Minireview

Nanocarrier-mediated curcumin delivery: An adjuvant strategy for CNS disease treatment

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Impact Statement

Neurological disorders present a global challenge, comprising a significant portion of disease burden worldwide. The complex nature of central nervous system (CNS) diseases demands innovative therapeutic approaches. Curcumin's potential as an adjuvant therapy for CNS diseases is hindered by its limited bioavailability and blood–brain barrier (BBB) permeability. Nanocarrier-mediated curcumin delivery holds promise in overcoming these challenges. This review highlights how nanocarriers can enhance curcumin's therapeutic efficacy by improving its bioavailability and BBB permeability. This approach has the potential to reshape CNS disease management, offering synergistic effects with existing drugs and improving safety profiles. Moreover, exploring intranasal curcumin delivery and its utilization as an adjuvant therapy offers novel possibilities for effective CNS disease treatment.

Abstract

Neurological disorders are a major global challenge, which counts for a substantial slice of disease burden around the globe. In these, the challenging landscape of central nervous system (CNS) diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and neuro-AIDS, demands innovative and novel therapeutic approaches. Curcumin, a versatile natural compound with antioxidant and anti-inflammatory properties, shows great potential as a CNS adjuvant therapy. However, its limited bioavailability and suboptimal permeability to the blood–brain barrier (BBB) hamper the therapeutic efficacy of curcumin. This review explores how nanocarrier facilitates curcumin delivery, which has shown therapeutic efficacy for various non-CNS diseases, for example, cancers, and can also revolutionize the treatment outcomes in patients with CNS diseases. Toward this, intranasal administration of curcumin as a non-invasive CNS drug delivery route can also aid its therapeutic outcomes as an adjuvant therapy for CNS diseases. Intranasal delivery of nanocarriers with curcumin improves the bioavailability of curcumin and its BBB permeability, which is instrumental in promoting its therapeutic potential. Furthermore, curcumin's inhibitory effect on efflux transporters will help to enhance the BBB and cellular permeability of various CNS drugs. The therapeutic potential of curcumin as an adjuvant has the potential to yield synergistic effects with CNS drugs and will help to reduce CNS drug doses and improve their safety profile. Taken together, this approach holds a promise for reshaping CNS disease management by maximizing curcumin's and other drugs' therapeutic benefits.

Keywords: Nanocarriers, curcumin, CNS diseases, neurodegenerative disorders, intranasal delivery, blood–brain barrier

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Introduction

Curcumin, a naturally occurring biologically active polyphenolic compound found in the spice turmeric (*Curcuma longa*), has a rich medicinal history dating back centuries in traditional medicine.[1] It has been utilized in Ayurvedic and Chinese medicine for its therapeutic properties in various conditions, including inflammation, pain, digestive disorders, and skin diseases.[1,2] Sourced primarily from the rhizomes of the turmeric plant, curcumin belongs to a class of compounds known as curcuminoids. Curcumin is a molecule that exhibits significant biological activities due to its unique composition (Figure 1), which includes a diarylheptanoid, a β-diketone, and an α,β-unsaturated β-diketone. These properties make curcumin valuable for its antioxidant, anti-inflammatory, and anticancer effects. Structurally, curcumin is a symmetrical compound, also known as diferuloyl methane, and its IUPAC name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It can be represented by the chemical formula $C_{21}H_{20}O_6$ and has a molecular weight of 368.38. Its structure comprises three distinct components: two aromatic ring systems that incorporate o-methoxy phenolic groups, linked together by a seven-carbon chain containing an α,β-unsaturated β-diketone segment.[3] Curcumin is a lipophilic compound and therefore for optimal absorption, it is commonly ingested

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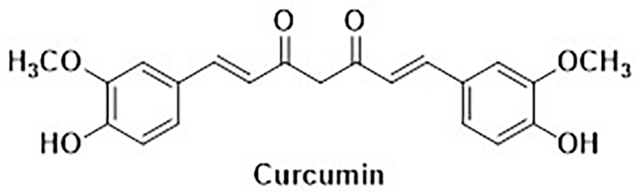

Figure 1. Chemical structure of curcumin.

with lipid-containing meals.[4] Upon absorption, curcumin binds to multiple cellular targets, including transcription factors, enzymes, and receptors, resulting in its diverse biological effects.[4] Curcumin's interactions with nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX-2) regulate cellular inflammation.[5] Curcumin exhibits potent antioxidant characteristics by neutralizing free radicals and mitigating reactive oxygen species (ROS)-associated cellular damage in various diseases.[6,7]

The conjugated structure of curcumin, marked by multiple double bonds, reinforces its antioxidant capacity by facilitating oxidation and reduction reactions.[3,6] Moreover, its abundance of hydroxyl and ketone groups allows interactions with various proteins and enzymes, influencing their activity and stability.[6] The planar structure of curcumin enhances its interactions with other planar molecules, enabling further engagement with receptors and enzymes and alteration in their activity/stability.[6,8] These molecular features collectively are responsible for curcumin's potential as a therapeutic agent to treat a wide range of diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions.[8]

Therapeutic spectrum of curcumin

Curcumin has demonstrated promising effects in various disease conditions. In cancer, curcumin has been shown to inhibit the growth of different types of cancer cells, including breast,[9] lung,[10] and colon cancer.[11] Its abilities to induce cell death and hinder tumor angiogenesis hold promise for cancer therapy. In rheumatoid arthritis, curcumin's anti-inflammatory and antioxidant effects have been shown to alleviate joint inflammation and oxidative stress by modulating proinflammatory cytokines like TNF-α and IL-1β, and increasing anti-inflammatory cytokines such as IL-10.[12,13] Furthermore, curcumin has been demonstrated as beneficial effects on inflammatory bowel disease, ameliorating symptoms in conditions like Crohn's disease and ulcerative colitis through its anti-inflammatory actions in the gut.[14,15] In diabetes, curcumin has shown potential in improving insulin sensitivity, reducing blood sugar levels, and lowering the risk of diabetes development by addressing inflammation and oxidative stress.[16,17]

