

REVIEW ARTICLE

Antioxidant, anti-inflammatory and epigenetic potential of curcumin in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) constitutes a multifactorial neurodegenerative pathology characterized by cognitive deterioration, personality alterations, and

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behavioral shifts. The ongoing brain impairment process poses significant challenges for therapeutic interventions due to activating multiple neurotoxic pathways. Current pharmacological interventions have shown limited efficacy and are associated with significant side effects. Approaches focusing on the early interference with disease pathways, before activation of broad neurotoxic processes, could be promising to slow down symptomatic progression of the disease. Curcumin—an integral component of traditional medicine in numerous cultures worldwide—has garnered interest as a promising AD treatment. Current research indicates that curcumin may exhibit therapeutic potential in neurodegenerative pathologies, attributed to its potent anti-inflammatory and antioxidant properties. Additionally, curcumin and its derivatives have demonstrated an ability to modulate cellular pathways via epigenetic mechanisms. This article aims to raise awareness of the neuroprotective properties of curcuminoids that could provide therapeutic benefits in AD. The paper provides a comprehensive overview of the neuroprotective efficacy of curcumin against signaling pathways that could be involved in AD and summarizes recent evidence of the biological efficiency of curcumins *in vivo*.

KEYWORDS

Alzheimer's disease, curcumin, epigenetic regulation, neuroinflammation, oxidative stress

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disorder characterized by a gradual decline in cognitive functions, including memory, language, and executive skills, surpassing the normal aging-related cognitive changes. AD accounts for approximately 60%–80% of diagnosed cases of dementia, making it the primary cause of dementia worldwide.¹ The number of AD diagnoses in the United States alone is projected to reach 13.8 million by 2050, leading to a significant disease burden.² The pathology of AD is characterized by the presence of neurofibrillary tangles composed of hyperphosphorylated tau proteins and β -amyloid plaques in the brain. These protein deposits accumulation has been associated with widespread neuronal damage and atrophy.³

Given the devastating impact of AD and the lack of effective treatments, there is a growing interest in exploring potential pharmacological and non-pharmacological therapies to delay or prevent the progression of the disease. Nutraceuticals, compounds with medicinal properties derived from food sources, have garnered attention due to their potential health benefits in AD. Curcumin is a naturally occurring polyphenol found in turmeric, which has long been utilized in traditional medicine for its anti-inflammatory and antioxidant properties.⁴ Curcumin's anti-inflammatory properties stem from its capability to inhibit multiple proinflammatory signaling pathways

mediated by nuclear factor kappa B (NF- κ B) and immune cell activation. Through this modulation of inflammatory mediators, encompassing cytokines, adhesion molecules, growth factors, and enzymes, curcumin holds the potential for therapeutic benefits.⁴ Numerous studies have investigated the therapeutic potential of curcumin against various neurodegenerative diseases, including AD.⁵ Some evidence suggests that curcumin may be able to counteract the formation of amyloid plaques.^{6,7} Additionally, curcumin has been found to modulate AD-associated epigenetic changes by influencing methylation patterns, microRNAs, and histone-modifying enzymes.⁸ However, the specific effects of curcumin on treating or preventing AD-associated changes have not been extensively studied.

The benefits of curcumin in modulating AD pathways warrant more investigation to explore its potential as a novel approach to counteracting disease progression. This manuscript presents a comprehensive literature review that delves into the potential therapeutic benefits of curcumin in AD. We extensively searched multiple databases to gather relevant studies and information about curcumin's biological activity and its potential interactions with AD-associated pathways. This review highlights curcumin's ability to influence various processes related to AD pathogenesis, including oxidative stress, inflammation, and epigenetic regulation of gene expression.

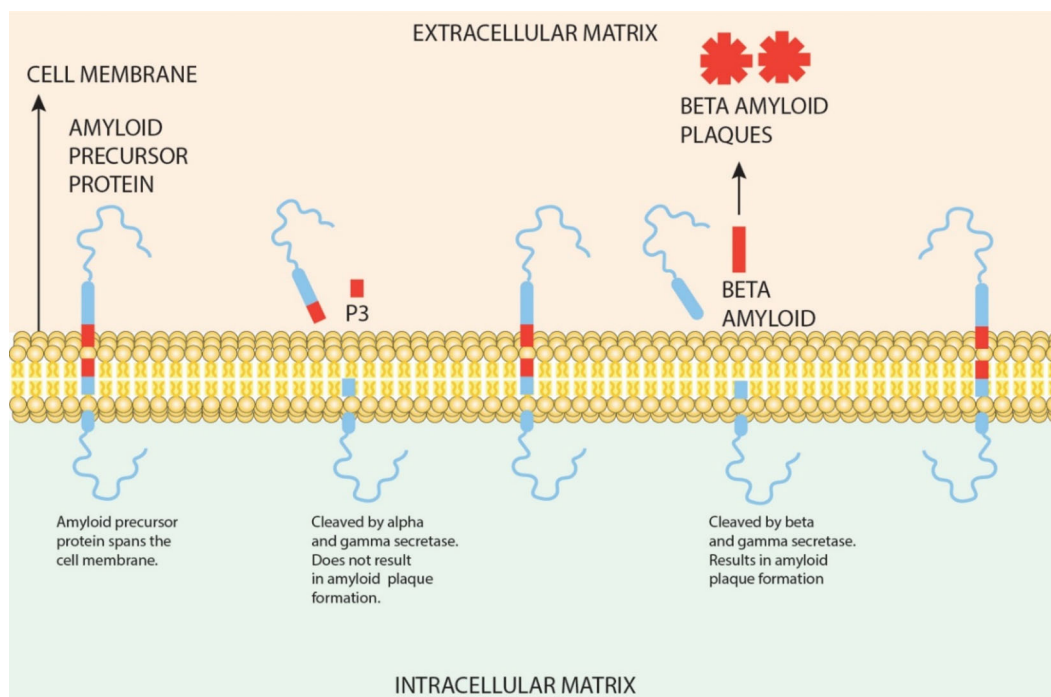


FIGURE 1 Formation of A β plaques. There are two pathways involved in App proteolysis: the amyloidogenic and non-amyloidogenic pathways. The Non-amyloidogenic pathway involves sequential alpha and gamma secretases processing to generate extracellular P3 and APP intracellular domains. The Amyloidogenic pathway involves the sequential APP processing by beta and gamma secretases to generate A β and APP intracellular domain.

