment (CUR1) or post-treatment (CUR2) for 90 days in rats with sporadic AD induced by aluminium chloride (AlCl₃). Curcumin significantly alleviated AlCl₃-induced neurotoxicity, improved memory and learning deficits, reduced anxiety-like behaviours, restored cerebral acetylcholinesterase (AChE) activity, restored lipid peroxidation and antioxidant enzymes and down-regulated apoptotic and inflammatory markers [20].

ICV-STZ Rats: In rats infused intracerebroventricularly with streptozotocin (ICV-STZ), Bassani et al. (2017) tested oral curcumin at 25, 50 and 100 mg/kg/day for 30 days. Curcumin (50 and 100 mg/kg) significantly improved short term spatial and recognition memory in object recognition test (ORT), object location test (OLT) and Y maze and had mild anti-inflammatory effect [17].

Ishrat et al. (2009) demonstrated that oral curcumin (80 mg/kg for 3 weeks) in ICV-STZ rats significantly reduced the levels of malondialdehyde (MDA) and H₂O₂, and restored GSH and GSH-dependent antioxidant enzymes (GPx, GR) and hippocampal cholinergic activity, and prevented cognitive decline [17].

7. Experimental Evidence In Vitro

The molecular targets of curcumin have been studied in cell models of AD and recent work has started to move from traditional 2D cultures to more sophisticated 3D biomimetic spheroids [33].

7.1 3D Advanced Modelling of Alzheimer's disease

3D Human Neuroblastoma Spheroids (MagLev Setup): A landmark study by 3D modelling researchers used differentiated human neuroblastoma SH-SY5Y spheroids cultured in a magnetic levitation (MagLev) system with gadobutrol as a paramagnetic agent. Spheroids were sequentially differentiated for 9 days using Retinoic Acid (RA) and BDNF and expressed mature neuronal markers β -III tubulin and NeuN. The established 3D AD model demonstrated a high neurotoxicity after addition of toxic A β 1-42 aggregates, with cell viability reduced to 51% and significant loss of cholinergic neurone activity (ChAT loss) [33].

Exogenous incubation of 25, 50, 75 and 100 μ M of curcumin with 50 μ M A β 1-42 aggregates for 72 hrs successfully disassociate preformed A β aggregates into smaller non-toxic fragments as confirmed by Thioflavin T and Congo red assay. Importantly, curcumin dose-dependently restored spheroid cell viability from 51% to 94% and attenuated A β neurotoxicity and rescued ChAT expression, suggesting its direct anti-aggregation and neuroprotective potential in a biomimetic 3D microenvironment [33].

7.2 Cell Cultures Monolayer (Cell Lines and Primary Neurones)

Mitochondrial and Synaptic Protection in SH-SY5Y Cells: Reddy et al. (2016) treated SH-SY5Y cells with 66.3 μ M curcumin for 24 h with A β 25-35. Curcumin remarkably restored cell viability and prevented A β -induced mitochondrial dysfunction and promoted mitochondrial fusion (upregulation of MFN1, MFN2, OPA1) and suppressed mitochondrial fission machinery (downregulation of DRP1, FIS1). It also up-regulated the mitochondrial biogenesis factors (PGC1 α , Nrf1, Nrf2, TFAM) and protected important synaptic proteins (PSD-95, synaptophysin) and protected neurones from amyloid induced apoptotic death [16].

Synergy with Vitamin D3 and Primary Cortical Neurones: Alamro et al. (2020) treated primary Wistar rat cortical neurones with A β 1-42 (1 μ M) in the presence of curcumin (5 μ M) and Vitamin D3 (1 nM) for up to 72 h. The synergistic combination substantially suppressed the lipid peroxidation and rejuvenated enzymatic activities of GST, catalase and SOD and upregulated the expression of Nerve Growth Factor (NGF) that supported the neuronal cell survival [16].

Suppressing microglial inflammation: Primary microglia cells from mice were treated with 10 μ M curcumin (Shi et al. 2015). Moreover, curcumin treatment was able to significantly suppress A β -induced microglial inflammatory responses, decreasing the release of toxic pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α). The anti-inflammatory effect was dose-dependent and mediated through direct inhibition of ERK1/2 and p38 MAPK phosphorylation and prevention of downstream NF- κ B nuclear translocation [16].