Besides, curcumin exhibits therapeutic potential in reducing human immunodeficiency virus (HIV)-associated inflammation and cellular damage by modulating autophagy via PI3K/AKT/IKK/NF-κB signaling.[18] Curcumin has been shown to counter gp120-induced neuronal apoptosis, safeguard synaptic plasticity, reduce ROS levels and microglia-induced inflammation, and accelerate the degradation of Tat protein.[19–21] It also inhibits Tat-mediated LTR transactivation and HIV-1 virus production.[21] These findings suggest curcumin's potential for mitigating HIV-related inflammation and neurotoxicity, warrants further therapeutic exploration in HIV treatment. Furthermore, curcumin's role in cardiovascular health has been attributed to its ability to reduce inflammation and oxidative stress, as well as its capacity to lower the levels of circulating cholesterol and blood pressure.[22–24] These findings support the potential of curcumin as a versatile therapeutic agent for various disease conditions.

Curcumin's neurotherapeutic applications

The therapeutic potential of curcumin shown in (Figure 2) in various brain disorders has been extensively investigated due to its anti-inflammatory, antioxidant, and neuroprotective properties.[25–27] In Alzheimer's disease (AD), curcumin has been shown to inhibit the formation of amyloid plaques and improve cognitive function.[28,29] The underlying mechanisms include modulation in the activity of enzymes involved in amyloid metabolism and reduction of neuroinflammation via inhibition of neuronal NF-κB signaling.[30] Similarly, in Parkinson's disease (PD), curcumin's anti-inflammatory and antioxidant actions have been studied in the context of Lewy body formation and motor function improvement.[31] Curcumin's ability to enhance the activity of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase, and catalase, in brain cells leads to a reduction in oxidative stress and neuroprotection.[32]

Moreover, curcumin's anti-inflammatory effects have been explored in depression, traumatic brain injury (TBI), and multiple sclerosis (MS).[33,34] In depression, curcumin's ability to inhibit proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are important for its antidepressant activity.[35] In TBI, curcumin has been shown to attenuate neuroinflammation and reduce neuronal damage through the inhibition of the p38/MAPK signaling pathway and regulation of pro-/anti-inflammatory mediators.[33] Similarly, curcumin's anti-inflammatory actions involving the suppression of immune cell activation and reduction of oxidative stress have been suggested as potential mechanisms for protecting from myelin and neuron damage in MS.[34]

Curcumin also holds a therapeutic promise in suppressing HIV-associated neurocognitive disorders (HAND) and NeuroAIDS by mitigating neuroinflammation and oxidative stress. Previous studies showed that curcumin reduces gp120-induced inflammation, modulates autophagy, and alters various inflammatory signaling pathways.[18] Nanoparticles comprising curcumin display pain-reducing properties by inhibiting the expression of the P2X3 receptor.[36] Moreover, it regulates HSP70 expression to counteract neuronal apoptosis induced by the gp120 V3 loop.[37] Curcumin also offers protection against synaptic plasticity impairment[20] and reduces HIV-1-mediated apoptosis by curbing ROS production.[19] In addition, curcumin targets the Tat protein and hinders the transactivation and replication of the virus.[21] Recent studies have linked curcumin's antioxidant properties with potential benefits in schizophrenia, where oxidative stress has been

