

REVIEW ARTICLE

PLGA-Based Curcumin Delivery System: An Interesting Therapeutic Approach in the Treatment of Alzheimer's Disease

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Abstract: Progressive degeneration and dysfunction of the nervous system because of oxidative stress, aggregations of misfolded proteins, and neuroinflammation are the key pathological features of neurodegenerative diseases. Alzheimer's disease is a chronic neurodegenerative disorder driven by uncontrolled extracellular deposition of β -amyloid (A β) in the amyloid plaques and intracellular accumulation of hyperphosphorylated tau protein. Curcumin is a hydrophobic polyphenol with noticeable neuroprotective and anti-inflammatory effects that can cross the blood-brain barrier. Therefore, it is widely studied for the alleviation of inflammatory and neurological disorders. However, the clinical application of curcumin is limited due to its low aqueous solubility and bioavailability. Recently, nano-based curcumin delivery systems are developed to overcome these limitations effectively. This review article discusses the effects and potential mechanisms of curcumin-loaded PLGA nanoparticles in Alzheimer's disease.

Keywords: Curcuminoids, polymer, PLGA, cognition, inflammation, drug delivery.

1. INTRODUCTION

Central Nervous System (CNS) disorders affect nearly 1.5 billion of the world's population [1]. Neurodegenerative diseases cause chronic impairment of sensory, motor, behavioral and cognitive functions due to progressive loss of CNS neurons. Most forms are associated with increased age and are likely due to oxidative stress, aggregations of misfolded proteins [2], and neuroinflammation [3]. Neuroinflammation is the main contributor to the progression of neurodegenerative disorders and is characterized by the breakdown of the integrity of the Blood-Brain Barrier (BBB), morphological changes in glial cells and extensive tissue destruction by invading leukocytes [4]. The enhanced expression of cytokines by lymphocytes and myeloid cells initiates the inflammatory cascade. It is then mediated by secondary messengers (nitric oxide and prostaglandins), ROS and cytokines, such as IL-1B, IL-6, IL-23, TNF- α , granulocyte/macrophage colony-stimulating factor (GM-CSF) and chemokines (like CCL2, CCL5, and CXCL1). The overproduction of the

above inflammatory mediators results in neuronal damage and death [5]. Neuro-inflammaging refers to the correlation between aging and neuroinflammation. During this process, activated microglia and astrocytes enhance cyclooxygenase-2 (COX2), nuclear factor-KB (NF-KB), and inducible nitric oxide synthase (iNOS). Subsequently, iNOS induces proinflammatory cytokines (e.g., interleukin (IL)-6, IL-1B) and neurotoxic factors like Reactive Oxidative Species (ROS) and Tumor Necrosis Factor (TNF-B) which contribute to neuronal damage [6, 7]. Also, Toll-Like Receptors 4 (TLR4) and NF-KB activation by innate immune signal transduction adaptor (MYD88) induce proinflammatory factors (TNF-B, IL-1B, IL-6 and iNOS), which in turn potentiate various inflammatory pathways. A significant contributor to maintain a neuroprotective state against neuroinflammation is the heat shock response [8, 9]. The respective genes involved are known as vitagenes, which are involved in the production of antioxidant and anti-apoptotic molecules and activation of pro-survival pathways [10-12]. The members of the heat shock protein family include heme oxygenase-1 (HO-1), heat shock protein (Hsp70), sirtuins (Sirt-1), γ -glutamyl cysteine synthetase (γ -GCS) and thioredoxin/thioredoxin reductase (Trx/TrxR) [13, 14].

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In addition, neurotoxicity could be due to proteotoxicity, which refers to the toxic effect of proteins/peptides misassembly and aggregation in several cell types. The proteotoxicity-associated neurotoxicity mechanisms are inadequately recognized; nevertheless, it is well known that protein aggregation is significantly associated with neurodegenerative disease development [15]. The recognition of proteotoxic insults accompanied protective cellular stress response pathways and chaperone networks associated with preventing protein misfolding and aggregation are required for the adaptation and survival of cells and organisms [16]. Cancer, metabolic and neurodegenerative diseases showed chronic proteotoxic stress where the cell's chaperones capacity and other homeostasis components seem poorly adapted [17]. In this way, the nonnative protein species accumulate, following the dysregulation of protein folding quality that can develop oligomers, aggregates, and compositions characteristic of neurodegenerative disease [18].

Consequently, damage of proteome integrity due to reduction in biosynthetic and repair activities affects protecting genes (vitagenes) that regulate aging, thereby affecting the health and lifespan of the organism [19, 20]. The pharmacological regulation of pathways involved in cellular-stress response is a potential target for some disease therapies like cancer, cardiovascular and neurodegenerative diseases [21].

The achievement of the therapeutic dose is crucial for any successful medical intervention. Understanding the dose-response nature, especially in the low-dose zone [22-26], is vital for clinical success. However, it is reported that conventional dose-response models (commonly accepted threshold and linear dose-response models) were unsuccessful in accurately predicting responses in the low-dose zone. In contrast, the hormetic dose-response has been reported remarkably powerful [9, 27-33]. Consequently, a hormetic dose-response consideration in the performance, toxicological and pharmacological studies analyses has been proposed to improve the drug development process and chemical hazard/risk assessment [9].