2 | PATHOLOGIC CHANGES IN AD

2.1 | Deposition of toxic proteins

Pathological hallmarks of AD include the accumulation of amyloid plaques and neurofibrillary tangles. Amyloid plaques arise from the proteolytic cleavage of amyloid precursor proteins (APPs), ubiquitously expressed across numerous cell types (Figure 1). The identification of rare mutations in APP and presenilin (PS1), an enzyme responsible for intramembrane cleavage of APP, resulting in increased amyloid- β (A β) deposits has given rise to the hypothesis that dysregulation of A β processing could be a causal factor in the disease.⁹ The sequential cleavage of APPs by β and γ -secretases gives rise to β -amyloid proteins. These proteins can undergo internalization, assume a β -folded or β -pleated configuration, and subsequently accumulate into extended fibrils and aggregates, constituting plaques.¹⁰ These plaques, routinely identified in the brains of AD patients, are speculated to form through free radical activity, a recognized instigator of some neurodegenerative events observed at AD initiation and throughout its progression.¹¹ Among these, β -amyloid 42 is particularly harmful. This naturally occurring protein abnormally aggregates in the Alzheimer's brain, accumulating plaque between neurons and consequent impairment of cell function.

In contrast to amyloid deposition occurring extracellularly in AD, tau, a microtubule-associated protein, aggregates intracellularly into filamentous structures.¹² Under physiological conditions, tau functions to stabilize neuronal microtubules. However, aberrant AD biochemical modifications lead to tau dissociation from microtubules and subsequent aggregation with other tau molecules. These alterations are triggered by hyperphosphorylation, a process that can be induced by conditions such as oxidative stress or compromised glucose metabolism, leading to decreased tau O-GlcNAcylation and hyperphosphorylation.¹² This, in turn, results in the formation of threads that ultimately amalgamate into neurofibrillary tangles within neurons (Figure 2). These tangles disrupt cellular transport mechanisms, impeding synaptic transmission between neurons. Contemporary research posits that the pathological brain changes in AD are likely attributable to a synergistic interplay between β -amyloid proteins and neurofibrillary tangles.

2.2 | Neuroinflammation and oxidative damage

Neuroinflammation, commonly associated with AD, is frequently characterized by hyperactive microglia,

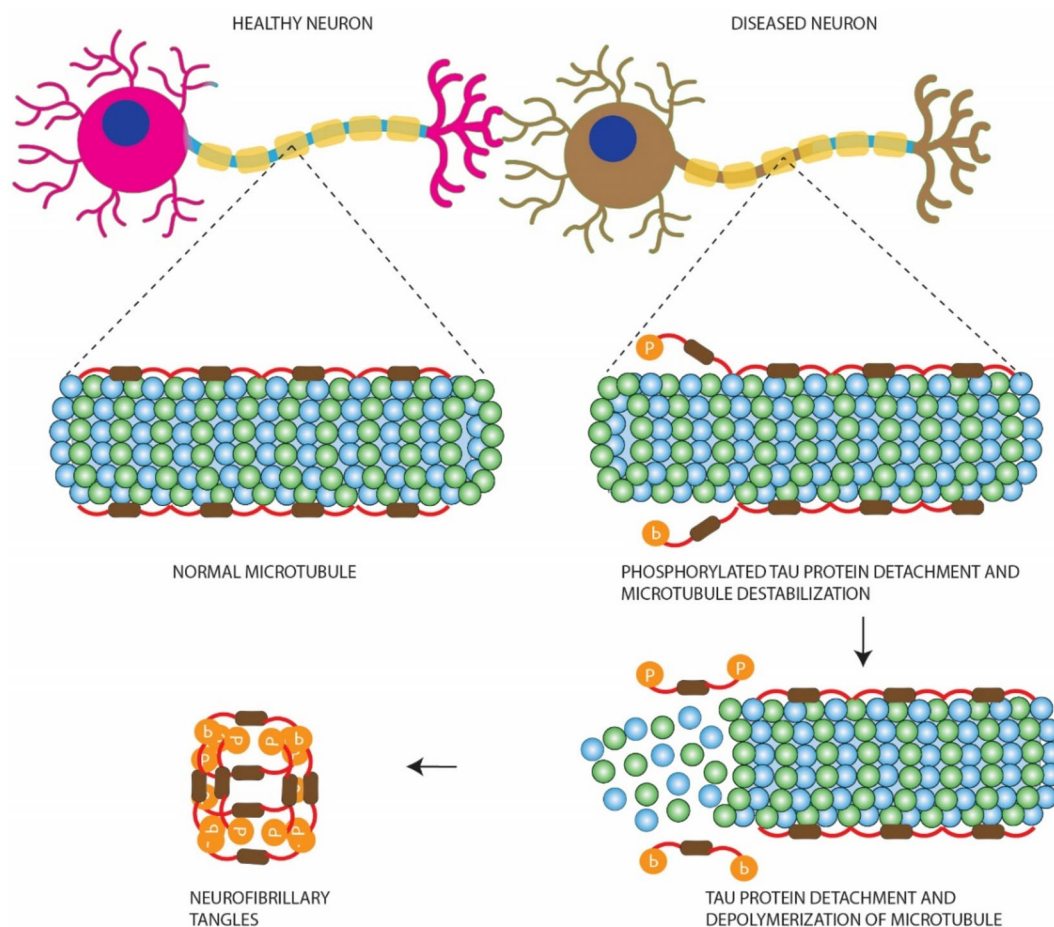


FIGURE 2 Formation of neurofibrillary tangles. Neurofibrillary tangles are formed due to hyperphosphorylation and dissociation of tau proteins from microtubules—dissociated tau proteins aggregate oligomers and ultimately form neurofibrillary tangles.

leading to elevated levels of chemokines, cytokines, and reactive nitrogen and oxygen species (RNS/ROS).¹³ This inflammatory state can precipitate an imbalance between the production of reactive compounds and their neutralization by cellular mechanisms, thereby causing oxidative damage. Observations from animal models of AD have reported such abnormal inflammatory responses in the hippocampus, with high levels of TNF- α , IL-1 β , cyclooxygenase-2 (COX-2), and nitric oxide.¹⁴ The overproduction of these inflammatory molecules can cause extensive cellular damage and result in neuronal death. An increase in oxidative damage has been linked with the deposition of A β in AD brains.¹⁵