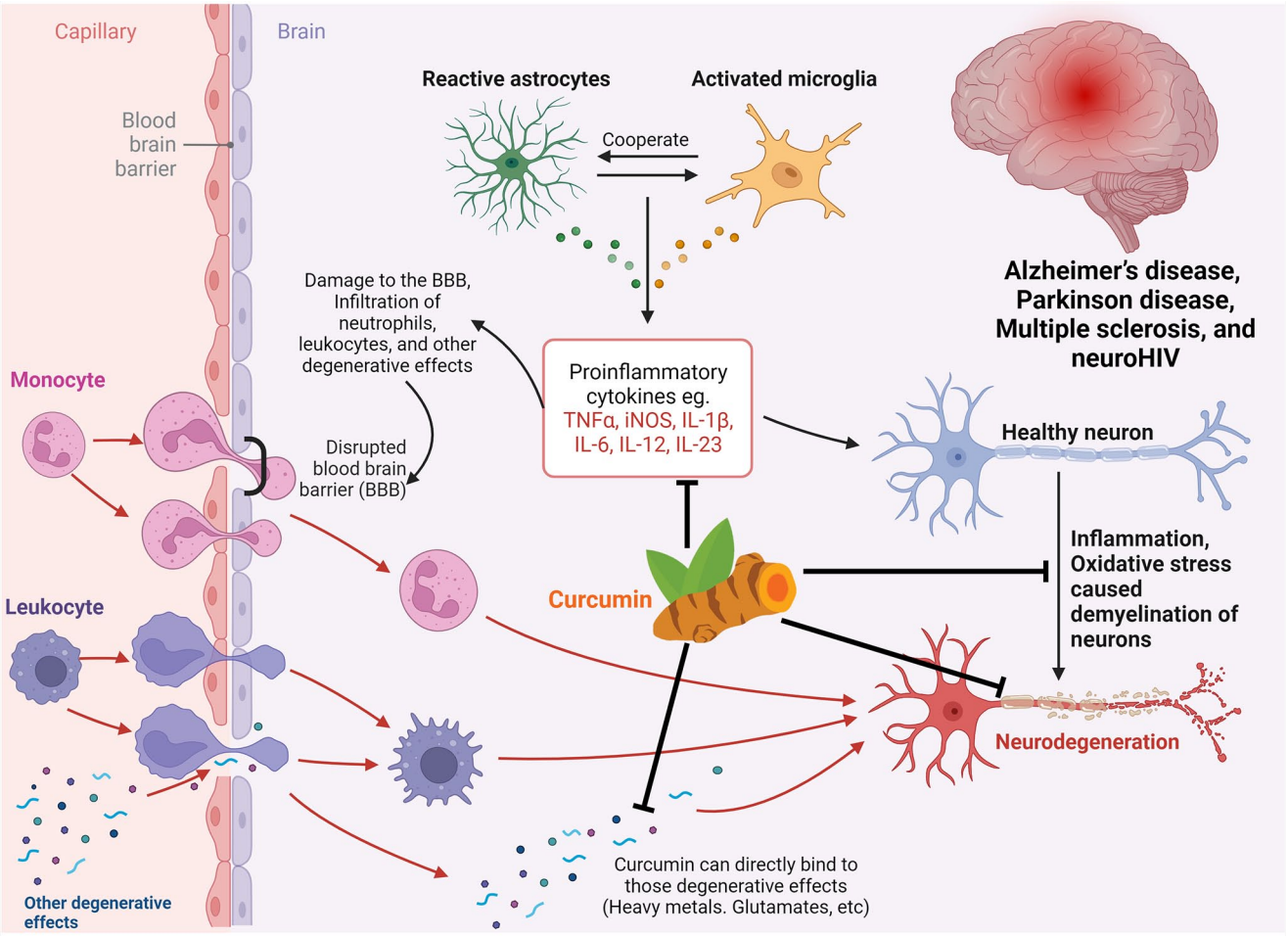

Figure 2. Diverse mechanisms of neuroprotection conferred by curcumin in CNS diseases.
This figure highlights curcumin's anti-inflammatory effects, antioxidant properties, reduction of degeneration, and support for neuronal regeneration to maintain neuronal health against CNS diseases.

implicated in the pathogenesis of the disorder.[38] Curcumin's ability to scavenge free radicals and upregulate antioxidant defenses, such as glutathione (GSH), may play a role in alleviating symptoms of schizophrenia.

Challenges in delivering therapeutic drugs to the central nervous system

Neurological disorders are the leading cause of disability-adjusted life-years globally and the second leading cause of death worldwide.[39] Among them, neurodegenerative diseases (NDDs) pose the most difficult management and are characterized by a gradual decline in neurological function and neuronal cell death. NDDs, including AD, PD, amyotrophic lateral sclerosis (ALS), Huntington's disease, and prion diseases, present a growing health concern worldwide.[39] These diseases share mechanisms involving abnormal accumulation of protein aggregates, which is responsible for selective neuronal damage and degeneration in specific regions of the central nervous system (CNS).[40] Factors such as neuroinflammation, aging, oxidative damage, and protein deposits disrupt neuronal communication, resulting in long-term cognitive and motor dysfunction.[41] Efforts to slow down or halt NDD progression through anti-inflammatory drugs, amyloid-targeting agents, and small molecules have limited success in alleviating the symptoms and improving the overall quality of life in patients with these pathologies. Most brain diseases currently lack effective treatment options, and future studies are required to find novel druggable targets and develop effective therapeutic strategies.[42] Current drugs for NDDs only slow down the progression of the disease but do not reverse its course.[43]

While systemic drug administration is convenient and has high feasibility for long-term brain disorder treatment, its therapeutic effect is limited by the suboptimal BBB permeability, which prevents most macromolecular and 98% of small molecule drugs from entering the brain to maintain CNS homeostasis.[44] Researchers have explored strategies to augment BBB permeability, such as changing osmotic pressure and using microbubble fixed-point ultrasound, to improve drug penetration across BBB.[45,46] However, these approaches may simultaneously increase the entry of toxic substances into the CNS.[47] Another innovative strategy is to enhance the penetration abilities of therapeutic substances while preserving BBB integrity. The BBB structure or permeability can change under pathological conditions, and exploiting these changes for designing a drug delivery system is a current focus of research.[48]

The effective treatment of brain diseases remains challenging due to complex underlying mechanisms and limited therapeutic options. While advances in targeted delivery systems offer hope for more efficient drug delivery to the brain, significant challenges persist. These challenges include suboptimal BBB permeability, fine-tuning secondary targeting within the brain, designing systems for specific disease microenvironments, and achieving optimal therapeutic effects through modulation of the disease microenvironment.

Overcoming limited CNS delivery: harnessing novel strategies for enhanced therapeutic efficacy

Nanomedicine-based drug delivery systems have emerged as a promising strategy to surmount the limitation with suboptimal BBB permeability.[47] These systems offer the potential to enhance the pharmacokinetic profile of therapeutic drugs, optimizing drug concentration within the brain and augmenting therapeutic outcomes.[49] Nanocarriers, such as liposomes, micelles, inorganic nanoparticles, hybrid nanoparticles, and exosomes, have garnered substantial interest in preclinical studies for their capacity to traverse the BBB and transport drugs to the CNS, thereby increasing drug availability at the target site.[47,49] This nanotechnology-driven approach holds the promise of reducing nonspecific accumulation while enabling targeted delivery, thereby enhancing therapeutic precision and efficacy.[49] Recent advancements in targeting technology have led to investigations into the secondary targeting effects of nanomedicines beyond BBB permeability, including the potential to target specific cells or even organelles at the subcellular level.[50] These multifaceted approaches offer the potential for controlled, on-demand drug release tailored to the specific disease microenvironment.

In the pursuit of more effective CNS disease treatments, adjuvant therapy using nutraceuticals has garnered attention, particularly due to its ability to enhance therapeutic responses.[51,52] Among these, curcumin has emerged as a promising candidate for CNS disorders due to its therapeutic activity against them as discussed in the previous section.[6,8] Importantly, curcumin's role as a modulator of the multidrug resistance protein P-glycoprotein (Pgp), a key efflux transporter at the BBB, offers a unique avenue for addressing CNS drug delivery limitations.[53] Pgp plays a pivotal role in extruding various compounds from the brain, thus limiting their accumulation and potential neurotoxicity. Curcumin's ability to suppress Pgp expression suggests its potential to overcome drug efflux barriers at the BBB. Thus, the utilization of curcumin not only enhances the BBB permeability of drugs for the treatment of CNS diseases, but it will also enhance target cellular concentration by inhibiting cellular Pgp expression. Furthermore, the utilization of novel nanocarrier-based delivery systems for curcumin holds promise for overcoming limited CNS delivery of curcumin and enhancing its therapeutic efficacy. Thus, the diverse activities of curcumin, coupled with its potential to modulate Pgp-mediated efflux, make it an ideal candidate for addressing CNS drug delivery challenges in the treatment of various CNS diseases.

