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Review

Curcumin-Based Nanocarriers for Alzheimer's Disease: A Promising Therapeutic Avenue

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Abstract

Globally, over 55 million people are affected by Alzheimer's disease (AD), a number that is increasing rapidly and projected to triple by 2050. AD is a type of neurodegenerative disorder for which there is no curative treatment. The accumulation of amyloid-β (Aβ) plaques and the formation of neurofibrillary tangles are the hallmarks of AD. Curcumin, a bioactive compound extracted from turmeric rhizomes, has shown significant neuroprotective properties, including anti-amyloidogenic, anti-inflammatory, antioxidant, and metal-chelating. Though much research has revealed the potential of curcumin as a promising therapeutic agent for AD, the limited bioavailability of curcumin restricts its effectiveness in pharmaceutical applications. To overcome this challenge, nanocarrier-based delivery systems have emerged as a promising strategy for enhancing the bioavailability and therapeutic efficacy of curcumin. This review provides an overview of recent findings on curcumin-based nanocarriers for AD therapy.

Keywords: Alzheimer's disease; curcumin; nanocarriers; neurodegenerative disorders; nanoparticles; therapeutic agent

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and is rapidly becoming one of the most expensive, deadly, and burdensome diseases of the 21st century. Currently, approximately 55 million people worldwide are affected by AD. Globally, the incidence (147.95%), prevalence (160.84%), and mortality rate (189.29%) associated with dementia have increased significantly over recent decades (between 1990 and 2021) and are projected to triple by 2050 [1–3], primarily affecting individuals over the age of 60 [4,5].

Pathologically, AD is characterized by the accumulation of amyloid-β (Aβ) plaques and the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, both considered hallmark features of the disease [6,7]. Figure 1 shows the difference between a normal and an Alzheimer affected neuron. Several risk factors have been associated with the development of AD, including smoking, poor diet, physical inactivity, and depression [8].

There are approved drugs by the US Food and Drug Administration (FDA) for the treatment of AD, namely acetylcholinesterase inhibitors (AChEIs): Donepezil, Rivastigmine, Galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine [6].

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These are symptomatic treatments that can slow cognitive and functional decline. However, they present notable limitations. Most of these drugs poorly penetrate the brain due to the restrictive nature of the blood–brain barrier (BBB), which tightly controls the entry of substances into the brain and blocks many therapeutic agents. Furthermore, many clinical trials targeting amyloid have failed to produce effective outcomes, despite achieving significant plaque reduction [8,9].

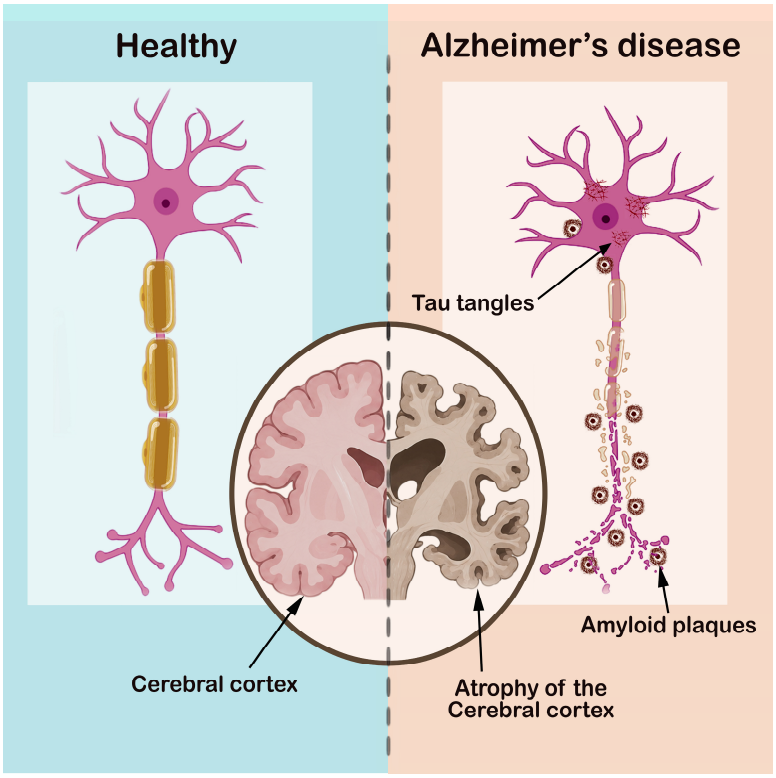


Figure 1. Comparison between healthy and AD-affected neurons.

To overcome these limitations, there is a growing interest in using natural polyphenols, such as curcumin, resveratrol, quercetin and epigallocatechin gallate (EGCG). Natural polyphenols are a diverse class of bioactive compounds extensively distributed across various living organisms, including plants, fungi, bacteria, and animals. Polyphenols can be classified into multiple categories based on the number of phenol rings and structural elements including phenolic acids, flavonoids, stilbenes, phenolic alcohols, and lignans [10,11].

Curcumin, a natural polyphenolic compound derived from *Curcuma longa* (turmeric), has been extensively studied for its therapeutic potential in AD. It exhibits a broad spectrum of pharmacological activities, including anti-amyloid, anti-inflammatory, antioxidant, and neuroprotective effects [12,13]. Despite these promising properties, the clinical application of curcumin is hindered by several limitations, such as poor aqueous solubility, rapid metabolic degradation, low oral bioavailability, and limited permeability across the BBB. To address these challenges, recent research has focused on the development of nanocarrier-based delivery systems, which aim to enhance the stability, bioavailability, and therapeutic efficacy of curcumin in the treatment of AD [14,15]. This review explores the latest advancements in curcumin-loaded nanocarriers and evaluates their potential as a novel therapeutic strategy for AD.

2. Curcumin and Its Neuroprotective Role

Curcumin, the principal bioactive constituent of *Curcuma longa* (turmeric), is derived from a rhizomatous, herbaceous perennial plant belonging to the *Zingiberaceae* (ginger)

family, which comprises approximately 133 species globally. Curcumin has been widely utilized in traditional Indian medicine due to its broad spectrum of therapeutic properties. Furthermore, curcumin serves as an essential component in various culinary spices, contributing to both flavor and potential health benefits [16].

Curcumin is a lipophilic polyphenol, constituting approximately 2–5% of turmeric powder. The primary bioactive constituents of turmeric are the polyphenolic curcuminoids, which include curcumin (diferuloylmethane), bisdemethoxycurcumin, dimethoxycurcumin, and cyclocurcumin. Among the yellow-pigmented curcuminoids, curcumin accounts for about 77%, followed by desmethoxycurcumin (17%), and bisdemethoxycurcumin (3%) (Figure 2) [17]. Curcumin is chemically denoted as 1,7-bis-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione or dipheruloylmethane, with the molecular formula of $C_{21}H_{20}O_6$ [13,18].

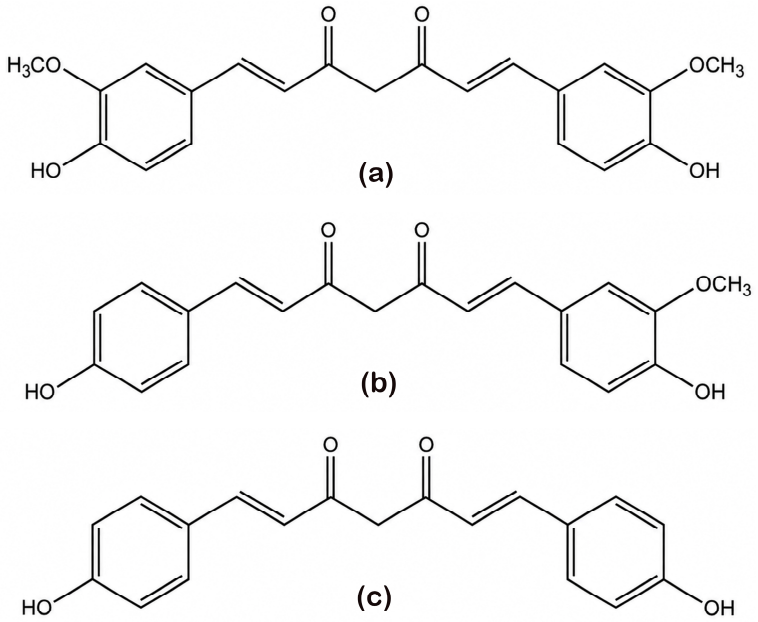


Figure 2. Chemical structures of the major curcuminoids present in turmeric (*Curcuma longa*): (**a**) curcumin, (**b**) desmethoxycurcumin, (**c**) bisdemethoxycurcumin.

Curcumin exerts a broad spectrum of biological activities through the modulation of multiple intracellular signaling pathways. It has been shown to influence the expression of various transcription factors, antioxidant defense enzymes, inflammatory cytokines, metabolic enzymes, growth factors, receptors, adhesion molecules, anti-apoptotic proteins, and cell cycle regulators [12,13,18]. These molecular interactions are associated with curcumin's ability to mitigate a wide range of chronic pathological conditions.

2.1. Molecular Mechanisms of Curcumin in AD

Curcumin modulates several intracellular signaling pathways that are directly involved in the pathogenesis of AD. Curcumin effectively represses the mechanistic target of rapamycin complex 1 (mTORC1) signaling through two main mechanisms: deactivation of insulin receptor substrate-1 (IRS-1) and activation of AMP-activated protein kinase (AMPK). Inhibition of mTORC1 by these routes promotes autophagy, a cellular process frequently impaired in AD brains, thereby facilitating the clearance of toxic protein aggregates [19].

Furthermore, curcumin promotes autophagosome–lysosome fusion, which enhances autophagic flux and improves the degradation of accumulated Aβ and hyperphosphorylated tau proteins. This enhancement of late-stage autophagy is considered a key neuroprotective mechanism [20].

Curcumin also directly inhibits the hyperphosphorylation and oligomerization of tau protein, a central pathological hallmark of AD. It suppresses the activity of major tau kinases such as glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), reduces the formation of neurofibrillary tangles, and promotes the disassembly of preformed tau oligomers [21,22]. These effects help preserve neuronal integrity and synaptic function.

Collectively, these mechanisms—including inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) through deactivation of insulin receptor substrate-1 and activation of adenosine monophosphate-activated protein kinase (IRS-1/AMPK), enhancement of autophagosome–lysosome fusion, and suppression of tau pathology—strengthen the therapeutic potential of curcumin in Alzheimer's disease. However, the poor bioavailability and limited brain penetration of native curcumin necessitate advanced delivery systems such as nanocarriers to fully realize these beneficial effects in vivo [23].