2. ADAPTIVE STRESS RESPONSES/HORMESIS ROLES IN THE NERVOUS SYSTEM

Hormesis is a common toxicologic term that refers to a dose-response phenomenon to a chemical agent or environmental factor identified by low-dose stimulation, zero dose and high-dose inhibition. Therefore, it may be graphically illustrated by a J-shaped or an inverted U-shaped dose-response (the "U" arms are inhibitory or toxic concentrations while the curve zone stimulates a beneficial response) [34, 35]. The normal physiological function of cells and organisms and some natural and synthetic molecules (nutrition) follows a hormetic curve with deficient homeostasis and toxicity regions. Homeostasis is a hormetic zone of physiological concentrations with a safe and beneficial dose and the therapeutic window, a synonym of the hormetic zone in pharmacology [34, 36].

It is reported that a different type of oxidative and other stresses could induce hormesis as an adaptive response that contributes to the resistance of cells/organisms to higher (and normally toxic) doses of the same stressing agent [37]. Studies have shown that reactive oxygen species (ROS)

impair cellular homeostasis through complicated and irreversible damage to cellular components [38]. During oxidative damage, the high reactivity of molecular oxygen and its intermediates is produced, resulting in DNA, lipids and proteins oxidative modifications [39]. Mitochondria is one of the main sources of ROS (superoxide anion radical) as unwanted by-products of oxidative phosphorylation. The excessive production of ROS has been involved in several pathological conditions, including inflammatory conditions, such as arthritis, cardiovascular disease and cancers [40-42]. In addition, superoxide production by mitochondria is considered to participate in neuronal damage varying from chronic intermittent cerebral hypoxia [43] to Alzheimer's Disease (AD) [44]. Besides the adverse effects of ROS on cell function and survival, it is now apparent that mitochondrial superoxide and hydrogen peroxide in lower subtoxic levels play critical roles in a variety of cellular functions and can also stimulate signalling pathways that improve cell survival and protect cells against injury and disease [15].

This neuroprotective impact of a subtoxic rise in cellular oxidative stress is known as "preconditioning" [45] but generally named mitochondrial hormesis or mitohormesis [46].

Based on the latest evidence, neuroprotective features of antioxidants, iron-chelating in addition to anti-inflammatory agents with distinct consideration to polyphenols have attracted particular attention [47, 48]. According to the hormesis theory, a stressor agent (drugs, toxins and natural substances), if administered at low doses, may trigger a positive response in the duration of adjustment or protection from the stressors. In contrast, at a higher dose, the toxic effect predominates [49-55]. Based on *in vitro* evidence, polyphenols stimulate the heat shock protein (Hsp) pathway by applying this paradigm, which represents a critical role in the cellular stress response [56, 57]. Two members of the Hsp family, Heme oxygenase-1 (HO-1) and Hsp70, also remembered as vitagenes, because of their antioxidant activity, have attracted significant attention [56-58].

Various studies on experimental models of cancer [59], neurodegenerative disease [60] and cardiovascular disease [61] reported some phytochemicals through activating adaptive stress response signalling, having favourable effects [62]. These pathways generally involve the kinases and transcription factors activation, including the antioxidant response element (ARE), Nrf-2 (a transcription factor) and its genetic target activation by sulforaphane and curcumin [63]; the transient receptor potential (TRP) calcium channels activation by capsaicin and allicin [64] and histone deacetylases and their target FOXO transcription factors activation by resveratrol [65]. These events finally result in increased cytoprotective protein production, including antioxidant enzymes, phase 2 enzymes, heat-shock proteins, growth factors and proteins required for regulating cellular metabolism [60]. For example, it is reported that Hidrox (HD) is a polyphenol complex from organic olives containing 40-50% of Hydroxytyrosol, which could inhibit the activation of NF- κ B and decrease the iNOS levels. This study showed that redox homeostasis regulation by Nrf2 presumably leads to the regulation of NF- κ B activity and the inflammatory response characteristic of Parkinson's disease (PD) [66]. Another similar study also revealed that hydroxytyrosol as polyphenols of

the olive oil inhibits neurodegeneration (Parkinson's-like phenotypes) in nematodes and rodents, presumably through the Nrf2 signalling pathway and hormesis response [67].

Consequently, from the viewpoint of hormesis response, the achievement of the right doses of administrated agents like phytochemicals or chemical drugs is required to manage various conditions, particularly neurodegenerative disease, effectively [68, 69]. In recent preclinical studies, natural products derived from plants and herbs, such as curcumin supplementation, have alleviated neuroinflammation progression [70-72].

3. ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disease mainly seen in the elderly population [73-76]. However, AD is a significant concern for the 21st century affecting more than 24.3 million people worldwide [77], which is expected to affect around 120 million cases by 2050 [78, 79]. The contributing factors in AD development include uncontrolled extracellular β -amyloid ($A\beta$) deposition in the amyloid plaques, intracellular tau protein hyperphosphorylation, which forms neurofibrillary tangles mitochondria dysfunction, inflammation and oxidative stress, and eventually cholinergic dysfunction due to progressive degeneration in the basal ganglia [80-85]. Amyloid proteins ($A\beta$) are a 42 amino acid long cleavage product of amyloid precursor protein (APP), a transmembrane polypeptide with neurotrophic activity. Under non-physiological conditions, the APP processing *via* β and γ -secretases [86] results in extracellular aggregation of $A\beta$ monomers, which are then modified through phosphorylation forming dimers, oligomers, protofibrils and mature fibrils [87]. These end products can form toxic AGEs (Advanced Glycation endproducts) or amyloid plaques in the parenchyma and blood vessels [88]. These plaques inhibit mitochondrial activity, modify intracellular Ca^{2+} levels, increase oxidative stress, and stimulate neuroinflammation by impairing proteasome function. In addition, $A\beta$ peptides can induce tau hyperphosphorylation (a microtubule-associated protein) through the interaction with the signaling pathways that disrupt axonal transport and increase neurofibrillary tangles and soluble tau seen in AD. Also, $A\beta$ restricts tau protein degradation [89, 90]. Furthermore, it is demonstrated that $A\beta$ s stimulate microglia to secrete proinflammatory cytokines, leading to neuronal damage in AD [91-93].

4. NOVEL THERAPEUTIC STRATEGIES DEVELOPMENT IN ALZHEIMER'S DISEASE

The current AD therapeutic approaches are categorized into mechanism-based strategies, including the Amyloid targeting (Suppressing $A\beta$ Production, stimulating $A\beta$ clearance and preventing $A\beta$ aggregation), Tau targeting (Tau stabilizers and aggregation inhibitors, therapies targeted at Tau post-translational modifications and anti-tau immunotherapy), targeting of apolipoprotein-E (ApoE) function, and neuroprotective therapies (neurotrophins and their receptor-based therapies, therapies targeted at neuroinflammation and oxidative stress). In addition, non-mechanism-based approaches in AD treatment included symptomatic cognitive enhancers, treatments and interventions for AD prevention (secondary AD prevention interventions and primary preven-

tion). Ultimately, lifestyle modifications and risk factor management, including non-pharmacological interventions, have been examined in AD prevention trials [94]. Besides, phytochemical's efficacy in the treatment of neurodegenerative diseases, including AD and PD, have been investigated by numerous studies. Various studies investigated the probable efficacy of phytochemicals like berberine, epigallocatechin-3-gallate, curcumin, quercetin, resveratrol and limonoids against the most common neurodegenerative diseases, including AD and PD [95].

Currently, nanomedicines for improving traditional therapy have entered the clinical practice of several diseases, especially allergy, cancer and cardiovascular disorders. There are several clinical studies on the use of liposomal, gold and polymeric nanoparticles [96-108]. In addition, a few nano-based products are already used by oncologists. Nanomedicines *via* loading and delivering drugs to the targeted site, specific release profiles (depot effects), preserve the loading drugs from enzymatic degradations and improve bioavailability, provide helpful information at the cellular and tissue scales for designing patient-specific therapeutic interventions in various diseases [109]. As mentioned, curcumin as a phytochemical offers promising safe and inexpensive preventive options for neurodegenerative diseases, particularly AD, because of its actions on several molecular aspects of these diseases [95].

5. BIOLOGIC EFFECTS OF CURCUMIN

Curcumin is a hydrophobic polyphenol produced by *Curcuma longa* L. [110]. It is dietary safe [111] and has a wide variety of pharmacological activities, including wound healing [112-114], anticoagulant [115], antimicrobial [116], anticancer [117-121], anti-inflammatory [122-125], antioxidant [126], anti-diabetic [127], lipid-modifying [128], anti-amyloid [129, 130] and neuroprotective effects [131]. Curcumin exerts its antioxidant effects through different mechanisms. It can directly scavenge free radicals *via* its two phenolic sites and suppress ROS and reactive nitrogen species (RNS) production in the cellular environment. It also suppresses protein and DNA oxidation through the reduction of low-density lipoprotein (LDL). The expression of ROS-generating enzymes is inhibited, whereas antioxidant enzymes are upregulated by curcumin [132]. Curcumin modulates neuroinflammation by the downregulation of various inflammatory cytokines [133, 134].

Curcumin has pleiotropic activities through its complex chemistry and its capacity to affect various signalling pathways, including angiogenic and metastatic pathways, survival pathways like those regulated by NF- κ B and growth factors Nrf2-dependent cytoprotective pathways [135-140]. It has been demonstrated that curcumin is a hormetic agent *via* biphasic dose-responses on cells. It is stimulatory at low doses (like activation of the mitogen-activated protein kinase signalling pathway and an antioxidant function) and inhibitory at high doses (like autophagy and cell death induction). This means that several curcumin effects are dose-dependent, and some effects might be more prominent at lower doses, characteristic of a hormetic response. Curcumin has a modulatory effect in neurological diseases, such as AD, with a hormetic dose-response [141].