Optimizing curcumin for neurological health: innovations to improve bioavailability and CNS delivery

Despite its remarkable efficacy and safety profile, curcumin has not yet been authorized as a drug due to its poor gut absorption, rapid metabolism, and systemic elimination, leading to its limited bioavailability. The hydrophobic nature of curcumin, characterized by a logP of approximately 3.2, renders it practically insoluble in water at >30 nM.[3] As a result, curcumin exhibits a short half-life, with studies reporting a mere 10-min half-life at a pH 7.4.[54] In mouse models, both intravenous and oral administration of curcumin resulted in rapid declines in its plasma concentrations within hours.[4] Even with oral administration of a significant dose (1.0 g/kg body weight), plasma levels peak at 0.22 μg/mL after one hour and fall below detectable levels by six hours.[4] Similar patterns were observed with intraperitoneal administration. These findings underscore the formidable challenge of sustaining therapeutic levels of curcumin in the bloodstream for a meaningful duration. The limitations in curcumin's bioavailability and pharmacokinetics have direct implications for achieving effective CNS delivery. Furthermore, due to its relatively large structure and hydrophobic nature, curcumin has suboptimal BBB permeability.[3] The intricate interplay between curcumin's limited pharmacokinetic profile and the complexities of CNS delivery necessitates innovative approaches to enhance its solubility, stability, and retention in the bloodstream, thereby enabling its efficient transport across the BBB. Addressing these limitations through innovative formulation approaches and targeted delivery strategies is crucial for harnessing curcumin's full therapeutic potential in the context of CNS-related pathologies.

In recent decades, extensive research efforts have focused on addressing the challenges associated with reduced curcumin bioavailability. Nanoparticles, micelles, and liposomes have emerged as promising solutions to enhance the aqueous dispersibility of hydrophobic drugs like curcumin, which inherently suffer from low solubility in their native forms.[55] By encapsulating curcumin within nanoformulations, researchers have harnessed several advantages. These nanocarriers, with sizes typically ranging from 1 to 100 nm offer a high surface area-to-volume ratio.[56] This unique feature contributes to elevating both the solubility and dissolution rate of drugs. Moreover, the reduced particle size extends the drug's presence in the systemic circulation, facilitating targeted drug delivery and enabling efficient transport across the BBB. Studies have demonstrated that nano-curcumin exhibits significantly higher bioavailability compared to conventional formulations, potentially up to ninefold higher *in vivo*.[57] The smaller aggregation size of nano-curcumin enables better tissue penetration. These nanocarriers, designed to migrate and home in various tissues, minimize the risk of invasiveness while offering enhanced therapeutic potential.

Researchers have utilized diverse nanocarriers (Figure 3) for delivering nano-curcumin, including chitosan, magnetic nanocomposites, polymer nanocomposites, and montmorillonite.[56] Importantly, curcumin's safety profile is well-established, with the US Food and Drug Administration (FDA)