2.2. Anti-Amyloidogenic

Extensive research over the years has shown that AD is linked to various cellular alterations, including mitochondrial dysfunction, synaptic loss, accumulation of Aβ peptides, activation of microglia and astrocytes, tau protein hyperphosphorylation leading to neurofibrillary tangle formation, and progressive neuronal loss [24,25].

Aβ peptides are generated through the proteolytic processing of amyloid precursor proteins (APPs) via two distinct pathways: the non-amyloidogenic and amyloidogenic pathways (Figure 3). In the non-amyloidogenic pathway, APPs are cleaved by α-secretase, which results in the release of non-toxic peptide fragments. In contrast, the amyloidogenic pathway involves β-secretase and γ-secretase to produce Aβ peptides (40–43 amino acids). Abnormal aggregation of Aβ peptides leads to extracellular plaque formation, neuronal dysfunction and cognitive impairment in AD, making Aβ accumulation a key therapeutic target [26].

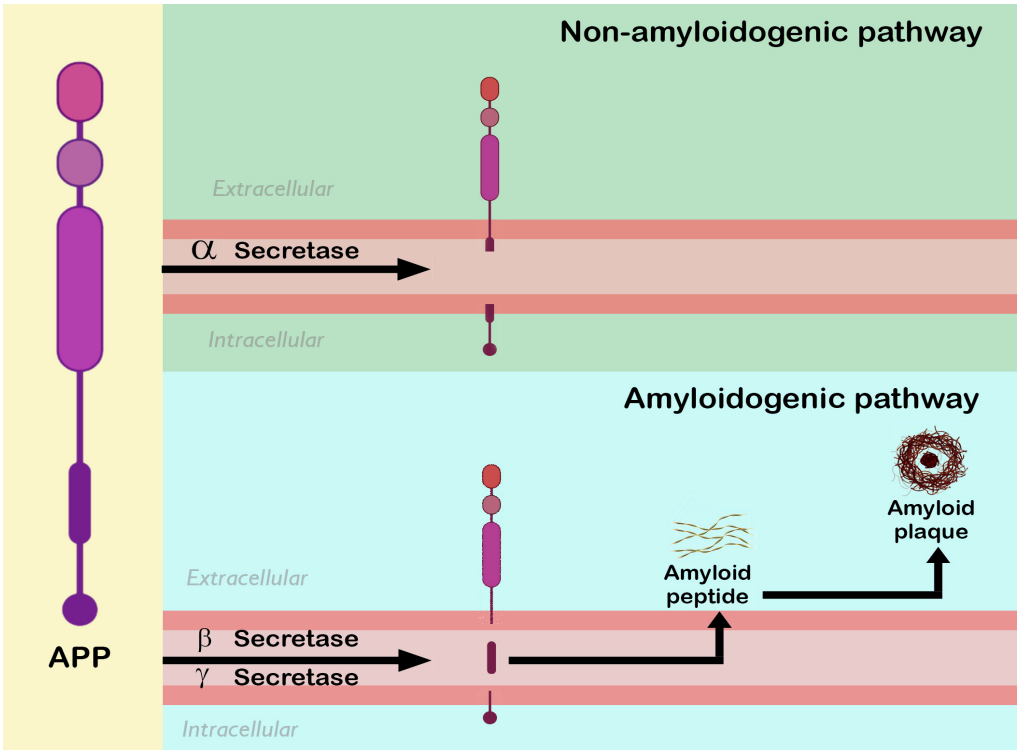


Figure 3. Amyloid precursor protein (APP) processing pathways in Alzheimer's disease.

Curcumin has been shown to have significant anti-amyloidogenic properties, making it a promising candidate for AD therapy. In vitro studies have demonstrated that curcumin effectively inhibits Aβ aggregation and promotes the disaggregation of preformed fibrillar $A\beta_{40}$ [27,28]. Studies conducted in vivo have revealed that curcumin promotes the disaggregation of existing amyloid deposits and prevents the aggregation of new amyloid deposits, even reducing the size of remaining deposits [28,29]. Fu et al. reported that curcumin interacts with the N-terminus of $A\beta_{1–42}$ monomers and prevents the enlargement of oligomers from 1–2 nm to 3–5 nm [30]. Similarly, by using electron microscopy, Mithu et al. also showed that curcumin was able to disrupt the $A\beta_{1–42}$ fibrils architecture [31]. Lim et al. demonstrated that dietary curcumin reduced insoluble Aβ, soluble Aβ and plaque burden by 43–50% [32]. Another study reported that curcumin effectively inhibited Aβ aggregation with an IC_{50} value of 0.8 μM and promoted the disaggregation of fibrillar $A\beta_{40}$ with an IC_{50} of 1 μM, indicating favorable stoichiometry for aggregation inhibition [33].

2.3. Anti-Inflammatory

Inflammation plays a critical role in the pathogenesis of various diseases, including neurodegenerative disorders. It is a complex biological response aimed at eliminating invading pathogens or repairing damaged tissue through the activation of diverse inflammatory mediators. However, excessive or prolonged activation of the immune system and inflammatory pathways can lead to additional tissue damage and contribute to disease progression [34].

Curcumin exhibits significant anti-inflammatory activity mainly mediated through the downregulation of various signaling pathways. Specifically, curcumin inhibits the activity of cyclooxygenase-2 (COX-2), mitogen-activated protein kinases (MAPKs), and Janus kinases (JAKs), while also suppressing the production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12, and the activation of adenosine monophosphate-activated protein kinase (AMPK) [35,36].

Comparative study of natural polyphenol has shown that curcumin exhibits stronger inhibition of NF-κB activation and broader suppression of inflammatory mediators than several flavonoids and resveratrol [37]. Davinelli et al. compared curcumin with resveratrol and epigallocatechin gallate and demonstrated that curcumin has stronger suppression of inflammatory pathways, including nuclear factor kappa B (NF-κB) and COX-2 signaling [38]. The anti-inflammatory properties of curcumin arise through potential inhibition of human recombinant5-lipoxygenase (5-LOX) activity ($IC_{50} \approx 0.7$ μM), leading to reduced synthesis of pro-inflammatory mediators derived from arachidonic acid metabolism [39]. Furthermore, a study reported that curcumin inhibited the Toll-like receptor 4 (TLR4)–MAPK/NF-κB signaling pathway and reduced pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), nitric oxide (NO), and intracellular reactive oxygen species (ROS) in a dose-dependent manner (5–30 μmol/L) [40].

2.4. Antioxidant

Antioxidants are compounds that can protect biomolecules from free radical-mediated oxidative damage, and most contain a phenolic group or a β-diketone group in their structure [41]. Curcumin possesses potent antioxidant activity owing to its unique chemical structure, which includes conjugated carbon–carbon double bonds, a β-diketone moiety and phenolic hydroxyl and methoxy groups. Curcumin's exceptional antioxidant potential is primarily attributed to its ability to donate hydrogen atoms from the phenolic groups, effectively neutralizing free radicals [42,43].

Meta-analysis of randomized clinical trials demonstrated that curcumin increased total antioxidant capacity (TAC) which is an indicator of the body's overall antioxidant

defense against oxidative stress (Standardized Mean Difference (SMD) = 2.696, Z = 2.003, CI = 95%, $p = 0.045$) and a tendency to decrease malondialdehyde (MDA) concentration (SMD = −1.579, $p = 0.086$). However, the TAC analysis was based on only three heterogeneous studies (I^2 statistic = 97.8%) [44]. Similarly, Alizadeh et al. have shown that curcumin has potential to increase TAC and decrease MDA levels [45]. A study evaluating the neuroprotection of curcumin in the primary cultures of the cerebellar granule neurons of rats has concluded that the use of curcumin as a pretreatment induces antioxidant protection against hemin-induced neuronal death [46].

Sarker et al. reported that in the human SH-SY5Y neuroblastoma cells, curcumin pre-treatment reduced Reactive Oxygen Species (ROS) production by 10% upon exposure to pesticide monocrotophos. Immunofluorescence analyses indicated that this antioxidant effect is mediated through the activation of the Nrf2 and APE1 pathways, highlighting curcumin's potential to counteract oxidative stress associated with neurodegenerative conditions [47]. In another study using mice, pre-treatment of Neuro-2a neuroblastoma and human HEK293 kidney cells with curcumin before exposure to H_2O_2 protected the cells from oxidative stress-induced damage [48].

2.5. Metal Ion Chelation

Curcumin's structure, which includes phenolic groups and a β-diketone moiety, enables it to act as an effective metal chelator. In aqueous solutions, curcumin exists predominantly in a keto-enol tautomeric form, allowing it to form stable stoichiometric complexes with various transition metals [49,50]. This metal-binding ability is particularly beneficial in the context of AD, as the accumulation of metal ions such as copper, iron, and zinc in the brain has been associated with increased oxidative stress and the aggregation of Aβ plaques [51,52]. Curcumin may help to reduce metal-induced toxicity, inhibit amyloid aggregation, and ultimately contribute to neuroprotection by chelating these metal ions [53,54].

Comparative analysis revealed that curcumin effectively chelates Cu^{2+}, Fe^{3+}, and Zn^{2+} ions through its β-diketone moiety, forming stable six-membered metal complexes [55]. Baum et al. demonstrated that curcumin has higher binding affinity against Cu^{2+} (K_d ~1.3 μM) and Fe^{2+} (K_d ~0.5–1.6 μM), indicating substantial metal-chelating potency relevant to AD-associated metal dyshomeostatasis [56]. Sarawi et al. reported that in a rat model of copper sulfate-induced cerebral toxicity, curcumin and its nano formulation reduced oxidative stress and inflammation while activating neuroprotective pathways, including the protein kinase B/Glycogen Synthase Kinase-3β (Akt/GSK-3β) pathway [57]. A study investigating the protective effects of curcumin against lead (Pb)-induced hepatotoxicity, with a focus on oxidative stress, inflammation, and Akt/GSK-3β signaling, demonstrated that curcumin reduced lipid peroxidation, DNA damage, and pro-inflammatory mediators while restoring antioxidant defenses in Pb-intoxicated rat models [58]. Ferrari et al. reported that the metal-chelating properties of curcumin derivatives can mitigate Aβ aggregation and oxidative damage by effectively binding Cu^{2+} and Ga^{3+} ions [59].

3. Challenges in Curcumin Therapy

Despite substantial evidence supporting curcumin's therapeutic potential against AD, its clinical application remains limited because of its low bioavailability, restricted penetration across the BBB, rapid metabolism, and poor aqueous solubility. According to the biopharmaceutics classification system (BCS), curcumin falls under the BCS class IV category due to its limited aqueous solubility and low permeability through intestinal epithelial cells [60].