Oxidative damage is manifested through various mechanisms, which in turn can be counteracted by the potential neuroprotective action of antioxidant compounds.¹⁶ Under normal physiological conditions, the body utilizes a variety of regulatory processes to maintain a balance in ROS activity. Oxidative stress, a condition arising from an imbalance between the generation and detoxification of ROS, has been implicated in several neurodegenerative disorders, including Parkinson's disease,

amyotrophic lateral sclerosis, and AD.¹⁷ ROS act as secondary messengers in the expression of several transcription factors and signal transduction molecules, including nuclear factor and heat shock-inducing factors.¹⁸ Moreover, they regulate immune response amplification, cell adhesion, and programmed cell death via redox-mediated pathways. The production of ROS can stem from endogenous sources such as mitochondria, lipoxygenases, peroxisomes, NADPH oxidase, and cytochrome P450 enzymes. At the same time, they can be counteracted by antioxidant defense mechanisms, which include superoxide dismutase (SOD), catalase, glutathione, glutathione peroxidase (GPx) (Figure 3), and vitamins A, C, and E. Exogenous sources, encompassing ionizing radiation, ultraviolet light, inflammatory cytokines, chemotherapeutics, and environmental toxins, also contribute to ROS production.^{19,20}

The brain is particularly susceptible to oxidative damage due to its high metabolic demand and limited antioxidant capacity.²¹ Increasing evidence suggests that AD brains display elevated levels of oxidative damage markers, possibly a consequence of both aging and environmental factors.²² Oxidative stress could differentially

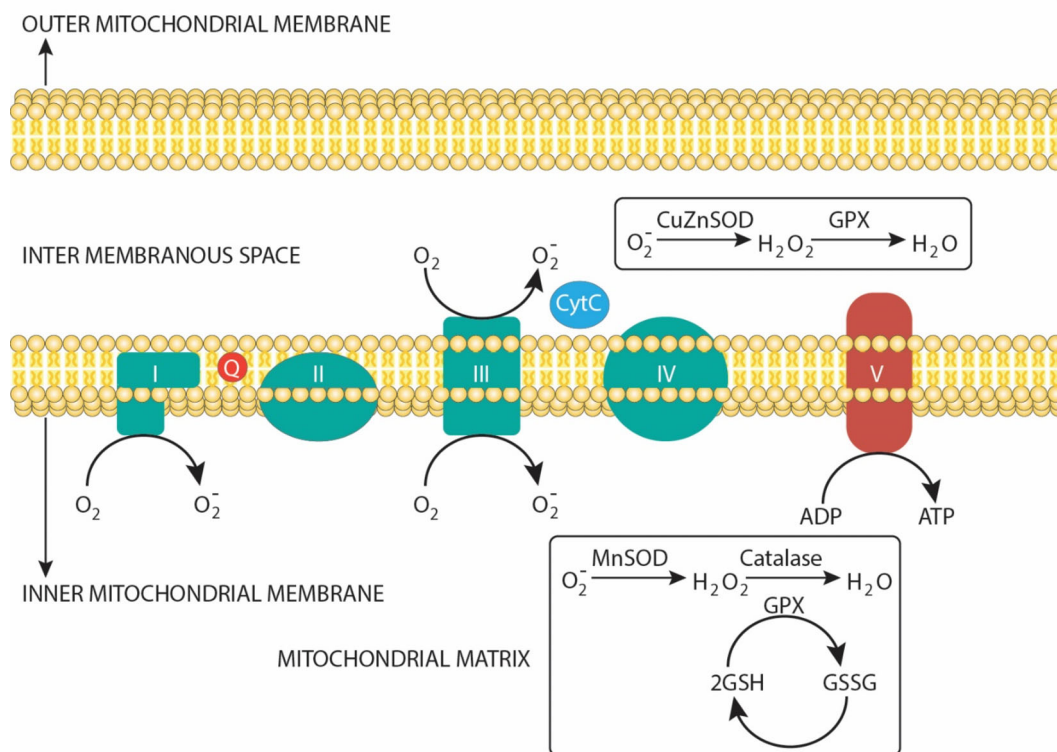


FIGURE 3 Illustration of production of ROS and antioxidant defense mechanisms in the mitochondria. Superoxide anions are produced during the transfer of electrons through the electron transport chain. I and III serve as the main source of ROS production. SOD, catalase, glutathione and GPx are antioxidant defense mechanisms that counteract ROS. (I) Ubiquinone oxidoreductase, (II) succinate dehydrogenase, (III) cytochrome c reductase, (IV) cytochrome c oxidase, (V) ATP synthase.

impact different brain regions. For instance, the amygdala, hippocampus, and cerebellum have been reported as most susceptible to oxidative stress.²³ The hippocampus, noted for its structural plasticity and regenerative capacity, stands out as particularly susceptible to AD. This brain region is among the first to be affected, reflecting its vulnerability to the disease's pathological processes. Studies have suggested that the pyramidal cells of the hippocampal CA3 region and the dentate gyrus (DG) granule cells are prone to oxidative stress, with significant functional implications.²⁴ Oxidative insults to the DG-CA system could disrupt cell proliferation, impede structural remodeling, alter structural plasticity, and inhibit neurogenesis, ultimately affecting synaptic neurotransmission and leading to cognitive impairments such as memory and learning deficits.²⁵

2.3 | Metal ion dyshomeostasis in AD

Metal ions play a crucial role in enzymatic reactions in the brain and are essential for proper neurological functioning. Given their ability to cross the blood-brain barrier, a fine balance of metal concentrations must be

maintained for optimal functioning. The dysregulation of metal ion homeostasis has been proposed as a contributor to the cognitive decline in AD through induction of oxidative stress, inflammatory responses, and the aggregation of A β .^{26–28} Redox-active metals can alter neurochemical pathways by catalyzing ROS formation, leading to an increase in cellular oxidative stress and subsequent inflammation.²⁹ Moreover, studies have demonstrated elevated levels of iron, copper, and zinc ions in the brains of patients with AD, especially in the regions with increased A β deposits accumulation.^{30,31}