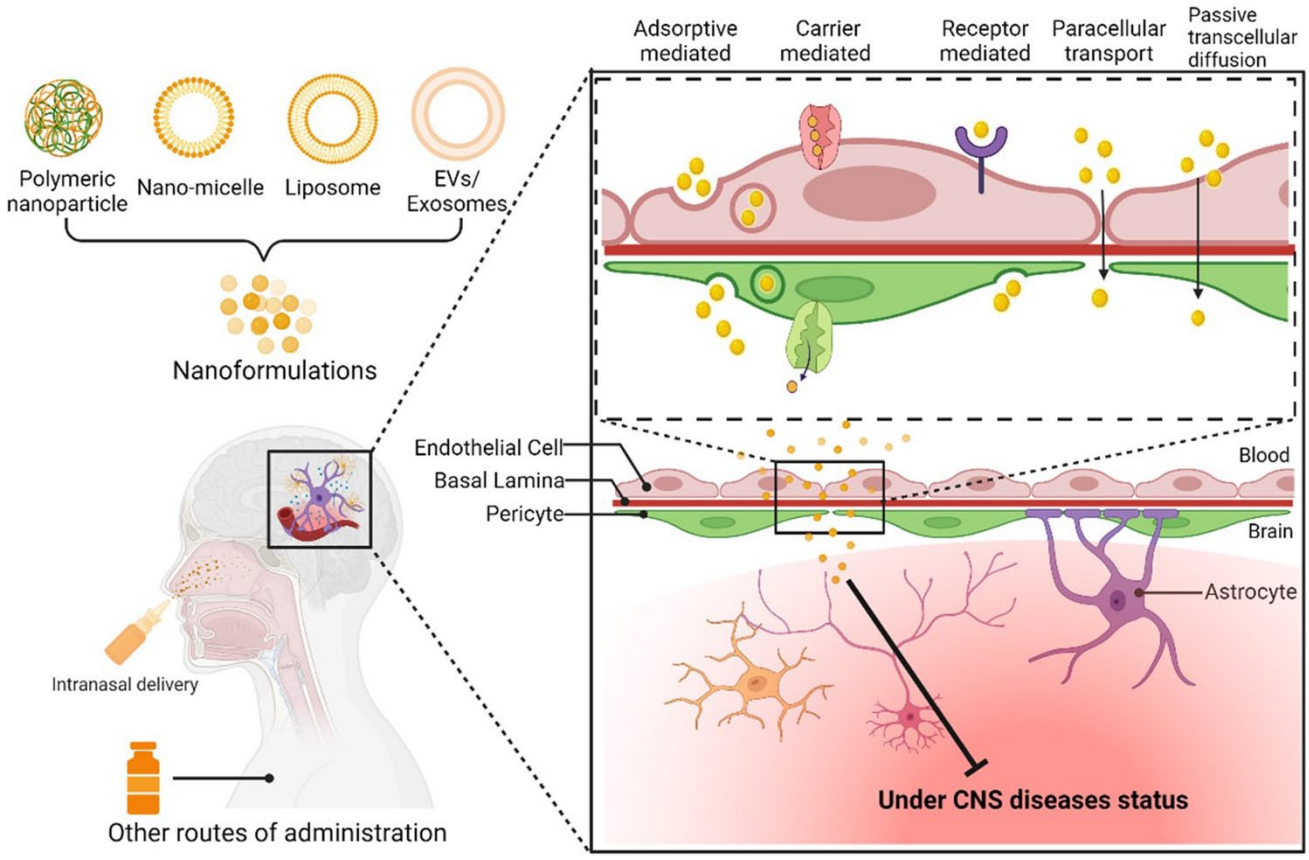

Figure 3. Approaches for targeted curcumin delivery in CNS disease therapy.
The figure show diverse strategies to enhance curcumin's delivery to the CNS, including polymeric nanoparticles, nanomicelle, liposomal encapsulation, and extracellular vesicles (EVs)/exosomes. The technology of conjugation with brain-targeting ligands has been used in this field to promote the target delivery of curcumin in the CNS.

classifying it as "generally recognized as safe."[58] Nano-curcumin's safety and tolerability have been highlighted in human studies, with reported adverse effects being generally mild and manageable. In the context of neurological diseases, nano-curcumin has emerged as a promising avenue for potential therapeutic intervention for AD, PD, HD, MS, epilepsy, and ALS. These investigations have shed light on the potential efficacy of nano-curcumin in clinical applications, offering renewed hope for addressing complex neurological challenges.

Therapeutic breakthroughs with nano-curcumin in preclinical studies

Nano-curcumin's diverse applications outside the CNS

Table 1 presents a comprehensive overview of therapeutic outcomes from diverse curcumin formulations that were tested in various animal models that target distinct disease conditions. These studies collectively emphasize the multifaceted potential of curcumin as a therapeutic agent across a broad spectrum of health concerns. Nanoformulations of curcumin have demonstrated significant potential in various cancer models. Curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles exhibited improved solubility, anticancer activity, and reduced hypoxic microenvironment in breast and lung cancer cells.[59] ZnO-PBA-Curcumin nanoparticles induced apoptotic cell death in breast cancer cells via oxidative stress and mitochondrial damage.[60] Silver nanoparticle-loaded cellulose hydrogel with curcumin demonstrated potent antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida auris* in chronic wounds.[61] Infectious diseases were tackled through innovative strategies like mannosylated chitosan nanoparticles targeting leishmaniasis, and PVA/Chi/ZnO-Cur patches aiding wound healing.[62,63] Both studies underscore curcumin's potential in targeted drug delivery and antimicrobial activity.

Nano-curcumin's potential for CNS applications

Several studies highlight the versatility and potential of nano-curcumin formulations in addressing various aspects of neurological disorders, ranging from anti-inflammatory effects and antioxidative properties to enhanced drug delivery and targeted action within the CNS (Table 2). In the context of subarachnoid hemorrhage-induced early brain injury, studies have explored the potential of PLGA nanoparticles loaded with curcumin. These nanoparticles have demonstrated a significant reduction in the expression of NF-κB (p65) in a rat model of double hemorrhage, indicating their ability to mitigate neuroinflammation, a common feature in brain injury scenarios.[64] Moreover, another study using the same PLGA nanoparticle formulation observed improved neurological

Table 1. Applications of nano-curcumin in preclinical studies: non-CNS.