3.1. Low Bioavailability

Curcumin possesses poor bioavailability and an unfavorable pharmacokinetic profile, which has significantly limited its clinical translation [61]. As reported by Sanidad et al. [62], Matthewman et al. [63], and Cas et al. [64] clinical investigations have shown that the following a single oral dose of 10–12 g, free curcumin remains scarcely detectable in human plasma, indicating minimal systemic absorption. As a result, high doses are often required to achieve therapeutic efficacy in vivo. Wang et al. reported that curcumin exhibits poor absorption even at very high doses (up to 12 g), and those specialized formulations can significantly enhance its bioavailability [65]. The hydrophobic nature of curcumin hampers dissolution in digestive fluids, resulting in poor bio accessibility. Moreover, curcumin rapidly degrades at neutral to basic pH, primarily through a radical-mediated oxidation process, producing less active or inactive by-products [66].

Absorption of curcumin in the small intestine is inefficient, and even when taken up, it is often expelled back into the gut lumen. Its distribution in body tissues after oral administration is minimal, with only trace amounts detected in organs like the liver and kidneys [67]. Among commonly studied dietary polyphenols, curcumin has been reported to exhibit the lowest bioavailability, reflecting its unfavorable physicochemical and pharmacokinetic characteristics [10]. One practical nutritional strategy to improve curcumin absorption is co-administration with piperine, the principal alkaloid of black pepper, which inhibits intestinal and hepatic glucuronidation. In a landmark human pharmacokinetic study, the administration of 20 mg piperine together with 2 g curcumin increased the bioavailability of curcumin by approximately 2000% (20-fold) without adverse effects [68]. However, although this strategy may enhance systemic exposure, the improvement remains substantially lower and less reproducible than that achieved with advanced nano formulations specifically designed to overcome poor solubility, rapid metabolism, and limited BBB penetration [69,70].

3.2. Limited Blood–Brain Barrier (BBB) Penetration

The BBB is a highly selective and critical interface within the central nervous system (CNS), primarily composed of brain capillary endothelial cells. It represents a major obstacle to effective drug delivery to the brain. The structural integrity of the BBB is maintained by a specialized basal membrane, tight junction-forming endothelial cells, pericytes embedded within the basal lamina, and astrocytic end-feet that envelop the cerebral vasculature. These components work synergistically to preserve CNS homeostasis and restrict the entry of most therapeutic agents [71].

Kocsis et al. reported that curcumin exhibits very low permeability across the BBB, indicating that curcumin does not efficiently cross the BBB [72]. Askarizadeh et al. and Mohi-Ud-Din et al. have revealed that the BBB is the major obstacle for the delivery of curcumin into the brain, limiting its therapeutic potential [73,74]. Comparative pharmacokinetic studies demonstrated that curcumin exhibits substantially poorer BBB-associated bioavailability than resveratrol. Native curcumin remained undetectable in cerebrospinal fluid following oral administration, while plasma concentrations were only 7.76 ± 3.23 ng/mL even at high doses [75]. Kaluza et al. reported that curcumin, resveratrol and quercetin exhibit very low oral absorption, with bioavailability generally reported to be less than 1% [76].

3.3. Rapid Metabolism

Structurally, curcumin contains two phenolic hydroxyl groups, which serve as reactive sites for conjugation reactions. These groups are particularly susceptible to biotransformation by Phase II detoxification enzymes. As a result, curcumin is rapidly converted into water-soluble glucuronide and sulfate conjugates. Although these metabolites are

more readily excreted, they exhibit significantly lower biological activity than the parent compound. Consequently, these metabolic processes contribute substantially to the limited systemic availability and therapeutic efficacy of orally administered curcumin [61,62].

In vivo studies using various animal models have consistently shown that curcumin undergoes rapid metabolism following systemic administration. Once absorbed, curcumin undergoes extensive biotransformation through conjugation (glucuronidation and sulfation) and reduction, leading to swift systemic elimination [77]. Jude et al. demonstrated that curcumin is rapidly metabolized in humans, with the turmeric matrix enhancing plasma levels of its reductive and conjugative metabolites [78]. In vivo studies have shown that curcumin undergoes rapid metabolism, with its metabolites formed quickly through reductive and conjugative pathways. Oral administration of curcumin significantly reduces its systemic exposure, as reflected by a decreased $AUC_{0–540}$ of 70.6% and 71.5%, respectively, to 50 and 100 mg/kg of curcumin [79].

3.4. Poor Water Solubility

Curcumin exhibits an estimated solubility of 3.21 mg/L at 25 °C in aqueous solutions. However, it is readily soluble in organic solvents such as ethanol, dimethyl sulfoxide, methanol, acetonitrile, chloroform, and ethyl acetate [80,81]. It is chemically unstable in both aqueous and alcoholic solutions, and exhibits greater stability at acidic pH levels (1.2–6) compared to alkaline conditions. Under hydrolytic degradation, it breaks down into several products, including trans-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal, ferulic acid, ferulic aldehyde, feruloylmethane, and vanillin [82].

Ucisik et al. revealed that the clinical application of curcumin is severely limited due to its extremely poor water solubility, resulting in very low plasma concentrations (≈approximately 11 ng/mL) after oral administration [83]. Studies have reported that curcumin exhibits poor water solubility (≈approximately 0.6 µg/mL) due to its inherently hydrophobic nature. This poor solubility contributes to minimal absorption from the gastrointestinal tract, leading to very low systemic bioavailability and limiting its therapeutic efficacy [84]. Shen et al. reported that approximately 90% of curcumin degraded within 30 min in phosphate buffer at pH 7.4, forming various degradation products. Similar degradation was observed when curcumin was added to cultured cells. Although its stability improved in cell culture medium containing 10% fetal calf serum and in human blood, approximately 50% of the curcumin had still decomposed after 8 h [82].

4. Structurally Modified Curcumin Analogues

Despite the remarkable neuroprotective potential of curcumin, its clinical translation remains significantly limited due to the abovementioned challenges. To overcome these limitations, researchers have developed curcumin derivatives and analogues to improve pharmacokinetic stability and therapeutic efficacy [85]. Liang et al. synthesized monocarbonyl analogues of curcumin, and several compounds showed promising candidates for new anti-inflammatory drugs to treat various inflammatory diseases [86]. In vitro studies demonstrated that new curcumin derivatives synthesized by etherification and esterification showed higher anti-inflammatory activity than did unmodified curcumin (2.23 ± 0.84 vs. 8.25 ± 1.25) and exhibited a strong anti-aggregation effect [87].

A study demonstrated new curcumin derivatives improved physicochemical and therapeutic properties, including enhanced solubility, compared to native curcumin. Moreover, several derivatives exhibited significantly greater inhibition of amyloid-β aggregation and improved SH-SY5Y cell viability (64.0–66.8%) compared with native curcumin (61.6%) [88]. Okuda et al. designed and synthesized curcumin derivatives as tau and amyloid-β dual aggregation inhibitors. The study demonstrated that the optimized derivative significantly

inhibited both Aβ and tau aggregation, with IC_{50} values reduced from 5.4 μM to 1.2 μM and from 3.0 μM to 0.66 μM, respectively. Furthermore, selected compounds exhibited markedly improved brain penetration, achieving a brain concentration of 276 ng/g tissue compared with only 13 ng/g tissue for curcumin following oral administration (50 mg/kg, 3 h post-dose) [89].

5. Nanotechnology in the Treatment of AD

Nanocarriers have demonstrated great potential in the treatment of AD by facilitating the delivery of therapeutic agents across the BBB. Depending on their specific chemical composition, certain classes of nanocarriers, particularly lipid-based systems (liposomes, solid lipid nanoparticles), polymer-based carriers (PLGA nanoparticles), inorganic nano systems (gold, iron-oxide nanoparticles), exhibit favorable biocompatibility and biodegradability. Under optimized formulation conditions, their surface can be tailored with targeting ligands to facilitate drug delivery across the BBB while preserving its neuroprotective integrity [90]. Nanoparticles (NPs) can traverse the BBB through multiple mechanisms, including modulation of tight junctions, transcytosis via brain capillary endothelial cells, and direct transcellular transport. These properties enhance the bioavailability, stability, and distribution of drugs to specific brain regions [91]. Consequently, NPs can be engineered to target key pathological features of AD, such as Aβ aggregation, tau hyperphosphorylation, neurotransmitter imbalance, neuroinflammation, oxidative stress, and neurotrophic factor deficiency [92]. Furthermore, NPs can carry fluorescent markers to enable early diagnosis of neurological disorders, reinforcing their promise in the diagnosis and treatment of AD [93].

5.1. Curcumin-Loaded Nanocarriers

Despite its well-documented therapeutic potential, the clinical application of curcumin is significantly constrained. Therefore, nanoparticle-based drug delivery systems have emerged as a promising approach to address these limitations. Encapsulation of curcumin within nanoparticles enhances its aqueous solubility and protects against enzymatic and chemical degradation in the gastrointestinal tract, thereby improving its absorption and systemic bioavailability [94,95]. Moreover, nanoparticle-based delivery systems provide sustained curcumin release, therapeutic efficacy and patient adherence. The functionalization of nanoparticles enables targeted site-specific delivery and enhanced intracellular uptake by overcoming cellular membrane barriers (Figure 4) [96]. Various delivery platforms have been employed for curcumin encapsulation.

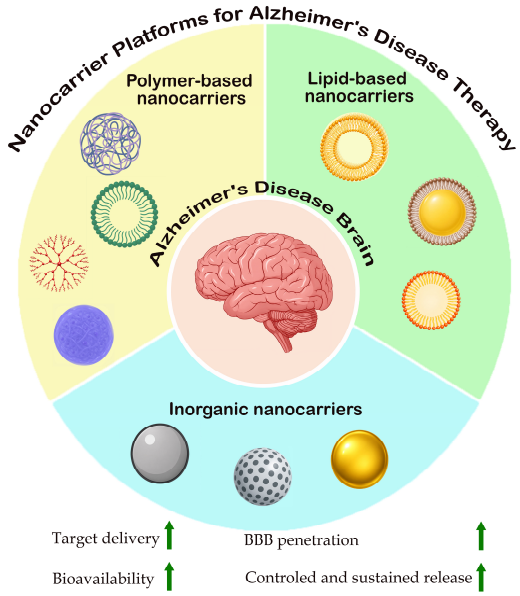


Figure 4. Schematic representation of the major nanocarrier platforms used for AD therapy.

5.1.1. Polymer-Based Nanocarriers

Polymer-based nanocarriers have emerged as one of the most extensively investigated drug delivery platforms because of their favorable biocompatibility, biodegradability, structural versatility, and ability to provide controlled and targeted drug release. However, their biological performance and safety profiles are highly dependent on polymer composition, physicochemical properties, surface characteristics, and specific application conditions [97]. Figure 5 represents the different types of polymer-based nanocarriers used in AD therapy.