Excitotoxicity and Stress Protection: Curcumin (1.25–10 μ M) significantly protected primary cultured rodent cortical neurones from glutamate-induced excitotoxicity. It suppressed ER stress-induced TXNIP/NLRP3 inflammasome activation, suppressed the activation of caspase-3 and caspase-9, and increased the expression of BDNF, TrkB, and Bcl-2 to enhance cell survival via Akt [16].

Kim et al. (2001) reported that curcuminoids at concentrations of 0.1–5.0 μ g/mL prevented the oxidative death of PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells (HUVECs) induced by A β 1-42, and reduced protein oxidation and cell apoptosis [16].

8. Clinical Trials in People

The therapeutic efficacy of curcumin in AD has been investigated in human clinical trials and the results are very heterogeneous, showing a sharp contrast between standard and advanced bioavailable formulations [12, 17].

8.1 Clinical evidence is negative and inconsistent

The Hong Kong Pilot Trial (Baum et al., 2008): A 6-month randomised, double-blind, placebo-controlled pilot clinical trial on 34 patients with probable AD who received oral standard curcumin powder at a dose of 1 g/day or 4 g/day. No significant differences in Mini-Mental State Examination (MMSE), serum A β 40 or systemic antioxidant biomarker levels were observed

between the groups in the trial and the treatment was extremely well tolerated [17].

UCLA/C3 Complex Trial (Ringman et al., 2012): This was a 24-week randomised double-blind, placebo-controlled trial of oral Curcumin C3 Complex (a standardised extract containing three curcuminoids) at 2 g/day and 4 g/day in 36 patients with mild to moderate AD. The trial confirmed excellent oral safety and tolerability, but reported absolutely no significant clinical, cognitive (measured by ADAS-Cog and MMSE), or biomarker (plasma and CSF A β 40, A β 42, total tau and phosphorylated tau) efficacy [17].

Systematic Meta-analyses: A number of comprehensive systematic reviews and meta-analyses of these early clinical trials have concluded that no cognitive or disease-modifying benefits of standard oral curcumin preparations could be established in patients with established, symptomatic AD, largely due to inadequate plasma and brain concentrations [12, 17].

8.2 Positive and Encouraging Clinical Data

Theracurmin Study (Small et al., 2018): Double-blind placebo-controlled 18-month trial of Theracurmin, a colloidal sub-micron dispersion of curcumin with high bioavailability, at 180 mg/day (90 mg BID) in 40 non-demented middle-aged and older adults (aged 51–84 years). There were significant sustained improvements in verbal and visual memory and attention associated with Theracurmin treatment. Importantly, PET imaging (using the FDDNP tracer) showed a large reduction in the deposition of amyloid plaques and tau tangles in the amygdala and hypothalamus – regions of the brain involved in memory, attention and emotional control. Data suggest bioavailable curcumin crosses the human BBB, interacts with neuropathological targets and stabilises cognitive health [12, 17, 24].

Longvida Study (Cox et al., 2015): A randomised, double-blind, placebo-controlled trial was performed in 60 healthy older adults (aged 60–85 years) examining the use of Longvida, a Solid Lipid Curcumin Particle (SLCP) formulation (400 mg/day, of which 80 mg was free curcumin). Results showed significant acute (1 hour post-dose) and chronic (4 and 12 weeks daily dosing) improvement in attention, working memory and mood (reduction in state anxiety and fatigue). Lipidated curcumin significantly increased plasma catalase activity and significantly decreased plasma circulating A β levels, showing a strong systemic antioxidant and anti-amyloid effect [17, 24].

BCM-95 (Biocurcmax) Study: A 12 month clinical study on BCM-95, a standardised extract of curcuminoids and essential oils from turmeric, at a daily dose of 1500 mg, in healthy older adults. BCM-95 was shown to significantly maintain cognitive function and stabilise the Montreal Cognitive Assessment (MoCA) score compared to a decreasing trend observed in the placebo group [11, 24].

9. Challenges/Problems/Issues

There are several fundamental challenges underlying the translational gap between the robust neuroprotective efficacy of curcumin in preclinical models to the variable outcomes in human clinical trials [2, 12]

The Pharmacokinetic Barrier: The use of normal oral curcumin is greatly impeded by low water solubility, hydrophobicity and high intestinal and hepatic first-pass metabolism. Curcumin administered orally to humans in standard doses is not found as free unmetabolized curcumin in plasma, as it is quickly conjugated to glucuronides and sulphates and so is restricted in its access to the brain for therapeutic purposes [21].