CUR formulation	Animal – study model	Disease condition	Major findings	Ref
PLGA-NP	C57BL/6 mice – cerebral malaria	Cerebral malaria	↑ therapeutic index	Dende *et al.*[99]
PLGA-NP	Swiss male albino mice malaria model	Malaria	↑ antiplasmodial activity and safety	Busari *et al.*[100]
PLGA-NPs in hydrogel	C57/BL6 mice – Psoriatic skin preparation	Psoriasis	↑ anti-psoriasis activity	Sun *et al.*[101]
Mannosylated chitosan NPs	Rat model of leishmaniasis	Leishmaniasis	↑ targeting to macrophages	Chaubey *et al.*[62]
PVP nano-CUR	BALB/c mice	Oral candidiasis	↑ antifungal effect ↓ candida colonies	Anwar *et al.*[102]
Solid lipid NPs	BALB/c mice Rat model of asthma	Asthma	↑ PK parameters: ↓ airway hyperresponsiveness, inflammation, and T-helper-2-type cytokines expression	Wang *et al.*[103]
Polyphosphazene nano-CUR	Mice with acute lung injury	Acute lung injury	↓ ALI inflammation, cytokines, ROS	Su *et al.*[104]
Nano-CUR	Rats exposed to inhaled paraquat	Acute lung injury	↑ lung function, antioxidant and anti-inflammatory activity	Ghasemi *et al.*[105]
Gal-POPC/Cur and Gal-DOTAP/siPTTG1 liposomes	Nude mice with human Huh-7 xenografts	Hepatocellular carcinoma	↑ tumor inhibition, Caspase-3 ↓ Bcl-2 gene expression, HCC treatment	Kim *et al.*[106]
Nano-liposomes	Zebrafish	Cancer	↑ CUR and TET solubility, efficacy, and safety. Strong inhibitory effect on cancer cells.	Song *et al.*[107]
PLGA NPs	Orthotopic mouse model of cervical cancer	Cervical cancer	↓ cell growth ↑ apoptosis and cell cycle arrest	Zaman *et al.*[108]
PLGA-DSPE-PEG hybrid NPs	RG2 tumor model (rats)	Glioblastoma	↓ tumor volume	Orunoglu[69]
PLGA NPs	MDA-MB-231 and A549 cell lines	Breast and lung cancer	10-fold ↑ in solubility threefold ↑ in anticancer activity	Khan *et al.*[59]
HSA-NPs	Breast cancer cell lines	Chemotherapy-resistant cancer	↓ CUR solubility, stability, and anticancer effects	Matloubi and Hassan[109]
ZnO-PBA-NPs	Ehrlich ascites carcinoma tumor-bearing mice	Breast cancer	↑ Targeted delivery ↓ tumor growth without systemic toxicity	Kundu[60]
Ag NPs	MM-138, FM-55, and MCF-7 cell lines	Melanoma and breast cancer	↑ anticancer activities	Ali *et al.*[110]
Chitosan/Hyaluronic Acid NPs	Glioblastoma cell culture	Glioblastoma	↑ Efficient drug delivery, controlled release, cell killing, NGF-driven nerve growth.	Sabourian *et al.*[111]
PVA/Chi/ZnO patch	Wistar albino rats model of wound	Wound healing	↑ antimicrobial activity, sustained drug release ↑ biocompatibility	Niranjan *et al.*[63]
C-alginate – nanomicelle	Rats	Colorectal wound healing	↑ GI wound healing through collagen induction ↓ bacterial activity	Zhang and Zhang[112]
Gelatin/CUR nanofiber membrane	BALB/c mice	Cartilage formation	promote thicker, homogenized cartilage.	Kang *et al.*[113]
CUR/gelatin – nanofibrous mats	Rat skin wound model	Acute wounds	↑ wound healing, persistent inhibition of inflammatory response ↑ regenerative process.	Dai *et al.*[114]
PVA/Chi/CUR patch	Wistar rats	Epidermal wounds	↑ cell proliferation, antibacterial activity against major bacterial strains ↑ wound healing	Niranjan *et al.*[73]
CUR/TiO_2—chitosan scaffolds	MRSA-infected wound healing	Infected wounds	↑ antibacterial activity against Gram +ve and Gram –ve bacteria ↑ wound healing	Marulasiddeshwara *et al.*[115]
Cellulose nano crystals loaded chitosan films with CUR/Ag NPs	Rabbit model of Skin irritation, Rat model of Wound.	Skin irritation, Wound healing	zero skin irritation ↑ wound healing	Bajpai *et al.*[74]
Ag NPs-loaded bacterial cellulose hydrogel	Antimicrobial test against *P. aeruginosa*, *S. aureus*, and *C. auris*	Chronic wounds	↑ cytocompatibility and antimicrobial activity against *P. aeruginosa*, *S. aureus*, and *C. auris*	Gupta *et al.*[61]

(Continued)

Table 1. (Continued)

CUR formulation	Animal – study model	Disease condition	Major findings	Ref
CUR-silica NPs	Antimicrobial test against *P. aeruginosa*, *S. aureus*	Multidrug resistant bacterial infections, Chronic wound infection	↑ antimicrobial activity against *P. aeruginosa*, *S. aureus* in planktonic and biofilm forms No cytotoxicity	Mirzahosseinipour *et al.*[116]
Nanostructured lipid carriers	Streptozotocin induced diabetic rat model	Chronic wound	↑ wound closure ↑ antioxidant enzyme activity	Mirzahosseinipour *et al.*[117]
CUR-silica NPs	BALB/c mice burn model	Burn wounds, infection	⊥ in vitro growth of MRSA and *P. aeruginosa* ↑ wound healing	Krausz *et al.*[118]
HAp with curcuminoids and 5-fluorouracil nanocomposite	SKOV-3 and HepG2 model cell lines	Cytotoxicity	↑ intake of biologically active compounds in HAp.	Nguyen *et al.*[119]
Nano-CUR	Rat (Wistar)	Varicocele	↑ sperm motility ↓ abnormal morphology	Sadraei *et al.*[120]
CUR and Resveratrol Nanoemulsion	Rat (Albino)	Protein-deficient diet (PDD)-induced hyperammonemia	↓ ammonia levels ↑ liver and brain function	Nasr *et al.*[121]
PLGA-NPs	RIN-m5F cells; Sprague Dawley Rats	Type 1 diabetes mellitus	↑ oral bioavailability ↓ glucose levels ↓ inflammation, and apoptosis in pancreatic islets ↑ beta cell function	Ganugula *et al.*[122]
CUR-loaded pluronic nanomicelles	Rat model of streptozotocin-induced diabetes	Diabetes	↑ solubility and bioavailability, optimal redox balance, alleviation of streptozotocin-induced β-cell damage.	El-Far *et al.*[123]

CNS: central nervous system; CUR: curcumin; PLGA: poly(lactic-co-glycolic acid); NP: nano particle; ↑: increased/improved; ↓: decreased/reduced; PVP: polyvinylpyrrolidone; ROS: reactive oxygen species; Ag: silver; ⊥: inhibition; PK: pharmacokinetic; ALI: acute lung injury; HCC: hepatocellular carcinoma; TET: tetrandrine; DSPE- PEG : 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol); RG-2: rat glioma 2; MDA-MB-231: human breast cancer cell line; HAS: human serum albumin; PBA: phenyl boronic acid; NGF: nerve growth factor; GI: gastrointestinal; MRSA: methicillin-resistant staphylococcus aureus; HAp: hydroxyapatite; SKOV-3: human ovarian cancer cell line.

function in a rat model of subarachnoid hemorrhage-induced early brain injury.[65] In the realm of AD, novel nanosystems have emerged as potential therapeutic interventions. T807/TPP-RBC-NPs loaded with curcumin have been investigated for their antioxidative effects in AD.[66] By specifically targeting neuronal mitochondria, these nanosystems hold promise in alleviating AD symptoms and addressing the underlying oxidative stress. Furthermore, a self-nanomicellizing solid dispersion formulation of curcumin demonstrated cognitive function improvement and enhanced cellular uptake in a transgenic AD mouse model.[67] Nano-curcumin formulations have also been explored in the context of PD. Curcumin-loaded polysorbate 80-modified cerasome nanoparticles have exhibited enhanced delivery to brain cell nuclei via BBB opening and ultrasound-mediated microbubble destruction.[68] This approach has shown improvement in motor behaviors and dopamine levels in a mouse model of PD. In highly aggressive brain cancer glioblastoma, various nano-curcumin formulations have revealed potential therapeutic effects. Curcumin-loaded PLGA-1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) hybrid nanoparticles reduce tumor volume when administered intratumorally in an RG2 tumor model.[69] These nanoparticles present a promising strategy for targeting and treating glioblastoma. In addition, PLGA nanoparticles loaded with Aβ generation inhibitor S1 (PQVGHL peptide) and curcumin improved spatial memory, reduced amyloid-beta, and enhanced antioxidant activity in a transgenic AD mouse model.[70]