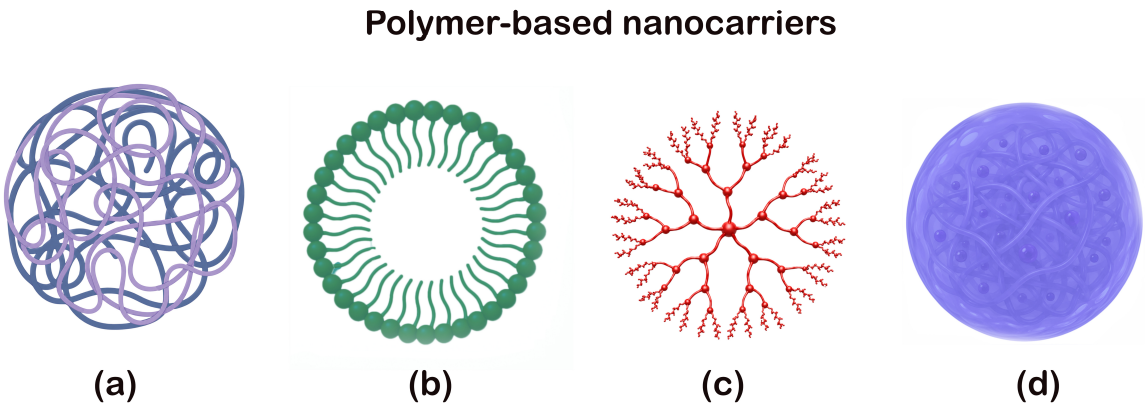


Figure 5. Classification of curcumin-loaded polymer-based nanocarriers for AD therapy: (**a**) Polymeric NPs, (**b**) Micelles, (**c**) Dendrimers, (**d**) Nanogels.

Polymeric Nanoparticles

The polymeric materials exhibit high biocompatibility, low immunogenicity, non-toxicity, and complete biodegradability, rendering them ideal for both therapeutic and dietary applications [97,98]. Moreover, their structural versatility allows for precise tuning of nanocarrier attributes such as particle size, surface characteristics, and degradation kinetics. This adaptability enables controlled drug release and targeted biodistribution, ultimately improving therapeutic outcomes while minimizing off-target effects [99].

Synthetic polymers are frequently employed, including poly(D, L-lactide) (PDLLA), poly(lactic acid) (PLA), poly(D,L-glycolide) (PLG), poly(lactide-co-glycolide) (PLGA), poly-ethylene glycol (PEG), and poly(cyanoacrylate) (PCA), in nanomedicine owing to their favorable biodegradability, biocompatibility, and versatility in drug delivery applications [97,100]. The study by Rabanel et al. reported that curcumin-encapsulated PEG nanoparticles exhibited superior long-term neuroprotective effects compared to free curcumin, along with sustained release properties [101]. Doggui et al. prepared curcumin-loaded biodegradable PLGA-based nanoparticles where the diameter of them ranges from 80 to 120 nm. The entrapment efficiency was 31%, with 15% drug-loading capacity [102]. The PLGA and PLGA-PEG nanoparticles could increase the bioavailability of curcumin by 15.6- and 55.4-fold, respectively, by increasing the mean half-time of curcumin, decreasing the metabolism of curcumin and sustaining the curcumin delivery compared to the curcumin aqueous suspension [103].

Fan et al. developed curcumin-loaded PLGA-PEG-B6 polymeric nanoparticles with a drug-loading capacity of 15.6% and particle sizes below 150 nm. In vitro studies demonstrated excellent biocompatibility and enhanced cellular uptake from 8.94 ± 1.10% for free curcumin to 45.72 ± 0.48% for the nanoparticle formulation [104]. Curcumin-loaded PLGA nanoparticles conjugated with Tet-1 peptide exhibit enhanced neuronal uptake and >70% cell viability in vitro, while Tet-1 functionalization further improves targeting efficiency. In vivo studies have also shown that curcumin reduces amyloid-β plaque burden and inhibits plaque formation in AD mouse models [105].

Natural polymers used as nanocarriers include albumin, gelatin, alginate, collagen, dextran, and chitosan [93]. Among them, chitosan is the most widely used natural polymer for brain-targeting applications due to its superior bioadhesive and biocompatible properties [94]. Patlan et al. reported curcumin-loaded nanoparticles with an average size of 116.7 ± 3.2 nm, a low dispersity index of 0.107, and a zeta potential of 24.4 ± 2.1 mV, achieving approximately 90% encapsulation [106]. Similarly, Magdy et al. reported that prepared nanoparticles exhibited a drug-loading capacity of 86.81% ± 5.44%, 68.12% ± 4.24% entrapment efficiency, and a sustained drug release of 88.24% ± 6.89% over 24 h [107]. In addition, curcumin-loaded chitosan–bovine serum albumin nanoparticles have been shown to enhance BBB penetration (60.2% at 3 h) and increase intracellular drug concentrations compared to free curcumin, thereby stimulating RAW cell-mediated phago-cytosis of $A\beta_{42}$. Further studies have demonstrated that curcumin-loaded chitosan nanoparticles exhibit high entrapment efficiency (>80%), along with superior drug release profiles, enhanced transdermal permeation, and improved cell viability [108,109].

The physicochemical characterization of curcumin-loaded polymeric nanoparticles is presented in Table 1.

Table 1. Physicochemical properties and therapeutic performance of curcumin-loaded polymeric nanoparticles.

Parameter	Summary	Outcomes	References
Particle size	Typically range from 10 to 200 nm, depending on polymer type and method	Nanoscale size improves BBB penetration, stability and controlled biodistribution	[102,104]
Encapsulation efficiency	Reported to vary between 30 and 90%, influenced by polymer type (e.g., PLGA, PEG, chitosan)	Higher efficiency increases therapeutic payload while maintaining drug stability	[104]
BBB penetration	Enhanced through mucoadhesion (chitosan) or ligand/PEG surface modification	Enables targeted delivery to neurons, enhancing memory improvement and neuroprotection in AD	[104,105]
Release profile	Exhibits a sustained release (24–72 h), protecting curcumin from rapid metabolism and degradation	Ensures long-lasting therapeutic effect and reduces frequency of administration	[101]
In vivo efficacy	Demonstrated ability to improve memory and reduce oxidative stress in AD models	Provide neuroprotective benefits and support potential therapeutic use in AD	[93]
Toxicity	Generally nontoxic and biocompatible, safe for neuronal and systemic use	Confirms suitability for long-term therapeutic applications in chronic conditions	[97,98]

Polymeric Micelles

Micelles are relatively small colloidal particles that form spontaneously when certain types of surfactants are dispersed in water. The surfactant molecules assemble so that their nonpolar tails are located in the interior of the particle, while the polar heads are located at the exterior of the particle [62]. Micelles are usually formed from relatively hydrophilic nonionic surfactants [hydrophile–lipophile balance (HLB) > 10], such as Tweens and sodium dodecyl sulfate [110]. Micelles tend to have a spherical shape, although non-spherical shapes can be obtained for certain types of surfactants and environmental conditions.

Micelles can solubilize nonpolar curcumin molecules into their hydrophobic cores, thereby increasing their water solubility and altering their transport properties [111].

Wang et al. developed curcumin-loaded polymeric micelles with anti-inflammatory activity, exhibiting an average diameter of 20 nm and high encapsulation efficiency for curcumin (89.43%). The study further demonstrated that oral bioavailability of nanoparticles was higher than that of curcumin-active pharmaceutical ingredients (about 9.24-fold) [112]. A study demonstrated that self-assembled curcumin-loaded amphiphilic modified chitosan micelles exhibited high drug entrapment efficiency, and loading capacities were up to 80.80 ± 0.99% and 19.02 ± 0.46%, respectively. In vitro release studies further revealed a sustained and controlled profile of curcumin from the micelles [113].

Curcumin-loaded polymeric micelles with a mean size of 21 nm and a zeta potential of −16.64 mV inhibited glycation-induced amyloid fibrillation in vitro through suppression of β-sheet formation and advanced glycation end-product generation [114]. Maling et al. have reported the development of diblock copolymeric micelles for curcumin delivery, achieving an encapsulation efficiency of 60%, a mean particle size of 110 nm, and a zeta potential of −16 mV. These micelles significantly enhanced the bioavailability of curcumin, demonstrating an over 2.95-fold increase in cellular uptake and comparable cytotoxic activity to unmodified curcumin at equimolar concentrations [115]. Table 2 presents some key properties of curcumin-loaded micelles nanoparticles.

Table 2. Summary of the physicochemical characteristics and therapeutic applications of curcumin-loaded polymeric micelles.

Parameter	Summary	Outcomes	Reference
Particle size	Polymeric micelles generally range from 50 to 200 nm, depending on surfactant and formulation	Small size improves the water solubility of curcumin and facilitates cellular uptake	[112]
Encapsulation efficiency	Encapsulation efficiency is typically <90%, with curcumin trapped in hydrophobic micelle cores	Enhances curcumin stability against degradation and increases its bioavailability	[116]
BBB penetration	Micelles exhibit moderate BBB penetration, which improves with functionalization	Enables delivery of curcumin to neuronal sites relevant for Alzheimer's therapy	[117]
Release profile	Provides a sustained release, reducing rapid drug clearance	Extends therapeutic duration and maintains effective concentration in the brain	[117]
In vivo efficacy	Demonstrated to reduce Aβ plaques and improve memory in AD models	Confirms the therapeutic potential of micelles in targeting amyloid aggregation and cognitive decline	[118]
Toxicity	Reported as nontoxic and biocompatible in optimized formulations	Ensures safety for long-term use in chronic neurodegenerative conditions	[119]

Dendrimers

Dendrimers are highly branched, synthetic macromolecules characterized by monodispersity, radial symmetry, and a well-defined three-dimensional architecture at the nanometer scale. Structurally, dendrimers are composed of three fundamental elements: (i) a central core molecule or atom possessing two or more identical reactive functional groups; (ii) an interior branching framework consisting of repeating units that form successive layers known as "generations"; and (iii) terminal functional groups located on the periphery, which define the physicochemical characteristics and reactivity of the

dendrimer [120,121]. Two principal synthetic strategies are employed in dendrimer fabrication: the divergent and convergent approaches. The divergent method involves stepwise growth outward from the central core, whereas the convergent method assembles dendrons from the periphery inward toward the core [121].