Efflux Transport across the BBB: Although systemic exposure is attained, active efflux pumps, especially P-glycoprotein, at the BBB restrict therapeutic concentrations of curcumin in the brain parenchyma [21].

Morbidity and Timing of Intervention: Curcumin is typically administered early and prophylactically in animal studies, prior to the development of significant brain pathology. Conversely, human clinical trials enrol patients with established, clinically symptomatic AD, by which time severe, irreversible neuronal death and synaptic collapse have already occurred and targeted upstream amyloidogenic and oxidative processes are no longer modifiable [12].

Limitations of preclinical models: Transgenic rodent models express single familial AD mutations on a highly compressed time scale. They fail to replicate the complex genetic heterogeneity, sporadic onset, chronic ageing processes, and systemic multimorbidities of human sporadic AD, leading to a low rate of translational success in drug discovery [11, 12].

Methodological inconsistencies: Clinical trials on turmeric extracts have used different sample sizes, durations (many are limited to 6 months), dosing regimens and chemical compositions, which reduces statistical power and therapeutic reproducibility [12].

10. New Curcumin Formulations

In an effort to overcome the pharmacokinetic barriers of regular curcumin, advanced nanotechnological drug delivery vehicles and pharmaceutical strategies have been designed to improve solubility, protect from hepatic metabolism, and optimise BBB crossing [5, 21, 25].

10.1 Clinically Proven Formulas

Solid Lipid Curcumin Particles (SLCP / Longvida®): Curcumin is encapsulated in a solid lipid core, which protects the molecule from rapid breakdown in the GI tract. This lipid matrix improves lymphatic absorption and enables curcumin to avoid hepatic first-pass metabolism, which increases oral bioavailability of curcumin by up to 65 folds, maintains plasma concentrations and allows efficient BBB penetration into the brain [5, 21].

Colloidal Sub-micron Dispersions (Theracurmin®): Uses modern particle size reduction to disperse sub-micron colloidal particles (~100-300 nm) with gum ghatti. This formulation improves aqueous solubility and intestinal absorption resulting in up to 27-fold enhancement in oral bioavailability over standard curcumin powder [5, 21].

Curcumin-Lecithin Phytosome Complexes (Meriva® / Curserin®): Curcumin is complexed with amphipathic phospholipids (phosphatidylcholine) dramatically improving its gastrointestinal stability and transcellular diffusion with up to 29-fold increased oral bioavailability [5, 21].

Curcuminoids with Essential Oils (BCM-95® / Biocurcuma™): Combines the curcumin with the essential oils (turmerones) derived from turmeric and displays 7-9 fold increased systemic bioavailability and superior preservation of cognitive function in clinical trials [5, 21].

10.2 Novel Systems for Drug Delivery (NDDS) Preclinical

Polymeric Nanoparticles (Curcumin-PLGA): Biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NanoCurc) loaded with curcumin increase the solubility of curcumin, protect it from enzymatic degradation, and improve its delivery to the brain. PLGA-curcumin nanoparticles potently stimulate adult hippocampal neurogenesis and fully recover learning and memory deficits in STZ-induced AD rat models via activating the canonical Wnt/ β -catenin pathway [8, 25, 28, 34]. Targeted ligands like the B6 peptide (Cur-PLGA-PEG-B6) or Tet-1 peptide have been used to functionalise PLGA-PEG nanoparticles, which have demonstrated significant enhancement of cell-specific uptake across the BBB and direct inhibition of A β fibrillogenesis in the brains of transgenic mice [8, 25, 28, 34].

Multi Walled Carbon Nanotubes (MWCNT-COOH-PEG): Curcumin loaded functionalised PEGylated multi-walled carbon nanotubes for brain targeting were developed by Pawar and Suvarna (2025) [10]. The pharmacokinetic parameters of CUR-MWCNT-COOH-PEG were found to be superior (increasing C_{max}, t_{1/2} and AUC) and the brain distribution was significantly higher than oral or standard intranasal suspensions when administered through intranasal route (10 mg/kg in female Wistar rats) to overcome the BBB using olfactory pathway. The formulation showed excellent cellular biocompatibility and negligible cytotoxicity in PC12 cells, and histology of brain tissue showed restoration by the formulation.

Selenium-Polymeric Nanospheres: Co-encapsulation of selenium and curcumin in polymeric nanospheres synergistically inhibits A β aggregation, reduces oxidative stress and neuroinflammation, and restores memory performance in transgenic AD mice [25, 28, 34].