6. CURCUMIN LIMITATIONS

Despite the promising effects of curcumin in numerous clinical trials, it is not yet certified for clinical application. The main obstacles include low oral bioavailability, with an extremely low plasma concentration of 1% [142]. Low structural stability, limited absorption from the gastrointestinal (GI) tract, accelerated metabolism, and rapid systemic clearance are other reasons for curcumin's limited utility in the clinical setting [143, 144]. Limited stability of curcumin at alkaline conditions and light sensitivity are other concerns associated with curcumin [145-149].

7. DEVELOPMENT OF NOVEL CURCUMIN FORMULATIONS

To date, various formulations have been developed to improve curcumin bioavailability and drug delivery. Modifying the solid-state, formulating supersaturated solutions [150] and designing a more soluble compound like artificial analogs to resist *in vivo* removal and metabolism are some of the methods used to increase bioavailability. Other techniques include reducing particle size, combining curcumin with cellular metabolism and drug efflux suppressors [151]; the addition of adjuvant molecules, such as piperine, quercetin or silibinin, chemical combination of curcumin with polysaccharides, proteins or phospholipids and bio-conjugation of curcumin with turmeric oil or alanine [152, 153]. Despite the potential effects of these strategies in improving the solubility and bioavailability of curcumin, most of these formulations fail to target curcumin to specific sites of action and preserve its chemical structure, resulting in its rapid metabolism and removal. Nowadays, nanotechnology-based methods are introduced as promising substitutes for conventional formulations [154]. The main categories of nanof ormulation-based strategies are the application of stabilizers, adjuvants or polymer conjugates, and the development of liposomes, hydro/micro/nano gels, micelles, and nanoparticles (NPs) [152, 155, 156] (Fig. 1). Curcumin-nanoparticulated delivery methods represent potent carriers in treating neurodegenerative disorders since the desired size, chemical structure, surface zeta potential charge, and surface functionalization can be modified [156, 157]. It is demonstrated that curcumin encapsulation into nanoparticles remarkably improves its bioavailability, solubility, and chemical stability by protecting it from the outside environment's influence, such as enzymatic and pH degradation [110, 143, 158]. Nanocarriers' toxicity potential is the primary concern of many researchers since their composition and size must be non-invasive for medical purposes. The size of NPs and their elimination and biodegradation determine their safety. The average size of nanoparticles for drug delivery systems is less than 200 nm for brain applications but is conceptually expandable up to 1000 nm. The nanoparticles were developed based on two original opinions; the theory of magical bullets from Paul Ehrlich [159] and the idea of miniaturization from Richard Feynman [160]. The first investigation on drug transport to the brain by nanoparticles was performed in 1969 [161]. Afterwards, functionalized nanoparticles coated with polysorbate 80 facilitate their entry into the CNS. The same application was introduced by Müller *et al.*, [162] using lipid nanoparticles. Subsequently, cellular pharmacokinetic and mechanistic studies were performed to improve

vectorization. Recent studies focused on curcumin-loaded nanoparticle delivery systems, specific CNS targeting, and intranuclear levels in neurons [150]. Initially, polymeric nanoparticles were applied for drug delivery to the CNS, which included poly (lactic-co-glycolic acid) (PLGA), chitosan, and poly (butyl cyanoacrylate) (PBCA) [163]. Polymeric nanoparticles are approved by the Food and Drug Administration (FDA), and they are less toxic than the other compounds [164]. PLGA nanoparticles as biodegradable and biocompatible polymers with characteristics, such as the controlled release of various pharmacologically active groups [165, 166] like curcumin [167, 168], are commonly used for drug delivery [169]. The biodegradable and biocompatible properties of PLGA are due to their hydrolytic cleavage into natural metabolites (*i.e.*, lactic acid and glycolic acid), metabolized through the Krebs cycle and are then discharged as carbon dioxide and water [170]. The hydrophobic nature of PLGA guarantees significant entrapment and sustained release of curcumin [170]. It could also cross the lipophilic olfactory and trigeminal nerves [171]. Herein, the current experimental and clinical literature on the effects of curcumin-loaded PLGA particles on Alzheimer's disease (AD) is reviewed.

8. CURCUMIN EFFECTS ON AD

Curcumin inhibits two major pathological changes in AD; it blocks the self-assembly of A β plaques [129, 172-174] when binding to them and hinders tau hyperphosphorylation [175]. Also, curcumin has potent neuroprotective effects due to its anti-inflammatory and antioxidant effects. It inhibits the expression of inflammatory cytokines, cyclooxygenase enzyme (COX-2) [174] glycogen synthase-3 [176], and iNOS, possibly through the suppression of NF- κ B and JNK/AP-1-mediated gene transcription [177, 178]. An interesting feature of curcumin is its facilitated BBB penetration due to its unique charge and binding capabilities [179]. It is demonstrated that neuronal signaling, membrane homeostasis and cognitive defects following a traumatic brain injury could be improved by curcumin [180], as shown in Fig. (2).