A variety of dendrimer types have been developed, each tailored for specific functionalities. These include polyamidoamine (PAMAM) dendrimers, poly(amidoamine-organosilicon) (PAMAMOS) dendrimers, core–shell (tecto) dendrimers, liquid crystalline dendrimers, chiral dendrimers, glycodendrimers, peptide dendrimers, and hybrid dendrimers [122]. Dendrimers, owing to their modifiable surface groups and internal cavities, can encapsulate both hydrophilic and hydrophobic agents, thereby enhancing solubility and bioavailability. These properties make dendrimers versatile carriers for targeted drug and gene delivery [123]. Lactoferrin-functionalized low-generation dendrimers enabled sustained memantine release (51.23–58.36% over 48 h) and significantly improved brain bioavailability and cognitive performance in AD mice, increasing the discrimination index from 9.86 ± 6.52 to 33.43 ± 7.05 [124]. Dendrimers composed of a poly (propylene imine) core and a maltose histidine shell (G4HisMal) have been effectively developed, and show significant alleviation of AD manifestations like memory dysfunction. To improve biocompatibility and lessen the toxic effects of medications employed to treat AD, tacrine has also been administered in combination with generation 4.0 and PAMAM dendrimers as nanocomposites [125].

Mollazade et al. reported that PAMAM dendrimers could be considered as well-suited carriers for hydrophobic therapeutic agents such as curcumin due to their in-creased drug uptake and low cytotoxicity [126]. A novel polyamidoamine dendrimer was synthesized, achieving an encapsulation efficiency of 62% and a drug-loading capacity of 32%. The formulation exhibited no cytotoxicity and enhanced the water solubility of cur-cumin by approximately 200-fold compared to free curcumin [127]. Igartúa et al. reported that curcumin-loaded generation of 4.5 PAMAM dendrimers significantly improved the solubility of 1.6 μM to 105.5 ± 17.7 μM and extended its stability from a physiological half-life of 9.4 min to approximately 24 h at 25 °C [128]. The physicochemical characterization of curcumin-loaded dendrimer nanoparticles is presented in Table 3.

Table 3. Physicochemical characteristics, drug delivery performance, and therapeutic potential of curcumin-loaded dendrimers.

Parameter	Summary	Outcomes	References
Particle size	Typically range from 10 to 280 nm, depending on generation and surface modification	Nanoscale size allows efficient tissue penetration and potential for targeted brain delivery	[124,127]
Encapsulation efficiency	PAMAM-based dendrimers show high encapsulation efficiency, with stable curcumin loading	Improves curcumin solubility (~200-fold) and enhances therapeutic activity	[127]
BBB penetration	BBB transport is enhanced with ligand functionalization (e.g., lactoferrin, peptides)	Ensures brain-targeted delivery for Alzheimer's therapy	[121]
Release profile	Provides a controlled release, enabling gradual drug availability over time	Sustains therapeutic level, reducing dosing frequency and minimizing systemic side effects	[129]

Table 3. *Cont.*

Parameter	Summary	Outcomes	References
In vivo efficacy	Shown to reduce neuroinflammation and improve memory in AD animal models	Supports the role of dendrimers as multifunctional carriers in neurogenerative disease treatment	[121]
Toxicity	Toxicity is dependent, but biocompatibility improves with surface modification	Important for optimizing safety in clinical applications	[127]

Nanogels

Nanogels are hydrogel nanoparticles composed of swollen, physically or chemically cross-linked networks of hydrophilic or amphiphilic polymer chains. These nanoscale carriers have attracted significant attention in recent years as a promising class of drug delivery systems. Typically synthesized through physical self-assembly or chemical crosslinking, nanogels can be engineered to transport a variety of hydrophilic and hydrophobic drugs [130,131]. Their highly hydrated and swollen nature contributes to superior hydrophilicity, allowing them to mimic the properties of biological tissues. Moreover, nanogels offer high drug-loading capacity, excellent biocompatibility, and stimuli-responsive drug release behavior, making them ideal candidates for advanced and targeted drug delivery applications [132,133].

Wang et al. have prepared novel sodium alginate/ZnO hydrogel beads to optimize the release profile of curcumin, and the results showed that the composite hydrogel beads exhibit good pH sensitivity and controlled-release capacity. After exposure to UV irradiation for 6 h, the 1,1-Diphenyl-2-picrylhydrazyl (DPPH) scavenging capacity of curcumin-loaded hydrogel beads was decreased by only 13.70%, whereas that of pure curcumin decreased by 62.04% under the same conditions; therefore, the encapsulated curcumin showed a higher antioxidant activity [134]. Zhou et al. have developed curcumin-loaded supramolecular hydrogels with a drug-loading capacity of 12.14 $\pm$ 0.33% and an encapsulation efficiency of 93.57 $\pm$ 1.67%. This formulation also demonstrated enhanced solubility of curcumin compared to native curcumin [135]. A study on curcumin-loaded chitin nanogels reported particle sizes in the range of 70–80 nm, a zeta potential of 49.34 mV, and an entrapment efficiency of 95%. Swelling studies revealed that curcumin conjugation reduced the swelling ratio of chitin nanogels under alkaline, acidic, and neutral conditions, likely due to the decreased availability of free reactive functional groups [136]. Similarly, Khuwaja et al. reported that prepared curcumin-loaded nanogels exhibited a particle size in the range of 51.40 $\pm$ 21.70 nm with a zeta potential of -55 ± 13.5 mV, indicating good nanoscale stability and dispersion characteristics [137].

A study reported that curcumin- and piperine-loaded lignin-g-p gold nanogels with a spherical morphology exhibited a particle size of approximately 180 nm. Furthermore, drug release kinetics demonstrated an 86% release of hybrid curcumin–piperine from a gold nanogel after 250 min at pH 4 [138]. A modified nanogel delivery system, with PNIPAM and β-cyclodextrin grafted onto hyaluronic acid (PNCDHA), was utilized to enhance the solubility and delivery efficiency. The formulated nanogels exhibited an average particle size of 200 nm with a high encapsulation efficiency of 93.14 $\pm$ 5.6%, indicating effective drug loading [139]. Key findings on the physicochemical properties of curcumin-loaded nanogels are presented in Table 4.

Table 4. Summary of the physicochemical properties and biomedical applications of curcumin-loaded nanogels.

Parameter	Summary	Outcomes	References
Particle size	Nanogels usually range from 10 to 200 nm, with a highly hydrated and swollen polymeric network	Nanoscale structure allows tissue penetration and mimics biological environments	[135,140]
Encapsulation efficiency	Encapsulation efficiency is 50–99% depending on polymer composition and crosslinking	High efficiency improves curcumin solubility and therapeutic payload delivery	[136,140]
BBB penetration	Demonstrates moderate BBB penetration, which can be tuned with surface modifications	Facilitated delivery of curcumin into brain tissues for AD treatment	[141]
Release profile	Exhibits pH-sensitive controlled release, protecting curcumin from premature degradation	Allows site-specific and stimulus-responsive drug release in neurodegenerative conditions	[142]
In vivo efficacy	Shown to reduce neuroinflammation and improve memory in AD animal models	Supports therapeutic application in AD through neuroprotection and antioxidant activity	[143]
Toxicity	Generally nontoxic and biocompatible, safer for long-term biomedical applications	Ensures clinical safety for potential chronic treatment strategies	[143,144]

5.1.2. Lipid-Based Nanocarriers

The unique structural properties of lipid-based nanocarriers enable the incorporation of hydrophobic, hydrophilic, and amphiphilic therapeutic agents within their lipid matrices or aqueous compartments. Depending on their composition and architecture, lipid-based nanocarriers can be classified into liposomes, solid lipid nanoparticles (SLNs), or nanoemulsions (Figure 6). These systems offer several advantages, including high drug-loading capacity, protection of encapsulated molecules against degradation, prolonged circulation time, and the potential for surface functionalization with targeting ligands to improve delivery across biological barriers [145,146].

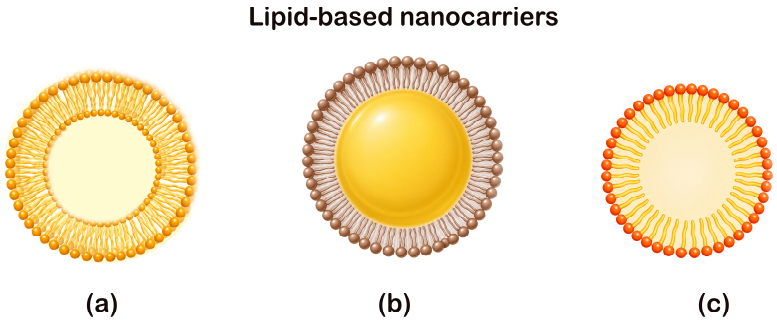


Figure 6. Classification of curcumin-loaded lipid-based nanocarriers for AD therapy: (**a**) liposomes, (**b**) nanoemulsion, (**c**) solid lipid NPs.

Liposomes

Liposomes are self-assembled, spherical vesicular structures composed of one or more phospholipid bilayers that enclose an internal aqueous compartment, effectively separating it from the external aqueous environment. Their formation is primarily attributed to the amphiphilic nature of phospholipids, which arises from unfavorable interactions between the hydrophobic lipid tails and surrounding water molecules [147,148]. In aqueous media, the hydrophilic head groups of phospholipids orient outward (toward the aqueous phases),

while the hydrophobic tails align inward, forming bilayer structures. Subsequently, the bilayer sheet is arranged as closed bilayer vesicles upon providing an adequate amount of energy for the aggregated phospholipids [140].

Encapsulation of curcumin in liposomes has been shown to significantly enhance its water dispersibility and chemical stability. These nanoparticles exhibited favorable physicochemical properties (entrapment efficiency = 57.1%, particle size = 68.1 nm, polydispersity index = 0.246, and zeta potential = −3.16 mV) [149]. In vitro studies have further demonstrated that liposomal encapsulation enhances the antioxidant and anti-inflammatory activities of curcumin. In vivo experiments in rat models indicate that liposomal formulations markedly improve the oral bioavailability and overall bioactivity of curcumin [62]. Shin et al. demonstrated that chitosan-coated curcumin nanoliposomes fabricated by the ethanol injection method exhibited enhanced storage stability, encapsulation efficiency (54.70%), mucoadhesive properties (56.47%), and bioavailability [150].