Curcumin-Primed Exosomes: Bioengineered exosomes loaded with curcumin cross the BBB, target neurones and suppress tau hyperphosphorylation by inhibiting GSK-3 β activity through the Akt pathway [25, 28, 34].

Niosome encapsulated curcumin: Niosome-encapsulated curcumin enhances memory and learning in AD rats associated with down-regulation of NF- κ B gene expression in prefrontal cortex [25, 28, 34].

Piperine co-administration: Co-administration of piperine (an alkaloid of black pepper) with curcumin inhibits hepatic and intestinal glucuronidation thus significantly increasing the bioavailability of curcumin (up to 2000%) in humans [21].

11. Current Problems and Future Prospects

Despite the barriers overcome by advanced bioavailable formulations due to pharmacokinetic limitations, several critical gaps remain before the curcumin can be integrated into routine clinical practice [12]:

11.1 Restrictions Existing

No Phase III human trials: The cognitive benefits of bioavailable formulations (e.g. Theracurmin and Longvida) have been shown mostly in healthy, non-demented older cohorts or small early-phase studies. To confirm the disease-modifying potential of curcumin in clinical AD patients, large-scale, multi-center, long-term phase III randomised clinical trials (RCTs) are needed [12].

Nanocarrier Toxicity and Long-Term Safety: New nanocarriers (PLGA, carbon nanotubes, metallic nanoparticles) have demonstrated high brain accumulation and target efficacy in rodents, but no clinical safety data in humans exist. Further studies are required to investigate the long-term accumulation in tissue, possible neurotoxicity and biodegradability of these synthetic

Sourcing and standardisation: Natural turmeric extracts are highly variable in chemical composition depending on the plant growth conditions. Standardised extraction protocols and strict quality control guidelines will be needed to obtain regulatory approval [12].

11.2 Looking Ahead

Biomarker-Guided Early Intervention: Future studies should incorporate highly sensitive biological AD criteria (e.g., PET neuroimaging, plasma/CSF biomarkers) to stratify and recruit patients in early prodromal AD stages (Mild Cognitive Impairment, MCI). At this early stage, synaptogenesis is still very active and neuronal loss is minimal, so the neurogenic and anti-amyloid multi-target properties of curcumin can be maximally utilised [12, 17]. Curcumin's multi-target efficacy can be further amplified when coupled with other active therapies:

Berberine: synergistic downregulation of soluble A β 1-42 by curcumin and berberine alleviates oxidative stress and improves cognition by activation of the AMPK-autophagy pathway [26].

Vitamin D3: Synergistic with curcumin to eliminate free radicals, replenish intracellular GSH and increase NGF [16].

Probiotics (Gut-Brain Axis): Co-administration of curcumin with probiotics (e.g., *Lactobacillus Rhamnosus*) synergistically improves spatial memory deficits, modulates the gut-brain axis, and decreases neuroinflammation [11].

Piperine Co-administration: Inhibits hepatic glucuronidation and bypasses first pass metabolism resulting in 2000% increase in the bioavailability of curcumin [21].

12. Conclusion

Curcumin is a very promising natural pleiotropic molecule targeting multiple pathological nodes of Alzheimer's disease. Preclinical studies have demonstrated its multi-modal neuroprotective profile, including: inhibition of A β production and direct biophysical inhibition of aggregation, inhibition of tau hyperphosphorylation and NFT formation, activation of Nrf2-mediated endogenous antioxidant defences, chelation of redox-active transition metals, down-regulation of NF- κ B to inhibit chronic neuroinflammation, and activation of canonical Wnt/ β -catenin and Akt/CREB pathways to promote adult hippocampal neurogenesis and synaptic integrity [29].

Standard oral curcumin has failed in early AD clinical trials due to its poor systemic bioavailability, extensive metabolism and limited BBB penetration, problems which have been overcome by innovative pharmaceutical delivery systems. Bioavailable complexes (Theracurmin, Longvida) clinically validated, and preclinical nanocarriers (PLGA nanoparticles, PEGylated multi-walled carbon nanotubes) are excellent brain targeting and have shown excellent safety and cognitive enhancing profiles [5, 21, 25]. A multidisciplinary approach with nanotechnology, precision medicine and biomarker guided RCTs will be required to successfully bridge the translational gap from laboratory bench to clinical bedside. Developing bioavailable formulations of curcumin for early, prodromal, AD populations is a very feasible and low cost way to change the management of Alzheimer's disease and modify its progressive course [12].

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