9. EXPERIMENTAL AND CLINICAL STUDIES RELATED TO AD

The *in vitro/in vivo* studies on curcumin-loaded PLGA NPs formulations and their application in AD are summarized in order of publication year (Table 1). Yin-Meng Tsai evaluated the curcumin-loaded PLGA NPs distribution and showed that Cur-NPs formulation significantly increased curcumin concentration in the spleen and lungs. Compared to free curcumin, Cur-Nps remarkably prolonged the maintenance time of curcumin in the cerebral cortex and hippocampus up to 96% and 83%, respectively [181]. It has been shown that curcumin-loaded PLGA NPs with high water solubility induced potent anti-amyloid effects [182]. Intravenous injection, liposomes, acrylic polymer, and PLGA formulations could pass the BBB and preferentially be concentrated in the hippocampus, striata, and brain stem to exert antioxidant, anti-inflammatory, positive neurogenesis, and neuroplasticity effects [183]. In another study by the same authors, synthetic amyloid-binding aptamer (described as NN2) conjugated with curcumin-loaded PLGA NPs reduced the plasma amyloid levels through its effective attachment to

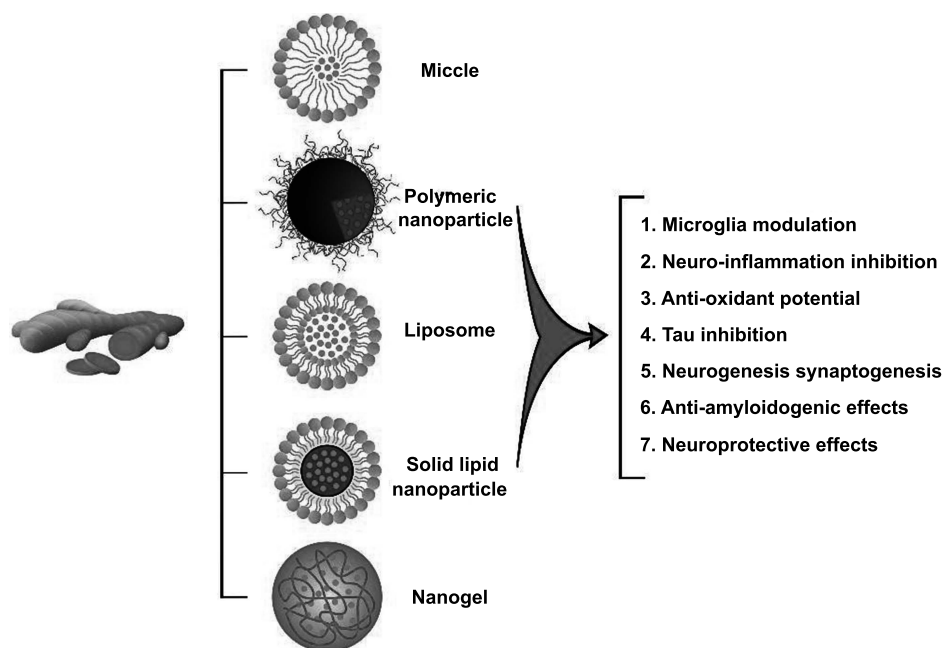


Fig. (1). Different types of curcumin-based nano formulations and their therapeutic effects. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