Lazar et al. developed curcumin-loaded nano liposomes to enhanced the therapeutic efficacy of curcumin against AD. The nano liposomal formulation reduced $A\beta_{40}$ and $A\beta_{42}$ secretion by 30% and 20%, respectively, improving cell viability from 69% to 82%, and exhibiting strong targeting of amyloid plaques, with approximately 70% labeling of senile plaque cores [151]. Balducci et al. have reported that bifunctionalized liposomes can disaggregate and hinder the formation of Aβ assemblies in vitro. In vivo administration for three weeks resulted in a 33% reduction in brain-insoluble $A\beta_{1–42}$ levels, as determined by ELISA, and a 34% decrease in amyloid plaque burden, evidenced by reductions in both plaque number and total plaque area [152]. The liposome carrier system that has been modified with a surface consisting of mannose ligand and cell-penetrating peptides has been employed to deliver apolipoprotein E (ApoE2) in the brain injured by AD. The findings exhibited that functionalized liposomes can deliver a significant concentration of genes to the target tissues safely and effectively for the treatment of AD [153]. Mourtas et al. developed curcumin-loaded nanoliposomes with particle sizes ranging from 131 to 207 nm and demonstrated high binding affinity for $A\beta_{1–42}$ fibrils, with dissociation constants in the range of 1–5 nM [154]. Table 5 provides stability of the profile of curcumin-loaded liposome nanoparticles.

Table 5. Physicochemical characteristics and therapeutic applications of curcumin-loaded liposomes.

Parameter	Summary	Outcomes	References
Particle size	Liposomes typically exhibit nanoscale diameters of 100–200 nm, ensuring stability and dispersibility	Small size enhances circulation time, cellular uptake, and penetration across the BBB	[153,155]
Encapsulation efficiency	Liposomes achieve ~85% encapsulation efficiency, protecting curcumin from rapid degradation	High drug loading improves therapeutic potential and reduces drug wastage	[150]
BBB penetration	Demonstrates moderate to high BBB penetration when surface modified with ligands or peptides	Enables targeted brain delivery for Alzheimer's therapy	[152]
Release profile	Provides a sustained release of curcumin, maintaining its stability and prolonging activity	Extends therapeutic effects and reduces frequency of administration	[153]
In vivo efficacy	Shown to stain Aβ plaques and improve memory in AD mouse models	Useful in both therapeutic delivery and diagnostic imaging for AD	[151]
Toxicity	Liposomes are nontoxic when surface modified, making them biocompatible for long-term use	Ensures safe administration in chronic neurodegenerative disease treatment	[151,155]

Nanoemulsions

Nanoemulsions are colloidal dispersions consisting of oil or water droplets with mean diameters typically below 200 nm, stabilized by surfactant or co-surfactant molecules and dispersed within an aqueous or lipophilic continuous phase [140,156]. Nanoemulsions have gained considerable attention as delivery systems for encapsulating bioactive compounds due to their small droplet size, large surface area, optical transparency, and improved kinetic stability, which collectively enhance the encapsulation, stability, and bioavailability of active ingredients [157].

Zheng et al. reported the impact of different delivery systems (aqueous dimethyl solutions, oil in water (O/W) nanoemulsions, and filled hydrogel beads) on the chemical stability of curcumin under both acidic and neutral conditions [158]. Another study has reported that curcumin-loaded nanoemulsions with a particle size diameter of 141.6 ± 15.4 nm and zeta potential of 6.9 ± 0.2 mV have an encapsulation efficiency of 90.56 ± 0.47% [159]. Water dispersibility of curcumin in NE was increased by 1400-fold compared to that of raw curcumin [160]. Aditya et al. have encapsulated curcumin and catechin in a water-in-oil-in-water (W/O/W) double emulsion using two-step emulsification. They reported that encapsulation of curcumin within an emulsion-based system enhanced their bio accessibility (72%) by four times compared to that of freely suspended curcumin (16%) [161]. In vivo pharmacokinetics analysis on mice confirmed that the oral bioavailability of curcumin in the organogel-based nanoemulsion was increased by 9-fold compared with unformulated curcumin [162].

Compared to native curcumin, the nanoemulsion formulation demonstrated a significant enhancement in aqueous solubility and resulted in a 9-fold increase in plasma bioavailability following oral administration in a rat model [163]. The size and composition of droplets in nanoemulsions significantly influence the rate and extent of lipid digestion, thereby affecting the bioavailability of curcumin. Pinheiro et al. have reported that curcumin nanoemulsions stabilized with Tween 20 and exhibiting a mean droplet size of approximately 300 nm achieved a bio accessibility of around 15% following in vitro ileum digestion. In contrast, emulsions stabilized with dodecyl trimethyl ammonium bromide and a larger droplet size of approximately 900 nm exhibited significantly lower bio accessibility, at only 1.5% [164]. Vecchione et al. have reported that incorporation of curcumin into nanoemulsions with a droplet size of 110 nm, compared to unformulated curcumin, increased the area under the blood concentration–time curve of curcumin after oral administration, much higher than that into 230 nm nanoemulsions, 64 times against 23 times [165]. Key physicochemical properties of nanoemulsions are tabulated in Table 6.

Table 6. Summary of the physicochemical properties and drug delivery performance of curcumin-loaded nanoemulsions.

Parameter	Summary	Outcomes	References
Particle size	Nanoemulsions usually have a droplet diameter below 200 nm, offering high surface area and stability	Enhances absorption in the gastrointestinal tract and improves biodistribution in the brain	[159,166]
Encapsulation efficiency	Reported efficiency is 80–90%, allowing curcumin to remain protected in the oil–water interface	Increases the solubility and stability of curcumin compared to the free drug	[159]

Table 6. *Cont.*

Parameter	Summary	Outcomes	References
BBB penetration	Intrinsically limited, but enhanced when surface modified with stabilizers or ligands	Facilitates targeted brain delivery to improve treatment outcomes in AD	[165]
Release profile	Can vary from rapid to sustained release, depending on droplet size and composition	Flexible drug release control allows optimization for either fast action or prolonged effect	[160,164]
In vivo efficacy	Demonstrates increased systemic absorption and reduced inflammation in animal models	Improves oral bioavailability and provides neuroprotective benefits in AD therapy	[165]
Toxicity	Generally low to moderate, but it depends on the surfactants used in the formulations	Safe when optimized with biocompatible surfactants for clinical applications	[151,155]

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) represent a significant advancement in drug delivery systems, offering several advantages in pharmaceutical applications. Utilizing solid lipids as the core matrix, SLNs provide a stable and biocompatible environment for encapsulating various therapeutic agents. This structure enhances the chemical stability, solubility, and targeted delivery of bioactive compounds [166].

Lipid NPs encompass two generations: the solid nanoparticles and Nano-Structured Lipid Carriers (NLCs) [155]. SLNs are composed of a lipid core that stays solid at both body and room temperature. On the other hand, NLCs comprise a mixture of both solid and liquid lipids to overcome some limitations of SLNs, including poor drug-loading ability and poor long-term stability caused by polymorphic transitions of lipids to a more stable form [167,168].

Encapsulation of curcumin within SLNs has demonstrated a substantial improvement in its water dispersibility, bioactivity, and chemical stability in aqueous solutions [169]. Dibaei et al. reported entrapment efficiency of curcumin in SLNs and NLCs was 82% $\pm$ 0.49 and 94% $\pm$ 0.74, respectively. The dynamic light scattering (DLS) analysis revealed that curcumin-loaded SLNs exhibited a mean particle size of 204.76 $\pm$ 0.36 nm with a poly dispersity index (PDI) of 0.194 $\pm$ 0.04, whereas curcumin-loaded NLPs were 117.36 $\pm$ 1.36 nm and 0.188 $\pm$ 0.020, respectively [170]. In vitro studies have demonstrated that curcumin-loaded SLNs significantly enhance the cellular uptake in model epithelial cells compared with free curcumin [171].

A modified synthesis method was employed to produce stable solid nanoparticles encapsulating curcumin, achieving a loading efficiency of 71%. Approximately 90% of the encapsulated curcumin was released within 48 h, demonstrating enhanced bioavailability [172]. In vivo studies in rats showed that administration of curcumin in SLNs greatly improved its bioavailability (more than a 12-fold increase) when compared to free curcumin [173]. Table 7 summarizes the principal characteristics and findings of curcumin-loaded solid lipid nanoparticles.

Table 7. Physicochemical characteristics and therapeutic efficacy of curcumin-loaded solid lipid nanoparticles and nanostructured lipid carriers.

Parameter	Summary	Outcomes	References
Particle size	SLNs and NLCs generally have particle sizes < 200 nm, ensuring stability and efficient uptake	Small size favors BBB penetration, improves drug distribution, and enhances oral bioavailability	[169]
Encapsulation efficiency	SLNs show ~80%, while NLCs reach up to 94% encapsulation efficiency	Higher entrapment improves therapeutic efficacy and reduces dosing frequency	[170,174]
BBB penetration	BBB transport is enhanced with surface ligands such as lactoferrin	Promotes targeted drug delivery to the brain, improving Alzheimer's treatment outcomes	[174]
Release profile	Exhibits a sustained release over 48 h, providing controlled drug delivery	Extends therapeutic effects, reduces degradation, and ensures prolonged circulation	[172]
In vivo efficacy	Shown to reduce Aβ plaques and improve memory in AD animal models	Confirms neuroprotective and anti-amyloid potential of curcumin SLNs/ NLCs	[175]
Toxicity	Reported as biocompatible with low systemic toxicity when optimized	Ensures safe long-term use in neurodegenerative disease management	[166]

5.1.3. Inorganic Nanoparticles

Inorganic nanoparticles are widely used in biomedicine due to their chemical and physical stability, tolerance to a wide range of organic solvents, low toxicity, cost-effectiveness, controllable laboratory production, and large surface area. Among them, the large surface area of inorganic nanoparticles enables high drug-loading capacity and precise controlled release, making them ideal for drug delivery applications [176]. However, surface modification, often through the incorporation of polymers or lipids, is typically required to enhance biocompatibility and ensure successful drug delivery [177]. Currently, a variety of inorganic nanoparticles have been extensively studied in laboratory settings, including mesoporous silica nanoparticles, gold nanoparticles, and iron-based nanoparticles (Figure 7) [178–180].

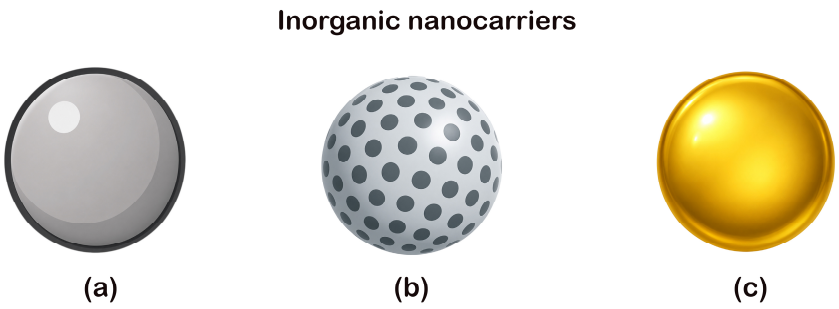


Figure 7. Classification of curcumin-loaded inorganic nanocarriers for Alzheimer's disease therapy: (**a**) iron-oxide NPs, (**b**) mesoporous silica NPs, (**c**) gold NPs.