Nano-curcumin in clinical trials: a promising adjunctive approach

Table 3 compiles various clinical trials investigating the effects of different curcumin formulations on various health conditions. Curcumin has garnered attention for its potential therapeutic properties, and these clinical trials aim to shed light on its effectiveness in improving various health outcomes. One intriguing study focuses on the use of nano-curcumin in COVID-19 patients. In a double-blind, placebo-controlled trial involving 60 hospitalized COVID-19 patients, nano-curcumin supplementation led to significant reductions in key inflammatory markers, including C-reactive protein (CRP), IL-6, and IL-1β.[71] Notably, nano-curcumin treatment demonstrated the potential to modulate immune response, which could be crucial in managing the hyperinflammatory state associated with severe COVID-19 infection. In patients with metabolic syndrome, a condition marked by a cluster of risk factors for cardiovascular disease, nanomicelle curcumin supplementation proved beneficial.[72] This study, involving 50 patients with metabolic syndrome, highlighted the role of curcumin in improving serum triglyceride levels. This finding is significant as elevated triglyceride levels are the hallmark of metabolic syndrome and it is associated with an increased risk of atherosclerotic cardiovascular disease. The clinical trial involving nanomicelle curcumin therapy in metabolic syndrome patients suggests an improvement in serum triglyceride profile, indicating its potential as a complementary therapeutic option with

Table 2. Applications of nano-curcumin in preclinical studies: CNS

CUR formulation	Animal-study model	Disease condition	Major findings	Ref
PLGA-NP	SD rats – SAH-induced EBI	Brain injury	↓ bio-expression of NF-κB (p65)	Chang *et al.*[64]
PLGA-NP	SD rats – SAH-induced EBI	Brain injury	↑ neurological function	Zhang *et al.*[65]
T807/TPP-RBC-NPs	Rat primary brain microvascular endothelial cells and primary astrocytes; ICR mice and SD rats	AD	↓ AD symptoms via antioxidative effects.	Gao *et al.*[66]
self-nanomicellizing solid dispersion	Transgenic AD (APPSwe/PS1deE9) mice	AD	↑ cognitive functions, ↑ cellular uptake exhibits safety	Zhang *et al.*[67]
CS-BSA NPs	Brain microvascular endothelial cell line, hCMEC/D3; RAW 264.7 cells	AD	↑ BBB penetration ↑ microglia activation ↑ Aβ peptide phagocytosis ⊥ inflammatory signaling	Yang *et al.*[124]
Polymeric NPs (NanoCurc™)	Athymic mice	AD	↑ CUR bioavailability, protects against ROS-mediated insults ↓ H_2O_2 levels ↓ caspase activities ↑ GSH concentrations	Ray *et al.*[125]
Lipid-core nanocapsules	Aged female mice	AD	↑ neuroprotection against Aβ1-42-induced cognitive deficit ↑ inflammatory cytokine	Giacomeli *et al.*[126]
AmyloLipid nanovesicles	SD rats	Brain delivery	↑ brain targeting	Sintov[127]
PLGA-NPs	Transgenic AD mice	AD	↑ spatial memory ↓ Aβ, ROS, TNF-α, IL-6 ↑ SOD and synapse numbers	Huang *et al.*[70]
PLGA-NPs	Transgenic AD mice	AD	↓ Aβ load ↑ memory deficiency	Huo *et al.*[128]
Polysorbate 80-modified cerasome NPs	MPTP-induced PD mice	PD	↑ delivery to brain nuclei via BBB opening and UTMD ↑ motor behaviors, DA levels, and TH expression	Zhang *et al.*[68]
Glyceryl monooleate NPs	PD mouse model	PD	↑ inhibition of αS protein aggregation ↓ rotenone-induced toxicity, oxidative stress, and apoptosis	Kundu *et al.*[129]
Lactoferrin NPs	SK-N-SH cell line	PD	↑ intracellular drug uptake sustained retention ↑ neuroprotection	Bollimpelli *et al.*[130]

CNS: central nervous system; CUR: curcumin; PLGA: poly(lactic-co-glycolic acid); NP: nano particle; SD: rat – Sprague Dawley Rat; ↓: decreased/reduced; ↑: increased/improved; AD: Alzheimer's disease: ⊥: inhibition; ROS: reactive oxygen species; BBB: blood–brain barrier; GSH: glutathione; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; SOD: superoxide dismutase; PD: Parkinson's disease; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; EBI: early brain injury; SAH: subarachnoid hemorrhage; T807: 7-(6-nitropyridin-3-yl)–5H-pyrido[4,3-b]indole; TPP: triphenylphosphine; RBC: Red blood cell; CS-BSA: chitosan-bovine serum albumin; RAW 264.7 cells- macrophage cell line; UTMD: ultrasound-targeted microbubble destruction; DA: dopamine; TH: tyrosine hydroxylase; SK-N-SH: human neuroblastoma cell line.

other lipid-lowering drugs.[72] Wound healing and dermatological applications were addressed by various formulations such as PVA/Chi/Cur patches and cellulose nano crystals loaded with chitosan films.[73,74] These studies demonstrated enhanced wound healing properties, antimicrobial activity, and potential for skin regeneration.