Iron is essential for oxygen delivery and maintaining conserved metabolic processes.³² Excess iron however, has been shown to worsen tau pathology^{33,34} and induce cell death due to toxic ROS formation.³⁵ Researchers have also observed a higher ratio of Fe³⁺ to Fe²⁺ in the brains of mice with a higher amyloid burden, suggesting a possible link between dysregulated iron homeostasis and protein deposition.³⁶ Moreover, iron has been implicated in the overstimulation of microglia in AD, with the possibility of triggering microglial activation through proinflammatory cytokines mediated by NF- κ B.³⁷

Copper and zinc ions have been shown to bind to A β , promoting protein aggregation.^{38–40} These aberrant

interactions are limited to patients with AD and may be involved in the disruption of synaptic functions.⁴⁰ In the brain, copper is involved in catecholamine synthesis, degradation, neuropeptide synthesis, and myelin formation, along with its capacity to modulate zinc and iron levels. Under normal conditions, most of the copper in the blood is bound to ceruloplasmin (85%–95%) while only a small trace is available for interactions with other molecules (termed copper not-bound to ceruloplasmin (noncp-Cu)). Noncp-Cu has been implicated in redox mediated toxicity and oxidative stress.

Interestingly, both AD and Wilson disease, a genetic condition characterized by abnormal copper excretion, have similar concentrations of plasma noncp-Cu levels with additional abnormalities in copper excretion described in AD.⁴¹ Moreover, studies have shown that patients with mild cognitive decline and elevated levels of noncp-Cu, have faster conversion to AD⁴² suggesting copper dyshomeostasis may serve as a modifiable risk factor contributing to cognitive decline. Similar to copper, zinc serves as an amyloid modulator, as well as a regulator of neurochemical processes. Broad chelation of copper and zinc, in effort to restore homeostasis, have shown to decrease amyloid deposition by 49%⁴³ and showed significant improvement in learning and memory in transgenic mice models.⁴⁴ As such, metal dysregulation could serve as a potential therapeutic focus to modulate AD pathophysiology in select patient populations.

2.4 | Epigenetic dysregulation

Epigenetic changes have been recognized as significant contributors to the development of AD, mediating alterations in gene expression through diverse pathways that include modifications in DNA methylation, histone chemistry, and microRNA (miRNA) expression perturbations.^{8,45,46} Epigenetic regulation is instrumental in governing the neurodevelopment of neurons and glial cells within the brain,^{47,48} with increasing evidence suggesting its crucial role in neurogenesis and development. Given the sporadic nature of over 90% of AD cases and their typical late onset, scientific inquiry has shifted towards understanding the epigenetic contribution to AD etiology and the impact of environmental stimuli on epigenetic processes.²² For instance, oxidative damage to DNA may lead to altered methylation patterns and transcription of genes crucial to AD progression.²² Epigenetic processes that could be affected by oxidative stress, such as methylation of cytosine-guanine dinucleotide (CpG), are thought to accelerate AD pathological processes and increase A β production.⁴⁹ Such demethylation of cytosines within the promoter region of the APP gene could

instigate an accumulation of A β in aging brains.⁵⁰ Histone modifications have also been associated with AD. For example, altered methylation levels of the H3 histone at the brain-derived neurotrophic factor (BDNF) promoter, a protein associated with improved mitochondrial function, have been noted in the brains of AD patients.⁵¹

MiRNAs are non-coding RNAs that post-transcriptionally regulate gene expression through binding to messenger RNA (mRNA) and inducing its cleavage or translational repression. Aberrant expression of miRNA molecules has also been implicated in AD.⁵⁰ It has been observed that miRNAs associated with pathways related to amyloid processing and innate immunity exhibited reduced expression in postmortem brains of AD patients compared to controls.⁵⁰ Van den Hove et al. examined epigenetically regulated miRNAs and their role in pathways associated with AD.⁵² Their meta-analysis suggests that changes in miRNA expression due to epigenetic mechanisms may account for the dysregulation of various neuronal processes by affecting the expression of numerous genes.

3 | ACTIVITY OF CURCUMIN IN AD-ASSOCIATED PATHWAYS

3.1 | Disaggregation of protein deposits

Curcumin's role in attenuating the development of A β plaques in the brain and promoting their disintegration has been well-established through numerous in vivo studies.⁵³ For instance, one study demonstrated that systemic curcumin administration to mice over a seven-day period reduced existing plaques.⁷ In a separate investigation, mutant APP overexpressing mice treated with low-dose curcumin displayed A β levels and deposits reductions by 40% and 43% respectively, compared to untreated APP mice.⁶ Another study by Ono et al. further noted that curcumin could destabilize amyloid- β 40 (A β 40) and amyloid- β 42 (A β 42), two principal isoforms of A β implicated in AD.⁵⁴ In-vitro studies have similarly demonstrated curcumin's ability to destabilize pre-existing fibrillar A β structures. Beyond its disintegrative action, curcumin has been shown to hinder the formation of A β plaques.⁵⁵ In an in-vitro study, Yang et al. revealed that A β aggregation was significantly suppressed with escalating curcumin doses.⁵⁶ Curcumin, particularly at high concentrations, binds to A β and obstructs its self-assembly by unfolding the α -helix on the pathway to the amyloid form.^{6,56} This ability to destabilize and disassemble existing A β , inhibit fibrillar A β formation, and block A β self-assembly makes curcumin a potential asset in AD

research. Notably, Narlawar et al. also reported that curcumin-derived pyrazoles and isoxazoles could interfere with APP metabolism, thus markedly decreasing amyloid formation.⁵⁷

Like Aβ, Tau protein self-assembles into insoluble fibrillar structures that deposit in the brain, marking another characteristic feature of AD and contributing to the disease's clinical symptoms.⁵⁸ Given the significant role of tau pathology in AD, curcumin's capacity to dismantle preformed tau filaments is noteworthy.⁵⁹ Curcumin can inhibit tau β-sheet formation, the initial step in tau aggregation,⁴⁸ and its derivatives can modify the pathways leading to tau oligomer aggregation and tau fibril formation.^{48,60,61} A nematode model study demonstrated curcumin's potential to alleviate tau-induced neuronal dysfunction, reducing neuritic anomalies and enhancing the nematode's erratic motility.⁶² Moreover, Ma et al. reported that curcumin could decrease soluble tau and boost heat shock proteins (HSPs), which are involved in clearing tau. Their findings suggested the possibility of ameliorating tau-dependent synaptic and behavioral impairments even after the formation of tau tangles.⁶³