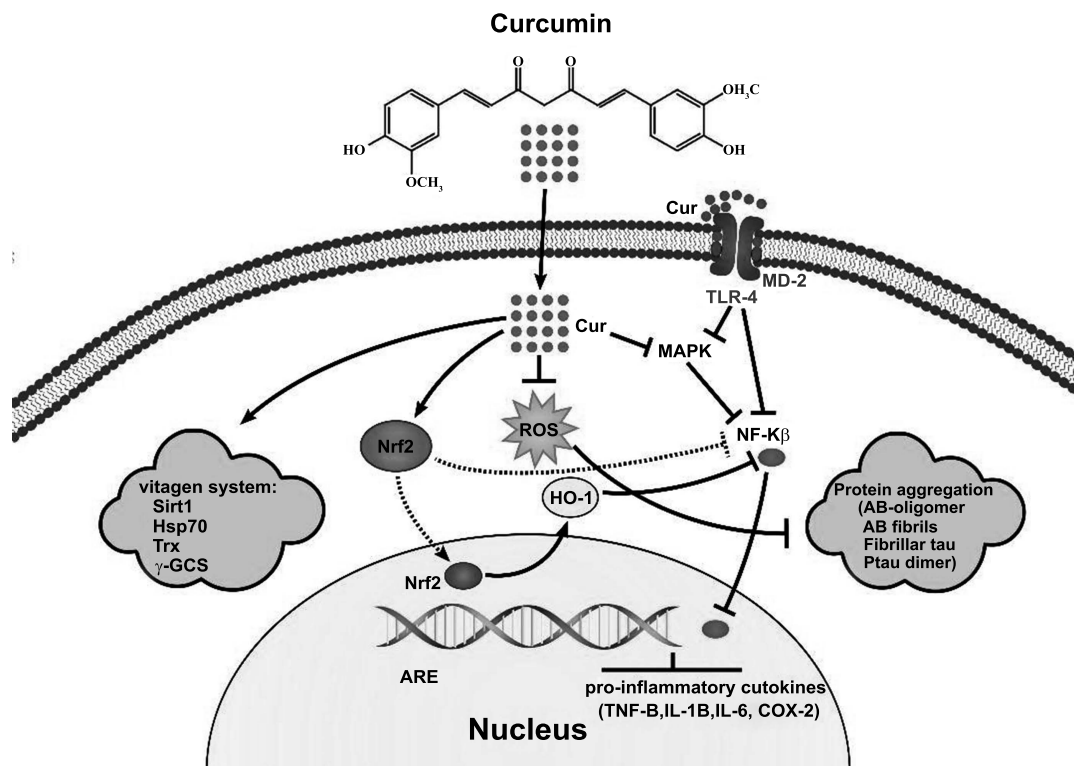


Fig. (2). The main pleiotropic functions of curcumin in neurodegenerative diseases; Curcumin exerts neuroprotection effects through Nrf2 activation, MAPK inhibition and downregulation of TLR-4 after binding to MD-2, leading to reduced expression of NF-κB and pro-inflammatory cytokines. Also, curcumin activates the protective systems and removes misfolded proteins by inhibiting ROS production.
Abbreviations: MD-2: myeloid differentiation factor 2, TLR-4: Toll-like receptor 4, MAPK: A mitogen-activated protein kinase, NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, ROS: reactive oxygen species, Nrf2: nuclear factor erythroid 2-related factor 2, HO-1: *Heme oxygenase-1*, ARE: antioxidant response element, COX-2: antioxidant response element, Hsp70: heat shock protein, Sirt1: sirtuins, Trx: thioredoxin/thioredoxin reductase, γ-γ-GCS: glutamyl cysteine synthetase. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

Table 1. Studies on the effects of curcumin-loaded-PLGA particles on AD.

Nanoparticle	Animal Models/Cell Culture	Clinical and Experimental Outcomes	Refs.
Curcumin-loaded PLGA nanoparticles	Male Sprague-Dawley rats	Increased the concentration and retention time of curcumin in various organs	2011 [181]
Curcumin-loaded PLGA nanoparticles	Neuroblastoma cell line and glioma cell line	Anti-amyloid effects	2011 [182]
Curcumin formulations composed of liposomes, acrylic polymer, and PLGA	Sprague-Dawley rats	Preferential concentration in hippocampus, striata, and brain stem	2011 [183]
Amyloid-binding aptamer (described as NN2), which conjugated curcumin loaded PLGA NPs	LAG cell line	Reduction in the size of protein aggregation after treating with aptamer bound curcumin nanoparticles	2012 [184]
Tet-1 peptide conjugated-curcumin - encapsulated-PLGA NPs	GI-1 glioma cells	Destroy amyloid aggregates and display antioxidative features	2012 [185]
Mitochondria-targeted curcumin-PLGA-b-PEG-triphenylphosphonium (TPP)	HeLa model cell line	Remarkable enhancement in drug management of AD	2012 [186]
Cur-encapsulated PLGA NPs	Human neuroblastoma SK-N-SH cells	Preventing H ₂ O ₂ -induced toxicity Inhibiting ROS elevation and GSH reduction, and activation of Nrf2	2012 [187]
Curcumin-loaded PLGA nanoparticles	Wistar rats	Induced endogenous Neural Stem Cells (NSC) proliferation by: increasing the expression of cell proliferation genes (reelin, Pax6, and nestin) increasing neuronal differentiation by inducing the expression of neuroigin, neurogenin, neuregulin, neuroD1, and Stat3 genes and activating the Wnt/ β -catenin pathway (regulator of neurogenesis) <i>in vitro</i> and hippocampus and subventricular zone	2013 [188]
Cur-encapsulated PLGA NPs	Human SH-SY5Y cell line	Promotes the therapeutic potential of curcumin against amyloid fibrillation and prevents toxicity	2015 [189]
Glutathione-functionalized PLGA nanoparticles loaded with curcumin	SK-N-SH cells, a human neuroblastoma cell line	- Non-acrolein toxic - higher and easier neuronal internalization - avoiding lysosomal degradation	2016 [190]
Curcumin and A β generation inhibitor S1 (PQVGH peptide) encapsulated NPS to target the harmful factors in AD progress and conjugating with brain targeting peptide CRT	Male AD model (APP/PS1dE9) mice (8-month-old) and human neuroblastoma SH-SY5Y cells, mouse microglial BV2 cells and mouse brain capillary endothelial bEnd.3 cells	Significant reduction of A β level, ROS, inflammatory cytokines increase the activity of SOD and number of brain synapses in AD mice spatial memory and recognition improvement in transgenic AD mice	2017 [191]
G7- curcumin- PLGA NPs	Primary hippocampal cultures from rat brains (embryonic day 18)	- Attenuated inflammation, oxidative stress, amyloid plaque load significant decrease of Ab aggregates	2017 [192]
Curcumin-loaded SPNs and Curcumin-loaded DPNs	RAW 264.7 cell line	Reduced production of proinflammatory cytokines	2017 [193]
Cur loaded Selenium-PLGA nanospheres	AD mice	Improved memory deficiency of AD mice through the reduction of amyloid- β load	2018 [194]

(Table 1) contd....