A novel method for the selective labeling of $A\beta_{1–40}$ fibrils has been reported with nonfluorescent, fluorescent rhodamine-tagged or Congo red encapsulated magnetic Fe_2O_3 NPs, even under competitive conditions. Moreover, these studies revealed the ability of iron oxide NPs to readily remove fibrils from solubilized Aβ aqueous samples by the simple use of an external magnetic field [181,182]. Zarei et al. have prepared curcumin loaded with dextran-coated superparamagnetic iron oxide NPs (~100 nm) to evaluate PC12 cells (pheochromocytoma cells). They confirmed that the biocompatibility of Fe_2O_3

nanoparticles significantly enhanced neuronal branching morphogenesis ($p < 0.01$), and their combination with curcumin further improved neurogenesis compared to curcumin alone [183]. Yallapu et al. developed a novel curcumin-loaded magnetic nanoparticle formulation, which enhanced the serum bioavailability of curcumin in mice by up to 2.5-fold compared to free curcumin [184]. Wang et al. reported cell viability remained above 75% after 24 h, 48 h and 72 h incubation with Fe_3O_4@Astragalus polysaccharide core–shell nanoparticles at iron concentrations of 0–50 μg/mL. These findings indicate that the nanoparticles possess favorable biocompatibility and exhibit minimal cytotoxicity [185].

Jambhrunkar et al. prepared curcumin encapsulated in mesoporous silica nanoparticles (MCM-41-CUR) with a mean size of 190 nm (PDI = 0.31), and they showed improved solubility by 70% for the in vitro release profile and significantly enhanced cell cytotoxicity compared to the pure drug [186]. The adsorption of curcumin in the nanopores of mesoporous silica nanoparticles was achieved via hydrogen bond interaction. MCM-41-CUR improved the curcumin solubility and increased the in vitro release compared with free curcumin [187]. Kalantari et al. developed curcumin-encapsulated gold nanoparticles with a zeta potential of −36.3 mV, indicating enhanced colloidal stability [188]. Muniyappan et al. reported the green synthesis of gold nanoparticles capped with curcumin, which demonstrated a maximum inhibition efficiency of 94% using the human red blood cell membrane stabilization method. The nanoparticles also exhibited significant antioxidant and radical scavenging activities [189]. Table 8 presents the physicochemical properties of curcumin-loaded inorganic nanocarriers.

Table 8. Summary of the physicochemical properties and therapeutic applications of curcumin-loaded inorganic nanoparticles.

Parameter	Summary	Outcomes	References
Particle size	Inorganic nanoparticles generally range from 10 to 200 nm, depending on core material (e.g., silica, gold, iron oxide)	Small size favors cellular uptake, magnetic targeting, and enhanced stability in circulation	[182]
Encapsulation efficiency	Reported as moderate to high, depending on surface chemistry and material type	Ensures efficient drug loading and protection of curcumin molecules	[180]
BBB penetration	BBB transport can be enhanced with magnetic guidance or surface ligands	Allows targeted delivery of curcumin to brain tissue, improving therapeutic outcomes in AD	[190]
Release profile	Provides a controlled release, influenced by nanoparticle surface modifications	Enables prolonged curcumin activity and minimizes burst release	[191]
In vivo efficacy	Demonstrated neuroprotective effects and enhanced uptake in AD animal models	Confirms ability to reduce amyloid burden and support neuronal survival	[186,192]
Toxicity	Toxicity is dependent on the core material (e.g., gold, iron oxide, silica)	Biocompatibility optimization is crucial to ensure safety in clinical applications	[185]

5.2. Comparative Analysis of Curcumin Nanocarrier Systems

Table 9 provides a comparative overview of the different nanocarrier systems developed for curcumin delivery in the management of AD. Figure 8 summarizes the approximate particle size (nm) and drug release time (h) reported for polymeric nanoparticles, micelles, dendrimers, nanogels, liposomes, nanoemulsions, and solid lipid nanoparticles. Overall, all the platforms indicate that curcumin nanocarriers consistently achieve

5–50+ fold improvements in systemic bioavailability and brain delivery compared to native curcumin. Surface functionalization strategies such as conjugation with peptides, lactoferrin, or PEG reliably enhance BBB transport and neuronal uptake. In preclinical AD models, these systems demonstrate multifaceted benefits centered on Aβ plaque reduction and disaggregation, inhibition of tau hyperphosphorylation, potent antioxidant and anti-inflammatory activities, and ultimately improved cognitive function and memory performance.

This collective evidence positions nanocarrier technology as a highly promising avenue to unlock curcumin's full neuroprotective potential in AD therapy.

Table 9. Comparative overview of key physicochemical and therapeutic properties of different curcumin-loaded nanocarrier systems for AD therapy.

Nanocarrier Type	Encapsulation Efficiency	BBB Penetration	Toxicity/ Biocompatibility	In Vivo Efficacy	Key Advantages/ Limitations	References
Polymeric nanoparticles	30–90%	High (with mucoadhesion or ligands like Tet-1, B6)	Generally non-toxic, biocompatible	Reduced Aβ plaques, improved memory, neuroprotection	Versatile surface modification and scalable but may require optimization for batch consistency	[101,102,104,105]
Polymeric Micelles	Up to 90%	Moderate (improved with functionalization)	Non-toxic in optimized forms	Inhibited amyloid fibrillation, enhanced bioavailability (~9-fold)	Excellent solubilization of hydrophobic curcumin, simpler preparation	[112,116–118]
Dendrimers	High (~62%)	Enhanced with ligands (lactoferrin)	Dependent on generation/surface modification	Improved solubility (~200-fold), reduced neuroinflammation, better cognitive outcomes	High loading and multivalency, potential cytotoxicity at higher generations	[106–109]
Nanogels	Up to 99%	Moderate	Generally non-toxic	Antioxidant protection, reduced neuroinflammation, memory improvement	High hydration, stimuli responsiveness, good sustained/local delivery	[135,136,141–143]
Liposomes	~85%	Moderate to high (with surface ligands/peptides)	Non-toxic when modified	Reduced Aβ secretion, plaque staining, memory improvement	High biocompatibility, dual hydrophilic/lipophilic loading, stability challenges	[148–151]
Nanoemulsions	80–95%	Enhanced with stabilizers	Low toxicity with proper surfactants	9-fold bioavailability increase, better absorption	Excellent oral bioavailability enhancement, kinetic stability	[156–161]
Solid lipid NPs	80–95%	Enhanced with ligands (lactoferin)	Biocompatible, low toxicity	Reduced A plaques, improved memory, 12-fold bioavailability	High stability for lipophilic drugs, potential polymorphic transitions	[164–169,172,173]
Inorganic NPs	Moderate to high	Enhanced (magnetic guidance/ligands)	Material dependent and need optimization	Neuroprotection, enhanced uptake, magnetic targeting	Multifunctional but potential long-term toxicity concerns	[176–178,183–185,192]

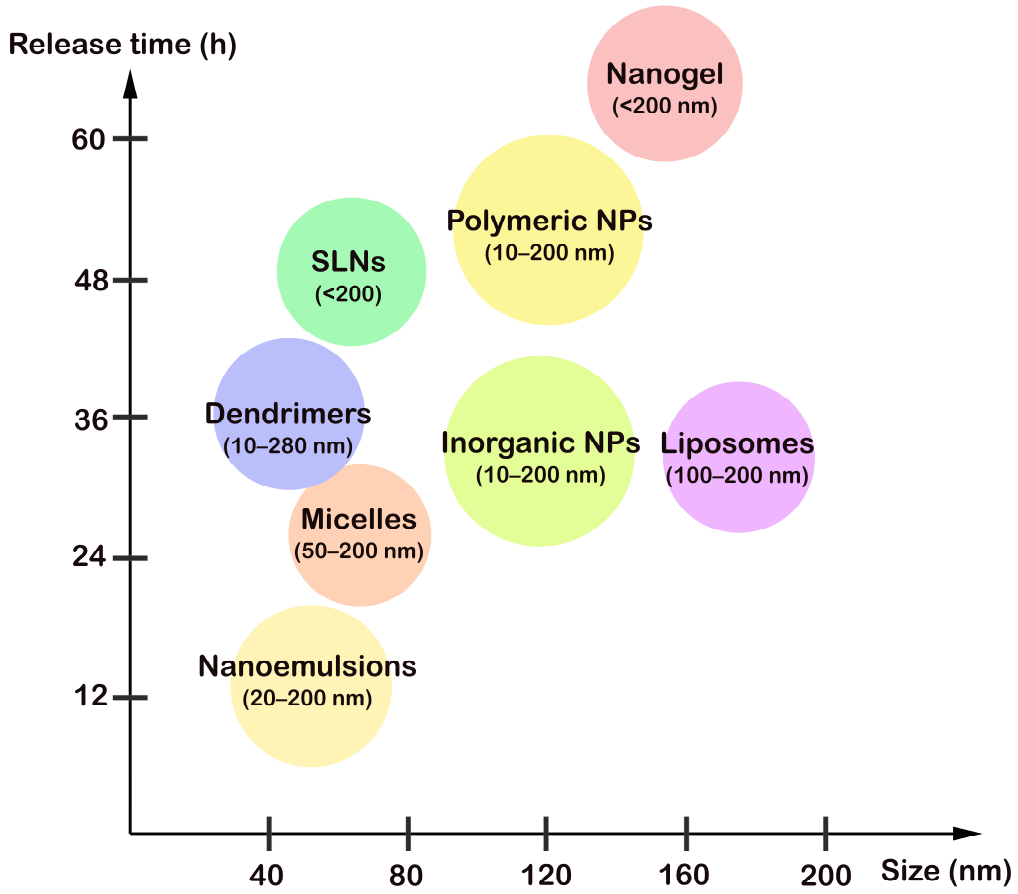


Figure 8. Comparison of the typical particle size and sustained drug release duration of major nanocarrier systems.

6. Commercial Nano Formulations

Although numerous curcumin nano formulations have demonstrated promising therapeutic efficacy in preclinical models of AD, only a limited number have progressed to clinical evaluation or commercial production. Translation from laboratory research to commercial products requires scalable manufacturing, reproducible quality, long-term stability, regulatory approval, and demonstration of clinical efficacy. Consequently, most curcumin nanocarriers remain at the preclinical stage despite encouraging experimental findings.