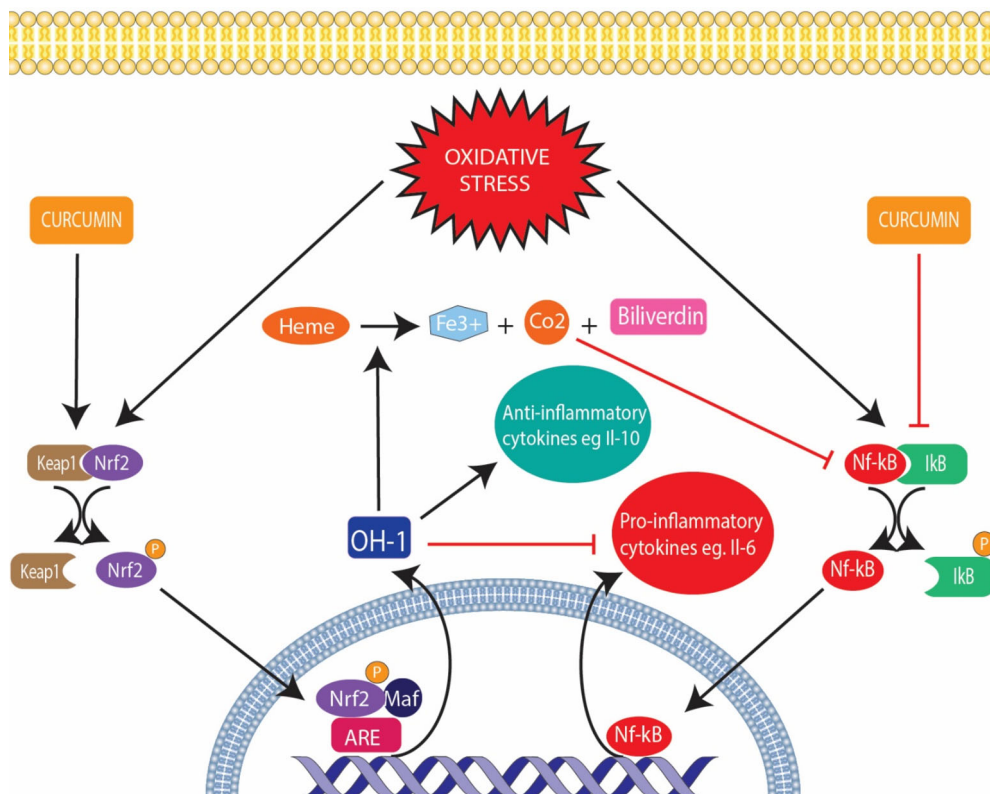
Additionally, curcumin exhibits anti-amyloid properties by modulating macrophage functions. Past research has shown that curcuminoids can enhance brain Aβ clearance in animal models.⁶⁴ Given that brain-native microglia are less efficient at clearing amyloid deposits

during AD-associated chronic neuroinflammation than bone marrow-derived macrophages,⁶⁵ curcumin's ability to increase the uptake of Aβ by macrophages in AD patients is promising.⁶⁶ Recent cell culture studies have illustrated that curcuminoids can rectify some innate immune cell deficiencies present in AD patients and enhance amyloid-phagocytosis by altering gene transcription.⁶⁷ These multifaceted effects of curcumin on aggregate deposition, clearance, and neuronal functions underline its potential value in AD research.

3.2 | Anti-inflammatory and redox activity of curcumin in AD

Numerous studies have underscored the neuroprotective role of curcumins in AD.^{53,68–70} The neuroprotective properties of curcumins arise from their anti-inflammatory and redox characteristics, which mitigate the detrimental impact of oxidative stress (Figure 4). Certain curcumin analogs have been shown to exhibit neuroprotective effects against Aβ-induced oxidative damage and cellular apoptosis, and have been proposed as potential AD treatment options.^{71,72} Curcumins, at both high and low doses, have been shown to decrease interleukin-1 and oxidized protein levels in the brains of mice.¹⁵ Another study demonstrated that curcumins could alleviate Aβ-induced neuroinflammation in AD rats via PPAR receptor activation.⁷³ In a separate study, curcumins

FIGURE 4 Mechanism of curcumin against oxidative stress and neuroinflammation. Curcumin exerts antioxidant and anti-inflammatory effects by upregulating and downregulating the transcription factors Nrf2 and NF-κB respectively. The upregulation of Nrf2 causes the transcription of genes involved in handling oxidative stress while the downregulation of NF-κB suppresses the production of proinflammatory cytokines such as IL-6.



have been found to inhibit LPS-induced inflammatory response in macrophages.⁷⁴ Curcumin therapy has been shown to restrict microglial cell activation, consequently reducing nitric oxide and proinflammatory cytokines including IL1, IL6, and TNFs. Additionally, curcumins counteract the activity of transcription factors such as activator protein 1 (AP1), NF- κ B, and other signal transducers to prevent LPS-mediated production of COX-2.⁷⁵ The research by ELBini-Dhouib and colleagues demonstrated that curcumin administration increased pro-oxidant levels, improved the functionality of antioxidant enzymes, boosted the production of anti-inflammatory cytokines, and decreased the number of apoptotic cells in the hippocampus of an AD rat model.⁷⁶ Given curcumin's proven antioxidant and anti-inflammatory capacity, it has been suggested as a potentially effective treatment against the oxidative and inflammatory damage observed in AD and other neurodegenerative disorders.⁷⁷

The chelating properties of curcumin make it a promising candidate for mitigating the adverse effects of metal ion dyshomeostasis in AD. Curcumin readily associates with redox-active metals such as copper and iron, which may attenuate inflammatory damage by preventing metal induction of NF- κ B.⁴⁷ Moreover, curcumin hydroxyl groups have been shown to help stabilize ROS to prevent further DNA damage.⁷⁸ Beyond modulating ROS, curcumin analogues have been shown to directly inhibit copper induced A β 42 cross-linking.⁷⁹ Curcumin's modulating effects on oxidative stress and neurotoxicity have also been demonstrated in animal models utilizing *Drosophila Melanogaster*.⁸⁰ One disadvantage worth noting however, is curcumin's low bioavailability and degradation within the body that limits its therapeutic capacity. Ultimately, further studies are warranted to evaluate its biological efficacy.