Nanoparticle	Animal Models/Cell Culture	Clinical and Experimental Outcomes	Refs.
Cur-PLGA-PEG conjugated B6 peptide	HT22 cell line and APP/PS1 A1 transgenic mice	- Increasing curcumin cellular uptake - adequate blood compatibility - improving spatial training and memory ability of APP/PS1 -decreasing hippocampal b-amyloid formation and deposition and inhibiting tau hyperphosphorylation	2018 [198]
Rosmarinic acid- and curcumin-loaded polyacrylamide-cardiolipin-PLGA nanoparticles with conjugated 83-14 monoclonal antibody	SK-N-MC cells, HBMECs, and HAS cells	Increasing the permeability coefficient of curcumin across the BBB and neural membranes improving the viability of SK-N-MC cells irritated with (A β) deposits	2018 [199]

Abbreviations: PLGA: Poly (lactic-co-glycolic acid), NMPs: Nanomicro particles, PEG: Polyethylene glycol, TPP: Triphenylphosphonium, CRT: Cyclic CRTIGPSVC peptide, BBB: Blood-brain barrier, A β : β -amyloid, AD: Alzheimer's disease.

amyloid plaques and their disaggregation [184]. Following this study, curcumin encapsulated-PLGA NPs decorated with Tet-1 peptide with a great affinity for neurons and retrograde transportation characteristics were developed. *In vitro* results showed that these NPs are non-cytotoxic, destroy amyloid aggregates and display antioxidative features [185]. Another interesting approach to improve curcumin delivery was developed by Marrachea *et al.* They synthesized mitochondria-targeted curcumin-PLGA-b-PEG-triphenylphosphonium (TPP) to facilitate curcumin entry into mitochondria. These targeted curcumin PLGA-b-PEG-TPP NPS notably enhance the therapeutic drug index for AD compared to nontargeted particles or their free forms [186]. Doggie *et al.* stated that Cur-PLGA NPs could protect human neuroblastoma SK-N-SH cells from oxidative injury, which is also seen in AD, by preventing H₂O₂-induced toxicity and inhibiting ROS elevation GSH reduction and activation of Nrf2. They suggested that this formulation is expected to have great potential for pharmaceutical application in neurodegenerative disorders, such as AD [187]. Also, Shashi Kant Tiwari reported that compared to free curcumin, Cur-PLGA-NPs induced endogenous neural stem cells (NSC) proliferation by increasing the expression of cell proliferation genes (reelin, Pax6, and nestin) and improved neuronal differentiation by the upregulation of neuroligin, neurogenin, neuregulin, neuroD1, and Stat3 genes and *in vitro* activation of Wnt/ β -catenin pathway (regulator of neurogenesis) in the rats. Besides, these nanoparticles reduced GSK-3 β levels and enhanced TCF/LEF and cyclin-D1 promoter activity. They also improved training and memory impairments in beta-amyloid-induced rat models of AD-like phenotypes by stimulating neurogenesis *via* activating the canonical Wnt/ β -catenin pathway and enhancing a brain self-repair mechanism [188]. Srivastava A *et al.* also reported that Cur-encapsulated PLGA NPs are potential regulators of gelsolin amyloidogenesis. These NPs increased curcumin's solubility and reduced the effective concentration to modulate amyloid plaques by ~1000 fold compared to their free forms. Consequently, PLGA encapsulation promoted the therapeutic potential of curcumin against amyloid fibrillation and toxicity [189]. Subsequently, Djiokeng Paka *et al.* developed glutathione-functionalized PLGA-nanoparticles (GSH-NPs) loaded with non-toxic curcumin, and the surface GSH presented a greater neuroprotective