Several nano-formulated curcumin delivery systems have progressed toward commercialization to overcome the poor bioavailability, limited aqueous solubility, rapid metabolic degradation, and restricted blood–brain barrier penetration associated with native curcumin. Theracurmin® is a highly bioavailable formulation developed by curcumin dispersed as colloidal submicron particles stabilized with natural dispersing agents. After the oral administration, Theracurmin® was found to be more than 40-fold higher than that of curcumin powder in rats. Moreover, the AUC of Theracurmin® was 27-fold higher than that of curcumin powder [193].

Aiming to increase curcumin's bioavailability, a polymeric nanoparticle-encapsulated curcumin named NanoCurc™ was formulated, which is completely water soluble. This treatment protects neuronally differentiated human SK-N-Sh cells against hydrogen peroxide-induced reactive oxygen species-mediated oxidative injury. In vivo, intraperitoneal NanoCurc™ injection at a dose of 25 mg/kg twice daily in athymic mice resulted in significant curcumin levels in the brain (0.32 μg/g) [194]. Mervia®, 1:2 phytosomal formulation of curcuminoids and lecithin, has significantly higher bioavailability (approximately 20-fold) than unformulated curcumin [195].

Longvida® is another commercialized product, which used a solid lipid curcumin formulation (free curcumin is encapsulated within a patented tri-lipid matrix). This lipid-based delivery system enhances the solubility and stability of curcumin, protects it from gastrointestinal degradation, and facilitates its absorption into the bloodstream [196]. NovaSol® is a surfactant-based liquid micellar formulation in which curcumin is incorporated into nano-sized polymeric micelles (~30 nm). The micelles greatly improve aqueous solubility, protect curcumin from degradation, and markedly enhance oral absorption and bioavailability [197,198]. BioCurc® is a proprietary curcumin formulation based on colloidal liquid droplet micro micellar technology, in which curcumin is solubilized within nanometer-sized micro micelles. This micro micellar delivery system improves the aqueous solubility and stability of curcumin, facilitates its gastrointestinal absorption, and enhances systemic bioavailability. Clinical pharmacokinetic studies have demonstrated that BioCurc® produces substantially higher plasma curcumin concentrations and AUC than conventional 95% curcumin, indicating significantly improved oral absorption [198].

Table 10 summarizes commercial nano formulations of curcumin and their formulation characteristics. These formulations are marketed primarily as dietary supplements to overcome the poor bioavailability of curcumin. However, they have not been approved as therapeutics for AD.

Table 10. Commercial nano formulations of curcumin and their formulation characteristics.

Commercial Formulation	Carrier Type	Composition	Outcomes	References
Theracurmin®	Colloidal nanoparticle dispersion	Surface-dispersed curcumin nanoparticles	27-fold higher bioavailability than native curcumin	[193,199]
Longvid®	Solid lipid particles	Curcumin encapsulated in solid lipid matrix	Enhanced BBB penetration, prolonged circulation, improved stability	[196,200,201]
NovaSOL®	Micellar formulations	Curcumin incorporated into liquid micelles	Up to 185-fold higher bioavailability than native curcumin	[198,202]
NanoCurc™	Polymeric nanoparticles	Curcumin-encapsulated polymeric nanoparticles	Improved aqueous solubility and stability	[194]
Meriva®	Phospholipid complex	Curcumin–phosphatidylcholine complex	Improved absorption and bioavailability compared to native curcumin	[195,203]
CurcuWin®	Hydrophilic carrier-based nanoparticle dispersion	Cellulosic/hydrophilic carrier system	46-fold higher bioavailability than native curcumin	[204]
BioCurc®	Micellar	Nano-dispersed curcumin	Improved oral absorption and stability	[198,200]

7. Commercialization Challenges and Future Perspectives

Although many nanomedicines are already in use or are being studied in clinical trials, many barriers impede bringing these drugs to market, especially in manufacturing, economic, regulatory, and clinical challenges. Addressing these issues is essential for translating laboratory-scale formulations into clinically approved therapeutics.

7.1. Manufacturing and Scale-Up Challenges

At the laboratory scale, various nanocarrier systems have demonstrated enhanced stability, bioavailability, and BBB penetration, highlighting their potential for AD and other neurological disorders. However, scaling up these formulations for industrial production remains a significant obstacle to their clinical translation. Most nanocarriers are developed using laboratory-scale techniques including nanoprecipitation, solvent evaporation, emulsification, and microfluidics, which enables precise control over nanoparticle characteristics under experimental conditions but is often difficult to reproduce during industrial-scale production. During scale-up, changes in hydrodynamic conditions, including momentum and mass transfer, can significantly alter critical quality attributes such as particle size, PDI, zeta potential, encapsulation efficiency, drug loading, and drug release behavior, leading to batch-to-batch variability [205,206]. Furthermore, successful clinical translation requires scalable manufacturing processes that ensure formulation reproducibility, long-term physicochemical stability, biocompatibility, biodegradability, and the use of materials with a generally recognized as safe status [207,208].

7.2. Clinical Translation Challenges

Despite extensive preclinical evidence demonstrating that curcumin-loaded nanocarriers effectively reduce amyloid-β accumulation, attenuate tau, mitigate oxidative stress, and improve cognitive performance in cellular and animal models, clinical translation remains limited [23]. Most published studies involve in vitro experiments or animal models, while relatively few formulations have progressed to early-stage clinical trials evaluating safety. To date, no curcumin nanocarrier has completed successful Phase III clinical trials for AD [23,209]. Moreover, substantial interindividual variability in curcumin absorption, metabolism, gut microbiota composition, age, disease stage, and genetic background contributes to inconsistent therapeutic outcomes among patients [61]. Additional challenges include identifying appropriate biomarkers, selecting suitable patient populations, determining optimal dosing regimens, and demonstrating meaningful cognitive improvements in long-term clinical studies [210].

7.3. Stability and Storage Challenges

Long-term physiochemical stability remains one of the principal challenges limiting the successful commercialization of nanocarrier-based drug delivery systems. Throughout manufacturing, storage, transportation and prolonged shelf life, nanoparticles may undergo irreversible physicochemical changes, including aggregation, particle growth, Ostwald ripening, polymer degradation, surface charge alterations, and premature drug leakage. These instabilities can affect critical quality attributes, leading to variability in product performance, pharmacokinetics, and manufacturing consistency [207].

Curcumin presents significant formulation challenges owing to its poor chemical stability. Under physiological and alkaline conditions, it readily undergoes hydrolytic degradation, autoxidation, and photodegradation, resulting in degradation products with markedly reduced biological activity and limiting its therapeutic efficacy. Furthermore, its poor aqueous solubility and rapid metabolic degradation contribute to low systemic bioavailability and may diminish the therapeutic effectiveness of nano formulations if adequate protection is not provided by the carrier system [61,211].

Although nanocarriers enhance the chemical stability and bioavailability of curcumin by protecting it from environmental degradation, maintaining the long-term stability of the nanocarrier itself remains a major challenge. Environmental factors, including temperature, humidity, oxygen, light exposure, mechanical stress during transportation, and repeated freeze–thaw cycles can destabilize nanocarriers, particularly lipid-based and polymeric

nanocarriers, resulting in changes to critical quality attributes, reduced shelf life and compromised batch to batch reproducibility [210,212].

7.4. Future Perspectives

Future research should focus on the development of clinically translatable nanocarrier platforms that integrate robust manufacturing reproducibility, long-term physicochemical stability, scalable production processes, cost-effective fabrication, and compliance with regulatory quality standards. Achieving these objectives requires careful optimization of both formulation and manufacturing parameters to ensure consistent critical quality attributes, including particle size, polydispersity index, zeta potential, drug loading, encapsulation efficiency, and release kinetics across production batches [207,212].

The emerging field of personalized nanomedicine offers promising opportunities to improve the treatment of AD by enabling patient-specific therapeutic strategies [213]. Future nanocarrier systems may be designed according to individual characteristics, including genetic factors, disease stage, molecular biomarker profiles, metabolic status, and gut microbiome composition, thereby supporting precision medicine approaches that optimize therapeutic efficacy while reducing interpatient variability [214].

The successful clinical translation of curcumin-loaded nanocarriers will require well-designed, multicenter randomized controlled trials employing standardized formulations manufactured under Good Manufacturing Practice (GMP) conditions [213]. Future studies should integrate comprehensive pharmacokinetic and pharmacodynamic evaluations, validated fluid and neuroimaging biomarkers, appropriate patient stratification based on disease stage and biomarker profiles, optimized dosing strategies, and long-term follow-up to assess sustained efficacy and safety [215]. Furthermore, demonstrating consistent therapeutic efficacy, favorable long-term safety, manufacturing reproducibility, and compliance with regulatory standards in adequately powered Phase III clinical trials will be essential for achieving regulatory approval and facilitating the routine clinical application of curcumin nanomedicines for AD [206,216].

8. Conclusions

Curcumin-encapsulated nanocarriers, including polymeric, micelles, nano emulsions, dendrimers, liposomes, inorganic nanocarriers, and nanogels, have revealed significant potential as a therapeutic agent for AD. In particular, their biocompatibility and ability to cross the blood–brain barrier enhance their therapeutic potential for targeting damaged neurons. This represents a remarkable advancement in the development of treatments for neurodegenerative disorders such as AD. However, further research is required to explore hybrid systems, functionalized nanocarriers, and modified nanocarriers. Additionally, comprehensive clinical trials should be conducted to evaluate their safety and efficacy.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's disease
Akt	Protein kinase B
Aβ	Amyloid-β
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
APE1	Apurinic/apyrimidinic endonuclease 1
ApoE2	Apolipoprotein E2
APPs	Amyloid precursor proteins
AUC	Area under the curve
BBB	Blood brain barrier
BCS	Biopharmaceutics classification system
CNS	Central nervous system
GMP	Good manufacturing practice
GSK-3β	Glycogen synthase kinase-3 beta
HLB	Hydrophile–lipophile balance
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MCM-41-CUR	Mesoporous silica nanoparticles
MDA	Malondialdehyde
mTORC1	Mechanistic target of rapamycin complex 1
NLCs	Nano-structured lipid carriers
NO	Nitric oxide
NPs	Nanoparticles
Nrf2	Nuclear factor erythroid 2-related factor 2
PAMAM	Polyamidoamine
PC12 cells	Pheochromocytoma cells
PDI	Poly-dispersity index
PNIPAM	Poly(N-isopropylacrylamide)
ROS	Reactive oxygen species
SLNs	Solid lipid nanoparticles
SMD	Standardized mean difference
TAC	Total antioxidant capacity
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-alpha
5-LOX	5-lipoxygenase

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