3.3 | Potential of curcumin to modulate neurotransmitter pathways

The cholinergic hypothesis of AD posits that a decrease in cholinergic neurotransmission, specifically acetylcholine (ACh), leads to cognitive abnormalities. ACh is predominantly produced by cholinergic neurons and is involved in a variety of cognitive processes such as learning, memory, attention, and executive functions. Post-mortem investigations have repeatedly shown a significant decrease in cholinergic indicators such as choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) in the brains of patients with AD compared to healthy controls.⁸¹ AChE inhibitors, such as donepezil and rivastigmine, are currently approved agents that decrease acetylcholine degradation and enhance cognitive function in AD, which is usually impaired due to cholinergic neuron deficiency.^{53,82}

Curcumin is emerging as a potential candidate for AD treatment due to its effects on cholinesterase activity.^{83–85} Curcumin has been shown in vitro to affect acetylcholine levels and cholinergic neurotransmission. Curcumin therapy has been demonstrated to increase the expression of the enzyme responsible for ACh synthesis, ChAT, in cultured cholinergic neurons.⁸⁶ Curcumin has also been shown to increase ACh release and cholinergic synaptic activity, implying a putative function in cholinergic neurotransmission.⁸⁷ A study by Aknyemi et al. in rats showed that neurotoxic agents like cadmium led to increased levels of AChE activity, which was subsequently reversed to control levels with curcumin treatment.⁸⁴ Another study by Touqueer et al. demonstrated that a curcuminoids mixture reduced AChE activity in the hippocampus and frontal cortex in ex-vivo studies.⁸²

Beyond its effects on acetylcholine, curcumin's influence extends to other neurotransmitter pathways, amplifying its potential neuropharmacological significance. Experimental investigations have revealed that curcumin interacts with dopamine and serotonin receptors, suggesting a role in modulating mood regulation and cognitive functions.⁸⁸ Moreover, curcumin's interactions with glutamate receptors imply a potential for regulating excitatory neurotransmission and synaptic plasticity.⁸⁹ These interactions underscore curcumin's multifaceted impact on diverse neurotransmitter systems.

3.4 | Potential of curcumin to modulate epigenetic changes in AD

Curcumin and its derivatives have shown a potential in mediating epigenetic alterations across various experimental models.^{90–93} As a lipophilic entity, curcumin and related curcuminoid compounds are capable of crossing the blood–brain barrier and influencing epigenetic regulation in brain cells.^{90,94–96} The multifaceted capacity of curcumin to induce epigenetic changes across various AD-associated pathways affirms its significance in future investigations and potential therapeutic applications. Moreover, the demonstrated epigenetic modulatory activity of curcumin analogs uncovers a wider scope for their therapeutic usage. Herein, we present an overview of evidence underscoring curcumin's ability to initiate epigenetic modifications in vital cellular processes and influence gene expression patterns implicated in AD.

Although the mechanisms by which curcumin might induce epigenetic modifications remain to be fully elucidated, studies suggest its potential in epigenetically modulating pathways implicated in amyloid depositions. For instance, a study with an AD mice model have shown that curcumin can reduce methylation levels of histone

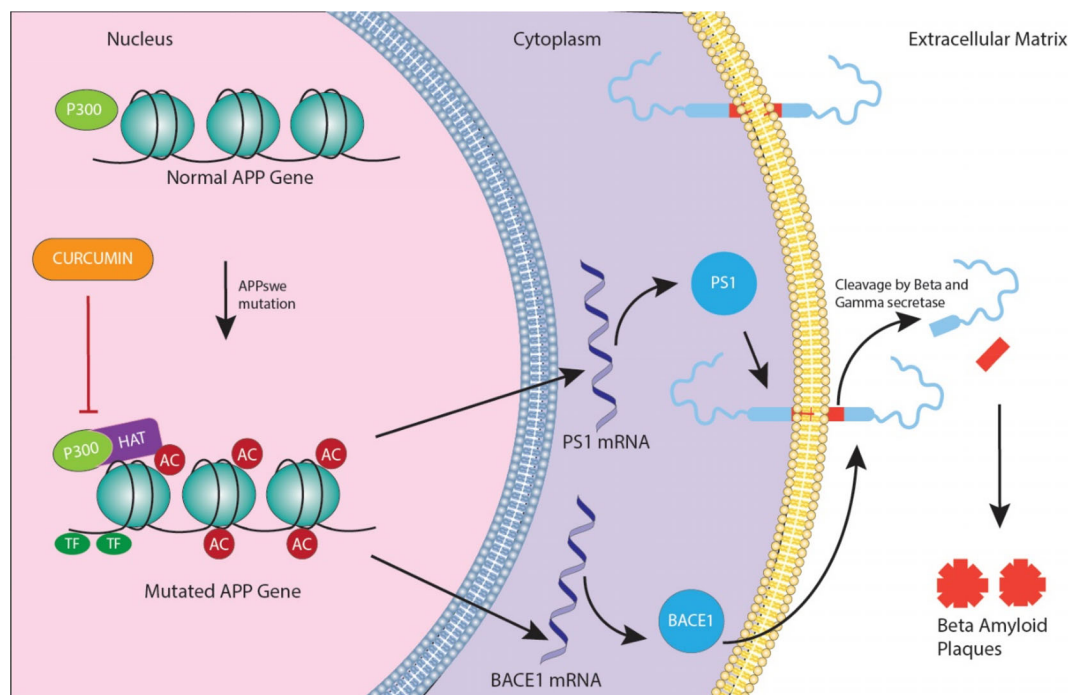


FIGURE 5 Mechanism of curcumin in suppression of AD-related genes PS1 and BACE1. Curcumin inhibits HAT/p300-mediated H3 acetylation and suppress expression of PS1 and BACE1.