effect against acrolein. These GSH-Cur-NPs had a higher and easier neuronal internalization than free curcumin due to a modified internalization route that enabled them to escape uptake *via* macropinocytosis, thereby avoiding lysosomal degradation [190]. Huang *et al.* designed NPs encapsulated with curcumin and A β generation inhibitor S1 (PQVGH peptide) to target the harmful factors in AD progression. These NPs were conjugated with brain targeting peptide CRT (cyclic CRTIGPSVC peptide), an iron-mimic peptide that targets transferrin receptors (TfR), for advanced BBB penetration. They showed that these NPs significantly reduced A β level, reactive oxygen species (ROS), inflammatory cytokines (*e.g.*, TNF- α and IL-6) and intensified the activity of superoxide dismutase (SOD) and the number of brain synapses, resulting in the improvement of spatial memory and recognition in transgenic AD mice. Consequently, co-delivery of an anti-inflammatory agent like curcumin and A β production inhibition (S1) conjugated with brain targeting peptide (CRT) revealed the most favorable effects in which CRT facilitated the BBB permeability of Cur-PLGA NPs, and curcumin decreased A β formation, gliosis, and proinflammatory cytokine production in the treatment of AD mice [191]. In a study by Barbara *et al.*, Cur-PLGA NPs conjugated with g7 ligand were formulated to improve BBB crossing. The primary hippocampal cell cultures subjected to these NPs showed no apparent toxicity, a significant reduction of A β aggregates and less inflammation, oxidative stress and amyloid plaque load. Hence, brain delivery of curcumin using NPs to cross BBB could be a promising approach in managing AD [192]. Later, Ameruoso *et al.* developed curcumin-loaded spherical polymeric nano constructs (SPNs) with a size of 200 nm and curcumin-loaded discoidal polymeric nano constructs (DPNs) with a size of 1000 nm using PLGA, polyethylene glycol (PEG) and lipid chains as building blocks. They evaluated specific curcumin delivery to macrophages, previously stimulated by incubation with Amyloid- β fibrils produced *in vitro*. The cytofluorimetric and confocal microscopic analyses demonstrated that Cur-SPNs are taken up more quickly by macrophages than Cur-DPNs. Also, Cur-SPNs diminished the production of proinflammatory cytokines (IL-1 β , IL-6, and TNF- α) in macrophages stimulated *via* amyloid- β fibers up to 6.5-fold [193]. Huo *et al.* reported that Cur loaded Selenium-PLGA nanospheres

could reduce the amyloid- β load in AD mice's brain specimens and considerably improve their memory deficiency through specific attachments to A β plaques [194]. It is demonstrated that other than the brain, peripheral organs like the liver can also produce amyloid proteins [195]. It is safer and easier to reduce peripheral amyloid due to difficulty in BBB penetration of drugs targeted to the CNS and cerebral toxicity [196]. In this regard, Takahashi *et al.* [197] initially developed amyloid-binding aptamers, preventing the aggregation of amyloid fibrils. In another study, curcumin-loaded PLGA-PEG were conjugated with B6 peptide as a brain target, which showed that these NPs possessed adequate blood compatibility and increased curcumin cellular uptake. Also, Cur-PLGA-PEG-B6 could remarkably improve the spatial training, and the memory ability of APP/PS1 mice versus native Cur. Further experiments confirmed that Cur-PLGA-PEG-B6 could decrease hippocampal β -amyloid formation and deposition and also tau hyperphosphorylation [198]. Recently, Kuo *et al.* developed polyacrylamide (PAAM)-cardiolipin (CL)-poly(lactide-co-glycolide) (PLGA) NPs grafted with surface 83-14 monoclonal antibody (MAb) to carry rosmarinic acid (RA) and curcumin (CUR), which was named as 83-14 MAb-RA-CUR-PAAM-CL-PLGA NPs. These NPs increased the permeability coefficient of curcumin across the BBB and improved SK-N-MC cells' viability irritated with β -amyloid (A β) deposits. Consequently, 83-14 MAb-RA-CUR-PAAM-CL-PLGA NPs may have a great neuroprotective capacity in medication management of AD to prevent neurodegeneration [199].

CONCLUSION

The pleiotropic functions of curcumin, including antioxidant and anti-inflammatory effects as well as protein aggregation inhibition, are the primary contributors to combat neurodegenerative diseases, particularly AD. The main properties of curcumin, which increased its application, are safety, low cost, easy accessibility and effective penetration into the BBB and neuronal membranes. Nevertheless, some curcumin characteristics limited its clinical application, including low water solubility, low bioavailability, and structural instability in the body fluids. Nano-based drug delivery systems are the emerging carriers to enhance medications' efficacy in a controlled target-oriented fashion. In the present review, we summarized the *in vitro/in vivo* studies and clinical trials on curcumin-loaded PLGA NPs to prevent and treat AD. However, most of the available results have been obtained from *in vitro* strategies using multiple nano-curcumin technologies that could promote curcumin delivery in the SNC.

Other than multiple nano-curcumin implications, more studies are yet expected to evaluate the toxicity and efficacy of these NPs on a larger group of patients. The main concerns regarding nanomedicine-based delivery systems are the possible toxic effects of curcumin-loaded NPs, including neuroinflammation, DNA damage, excitotoxicity, and allergic responses. Some methods, such as combination therapy and specific targeting, can minimize these toxic effects by decreasing the main therapeutic agent's dose and functionalizing the NPs, respectively. Consequently, nano curcumin carriers' preparation and purification methods play a pivotal

role in reducing the aggregation and mechanical properties of NPs to mitigate their toxicity.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

Muhammed Majeed is the founder of Sami Labs Ltd. and Sabinsa Corporation, involved in the production and sale of phytonutrients and standardized herbal extracts, including curcumin. The authors have no other conflicting interests to disclose.

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