H3 at lysine 27 (H3K27me₃) within the promoter region of the BDNF, subsequently decreasing amyloid aggregate formation.⁵¹ Li et al. demonstrated the protective role of curcumin in AD through modulating H3K27me₃ demethylase Jumonji domain-containing protein 3 (JMJD3).⁵¹ In AD mouse models, both JMJD3 and BDNF exhibited reduced expression levels, while methylation of the H3K27K histone was amplified compared to controls. BDNF is believed to be vital for brain development, neuron regeneration and synaptic plasticity, and exogenous supplementation with BDNF could improve mitochondrial function. Remarkably, curcumin supplementation restored this balance by increasing mRNA and protein expression levels of JMJD3 and BDNF while concurrently reducing H3K27me₃ levels at the BDNF promoter region. This effect of curcumin boosted mitochondrial function and limited the accumulation of A β aggregates.⁵¹

Curcumin has also been found to alter gene expression by regulating histone acetyltransferases (HATs) and histone deacetylases (HDACs) activity,⁹⁷ enzymes integral to cellular pathway regulation through chemical modifications of histones.⁹⁸ Research has unveiled that histone acetylation of AD-associated genes plays a novel role in familial AD pathology and potentially impacts the regulation of genes linked to memory and learning.⁹⁹ Curcumin has been shown to selectively inhibit the intrinsic E1A-associated 300-kDa protein (p300) p300 in HATs, thus suppressing the expression of AD-related

genes PS1 and beta-site APP cleaving enzyme (BACE1) through inhibition of H3 acetylation in their promoter regions (Figure 5).⁹⁹

DNA methyltransferases (DNMTs), part of the cytosine methyltransferase family, are major DNA modifying enzymes, primarily modulating the methylation of CpG sites, leading to either transcriptional gene silencing or activation.¹⁰⁰ Alterations in DNA methylation patterns linked to AD are known to be specific to certain brain regions and cell types.⁴⁵ Curcumin and its metabolites have been found to inhibit the catalytic thiol group in DNMT1, consequently reducing global DNA methylation levels.⁹² Curcumin analogs have been shown to upregulate A β -degrading enzyme neprilysin (NEP) activity, with DNA methylation modulation through DNMT1 inhibition being the proposed regulatory mechanism.^{96,101} Moreover, AD pathology has been associated with dysregulation of Wnt signaling pathways, culminating in increased A β aggregation, tau phosphorylation, and inflammatory pathologies.¹⁰² Curcumin is speculated to exert neuroprotective properties through Wnt pathway modulation.¹⁰³ Certain curcuminoid compounds, such as demethoxycurcumin and bisdemethoxycurcumin, found in commercial-grade curcumin mixes, have been shown to induce Wnt inhibitory factor-1 (WIF-1) promoter region demethylation by directly suppressing the activity of DNMT1, thereby inhibiting the canonical Wnt pathway.⁹⁰

Curcumin has also been shown to alter epigenetic mechanisms involved in regulating inflammatory pathways. Curcumin has been found to regulate the expression of transcriptional regulators known as sirtuins (SIRT6), involved in inflammation and stress response, by regulating histone acetylation levels. This modulation by curcumin leads to a downregulation of downstream inflammatory molecules and normalization of oxidative stress.¹⁰⁴ Nrf2 pathways, which upregulate antioxidant responses and other crucial cellular responses, mitigate multiple AD-associated pathogenic processes. As AD therapeutic agents, Nrf2 activators have been proposed for clinical trial evaluation.¹⁰⁵ Curcumin has also been demonstrated to induce Nrf2 promoter demethylation and restore its expression levels.⁹¹

Additionally, curcumin has demonstrated activity in modulating several pathogenic miRNAs, including those involved in the regulation of the AD-associated apolipoprotein E (apoE) gene.¹⁰⁶ Additionally, curcumin could potentially regulate the AD-associated elevation of miR-128 and miR-9, previously shown to control the levels of tau-clearing protein BAG2.¹⁰⁷ Through this mechanism, curcumin could diminish levels of phosphorylated tau protein and clear tau tangles from rat cortical neurons.¹⁰⁷

In conclusion, evidence supports curcumin's potential in effectuating epigenetic modifications that impact several cellular processes and gene expression patterns linked to AD. Its potential capacity to influence histone modifications, DNA methylation, levels of miRNAs to modulate Wnt signaling, amyloid processing and inflammatory pathways, offers promising prospects for AD therapeutics. Curcumin, with its diverse range of epigenetic modulatory properties, holds substantial promise as a potential therapeutic compound.

4 | EVIDENCE OF BIOLOGICAL ACTIVITY OF CURCUMINS AGAINST AD IN HUMAN STUDIES

At present, AD remains an unmet clinical challenge with no effective treatment approach. Devising strategies to delay the progression of this devastating disease could substantially attenuate its deleterious impact. One such strategy being investigated is the use of bioactive curcumin, known for its therapeutic potential in managing chronic diseases such as diabetes, depression, and obesity, among others.^{108,109} Considering the neuroprotective capabilities of curcumin we described, it represents a prospective candidate for further exploration for more potent AD interventions.⁹⁴

Multiple human studies suggest a potential of curcumin to modulate AD pathways in-vivo (Table 1). Zhang

et al.'s 2006 findings demonstrated in-vivo effectiveness of curcumin in clearing amyloid deposits.⁶⁴ In this study, macrophages were extracted from the blood of six AD patients and three healthy controls. It was observed that treatment of macrophages of AD patients with curcuminoids notably enhanced the uptake of A β . Research by DiSilvestro et al. extended these findings, investigating the effect of curcumin on inflammatory pathways and A β clearance in healthy middle-aged individuals.¹¹⁰ Daily administration of a low dose of curcumin has exhibited potential in reducing plasma levels of A β protein and augmenting antioxidant capacity by elevating the levels of radical scavenging enzymes catalase and myeloperoxidase.¹¹⁰ In a different study, a solid lipid formulation of curcumin was observed to enhance cognitive performance, alleviate fatigue, and mitigate the detrimental effects of psychological stress.¹¹¹ Further exploration into the therapeutic potential of curcumin in AD was initiated by Baum et al.'s double-blind study in 2008.¹¹² Their 6-month clinical study confirmed the previously described advantageous effects of curcumin in AD, as such showing its potential to promote disaggregation of A β and anti-inflammatory and antioxidant responses. Although the study showed beneficial effects of curcumin without any adverse effects, the researchers recommended larger and longer trials for more robust investigation of curcumin's effectiveness in AD treatment. Most recently in 2020, Thota et al. demonstrated that 180 mg daily oral curcumin supplementation for 12 weeks could decrease circulating levels of islet amyloid peptide (IAPP) and glycogen synthase kinase-3 (GSK-3 β), both implicated in insulin resistance. Impaired insulin signaling has been linked to the pathogenesis of AD through modulation of signaling cascades and accelerated aggregation of insoluble proteins.¹¹³

Controversy persists within the scientific community regarding the therapeutic potential of curcumin in AD due to inconsistent support across different studies. A 24-week randomized double-blind study conducted by Ringman et al. did not find compelling clinical or biochemical evidence supporting the effectiveness of curcumin.¹¹⁴ Nevertheless, a subsequent randomized double-blind trial in 2014, which investigated the cognitive and mood effects of a lipid curcumin formulation, suggested that curcumin may be effective in enhancing cognitive functions.¹¹¹ The study's findings revealed significant improvements in sustained attention and working memory tasks following curcumin treatment, alongside a concurrent improvement in mood during continued therapy.

Despite these promising results, further investigation through larger-scale human studies is required to definitively determine the therapeutic potential of curcumin in AD management.

TABLE 1 Demonstrated potential of curcumin in AD human trials.

Study	Cohort	Intervention	Primary endpoint	Main result
Baum et al. ¹¹²	34 patients having a 6-month history of memory loss and cognitive impairment who have been diagnosed with probable or suspected AD	1 or 4 g curcumin capsule once a day for 6 months	MMSE (Mini-Mental Status Exam), Amyloid B40 level in CSF	No significant changes found
Ringman et al. ¹¹⁴	36 individuals with mild to moderate AD	24 weeks with 3 groups: placebo, 2 g or curcumin, 4 g of oral curcumin each day.	Changes to amyloid plasma levels, and ADAS-Cog modifications	Changes in plasma level do not result in any appreciable alterations in the ADAS-Cog, NPI, ADCS-ADL, or MMSE scores
Hishikawa et al. ¹¹⁵	3 with AD	12 weeks of treatment with 100 mg curcumin daily	Agitation using NPI and cognitive ability using MMSE	All three patients experienced a decreased in NPI-questionnaire brief version (NPI-Q) and 1 had an elevated MMSE
Cox et al. ¹¹¹	60 healthy adults, age 60–85	Circumin formulation (400 mg as Longvida®) for 4 weeks	Memory tests, mood changes were recorded after 1 h (acute) and 4 weeks (chronic)	1 hour: serial three subtraction results, increased accuracy on digital vigilance tasks, lower fatigue levels 4 weeks: Further improvement from hour 1
Rainey-Smith et al. ¹¹⁶	Randomized control trial: 96 healthy patients	1500 mg/day of Biocurcumax™ (curcumin) or a placebo for 12 months	Baseline Montreal score (MOCA Cognitive Test), as well as the 6- and 12-month follow-up assessments	At 6 months, there was a significant reduction in function in the placebo group that was not seen in the curcumin treatment group
Small et al. ¹¹⁷	46 individuals with MCI or age-related memory decline	For 18 months, take Theracurmin, which contains 90 milligrams of curcumin twice a day, or a placebo	Change from Baselines on Brief Visual Memory and Selective Reminding Task	Increases from Baseline on Selective Reminding tests noted
Thota et al. ¹¹³	Randomized control trial: 29 people received placebo and 14 Circumin	Circumin (180 mg/day) for 12 weeks	Plasma levels glycogen synthase kinase-3 (GSK-3) and islet amyloid polypeptide (IAPP).	IAPP and GSK-3 levels were decreased with dietary supplementation with curcumin. GSK-3β (-2.4 ± 0.4 ng/mL vs. -0.3 ± 0.6 , $p = .0068$) and IAPP (-2.0 ± 0.7 ng/mL vs. 0.4 ± 0.6 , $p = .0163$)

5 | CONCLUSION

Alzheimer's is a debilitating neurodegenerative disease that affects millions of people worldwide. Over the years, the utility of numerous technologies for early AD detection has been explored, with recent studies examining

the aggregation of misfolded proteins using near-infrared fluorescent probes.^{118,119} Although there is currently no cure for AD, optical imaging probes may further assist in pharmacologic development by tracking disease progression and the benefit of different treatment modalities. Despite advances in imaging and symptomatic

management, current pharmacologic therapy's efficacy is limited. Interestingly, curcumin and its metabolites have been shown to play a neuroprotective role, with the capacity to alter the pathological sequelae that may lead to AD. Curcumin's demonstrated antioxidant and anti-inflammatory role, along with its high safety profile, poses an intriguing possibility in preventing and treating AD. Additional studies are warranted to explore this therapeutic potential in greater detail.

AUTHOR CONTRIBUTIONS

Conceptualization, Toufik Abdul-Rahman, Wireko Andrew Awuah; **Methodology**, Toufik Abdul-Rahman, Wireko Andrew Awuah; **Formal analysis**, Aashna Mehta, Jyi Cheng Ng, Megan Ariel Coghlan, Marija Zivcevska, Alexander J. Tedeschi, Emerson Costa de Oliveira, Akinchita Kumar, Emiliano Cantu-Herrera, Mykola Lyndin, Kateryna Sikora; **Investigation**, Aashna Mehta, Jyi Cheng Ng, Megan Ariel Coghlan, Marija Zivcevska, Alexander J. Tedeschi, Emerson Costa de Oliveira, Akinchita Kumar, Emiliano Cantu-Herrera, Mykola Lyndin, Kateryna Sikora; **Writing—original draft preparation**, Tatiana Mikhailova, Jacob Kalmanovich, Aashna Mehta, Jyi Cheng Ng, Megan Ariel Coghlan, Marija Zivcevska, Alexander J. Tedeschi, Emerson Costa de Oliveira, Akinchita Kumar, Emiliano Cantu-Herrera, Mykola Lyndin, Kateryna Sikora; **Writing—review and editing**, Athanasios Alexiou, Anwar L. Bilgrami, Khalid Mohammed Al-Ghamdi, Asma Perveen, Marios Papadakis, Ghulam Md Ashraf; **Supervision**, Athanasios Alexiou, Ghulam Md Ashraf; **Funding acquisition**, Anwar L. Bilgrami, Khalid Mohammed Al-Ghamdi, Marios Papadakis. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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