Curcumin's potential also extends to addressing mental health concerns. A study involving 80 patients with diabetes and depression showed that nano-curcumin supplementation effectively reduced depression and anxiety scores in patients with diabetic polyneuropathy.[75] This suggests that curcumin's anti-inflammatory and neuroprotective properties may contribute to alleviating mental health symptoms in diabetic individuals. In the realm of chronic conditions, the trials explore curcumin's impact on migraines and studies investigated a combination of omega-3 fatty acids and nano-curcumin in 80 episodic migraine patients. The combination therapy not only reduced the frequency of attack but also downregulated the expression of proinflammatory genes, indicating curcumin's anti-migraine effects.[76] Liver health is another area of interest, with studies focusing on non-alcoholic fatty liver disease (NAFLD). In a randomized, double-blind, placebo-controlled trial involving overweight/obese patients with NAFLD, nano-curcumin supplementation significantly improved glucose indices, including fasting blood sugar (FBS) and glycated hemoglobin (HbA1c).[77] These findings suggest a potential role for curcumin in managing metabolic parameters associated with NAFLD. The trials collectively demonstrate the promising potential of nano-curcumin as an adjunct therapy across various health conditions. Its ability to modulate inflammatory responses, improve metabolic markers, and alleviate symptoms in conditions like migraines and fatty liver disease indicates a versatile therapeutic role. From COVID-19 to metabolic syndrome, migraines, and liver diseases, nanoformulated curcumin demonstrates promising effects on inflammatory markers, metabolic profiles, and symptom relief. As research in this field advances, curcumin's role as a complementary

Table 3. Summary of clinical trials exploring nano-curcumin.

CUR formulation	Disease condition	Major findings	Ref
Nano-CUR	COVID-19	↓ IL-6 and IL-1β mRNA expression and cytokine secretion	Valizadeh *et al.*[71]
Nanomicelle curcumin	Metabolic Syndrome (MetS)	↑ serum TG levels	Bateni *et al.*[72]
Nano-CUR	Depression in patients with diabetic polyneuropathy	↓ depression and anxiety scores	Asadi *et al.*[75]
CUR Nanomicelles	COVID-19	↑ immune response	Hassaniazad *et al.*[131]
Nano-CUR supplementation	Sepsis	↓ WBCs, neutrophils, platelets, ESR, and IL-8 ↑ total lymphocyte count	Naeini *et al.*[132]
Nano-CUR supplementation	Mild-to-moderate hospitalized COVID-19 patients	↓ mRNA expression of IFN-γ and TNF-α differences in IFN-γ, IL-1β, and IL-6 expression and serum levels of IL-1β	Asadirad *et al.*[133]
Nano-CUR supplementation	Obese and overweight patients with migraine	↓ MCP-1 serum levels ↓ in headache attack frequencies, severity, and duration	Sedighiyan *et al.*[134]
Nano-CUR supplementation	Critically ill patients with sepsis	↑ inflammatory markers, endothelial function, oxidative stress ↓ SOFA score and ventilation duration.	Karimi *et al.*[135]
Nano-CUR	Radiation-induced skin reactions in breast cancer patients	↑ radiation-induced skin toxicity ↓ patient-reported pain.	Talakesh *et al.*[136]
Nano-CUR	Oral lichen planus (OLP)	No significant difference	Kia *et al.*[137]
Nano-CUR and CoQ10	Migraine	Synergistic effect on clinical features of migraine.	Parohan *et al.* [138]
Nano-CUR supplementation	Migraine	↑ IL-4 gene expression and serum levels	Djalali *et al.*[139]
Nano-CUR supplementation	Migraine	↑ adiponectin ↓ headache frequency/severity/ duration in migraines	Sedighiyan *et al.*[140]
Nano-CUR	Migraine	↓ IL-17 levels/expression	Djalali *et al.*[141]
Nano-CUR	Diabetic Sensorimotor Polyneuropathy (DSPN) in Type 2 diabetes mellitus	↓ HbA1c, FBS, total neuropathy score, reflex score, and temperature	Asadi *et al.*[142]
Nano-CUR	Hemodialysis	↓ inflammation, hs-CRP levels, and adhesion molecules (ICAM-1, VCAM-1)	Vafadar *et al.*[143]
Nano-CUR	Diabetes on hemodialysis	↓ fasting glucose, insulin levels, lipid levels, hs-CRP, and oxidative stress markers ↑ TAC and nitrite levels, ↑Improved metabolic profile.	Shafabakhsh *et al.*[144]
Nano-CUR	Type 2 diabetes with mild to moderate coronary artery disease	↓ inflammation (hs-CRP) and lipid metabolism disruption (LipoPr (a))	Dastani *et al.*[145]
ω-3 fatty acids, Nano-CUR	Episodic migraine	↓ serum levels and gene expression of VCAM Combination showed pronounced effect	Abdolahi *et al.*[76]
ω-3 fatty acids and nano-CUR	Migraine	↓ attack frequency synergistically and serum IL-1β levels	Honarvar *et al.*[146]
CUR Nanomicelles	Coronary heart disease	↑lipid profile, oxidative stress factors and inflammatory markers	Helli *et al.*[147]
ω-3 Fatty Acids, Nano-CUR	Migraine	↓ COX-2/iNOS gene expression ↓serum levels ↓ frequency, severity, and duration of headaches	Abdolahi *et al.*[148]
ω-3 Fatty Acids, Nano-CUR	Migraine	↓ IL-6 gene expression ↓ serum IL-6 and hs-CRP levels	Abdolahi *et al.*[149]
ω-3 Fatty Acids, Nano-CUR	Migraine	↓ TNF-α gene expression ↓ serum TNF-α levels	Abdolahi *et al.*[150]
ω-3 Fatty Acids, Nano-CUR	Migraine	↓ ICAM-1 serum levels and attack frequency	Soveyd *et al.* [151]
Theracurmin (colloidal CUR NPs)	Oral bioavailability study	27-fold ↑ bioavailability	Sasaki *et al.*[152]
CUR Mouthwash (0.1% w/v) and CUR-Nanocapsule (SinaCurcumin®40)	Radiotherapy-induced oral mucositis	↓ severity and pain of radiation-induced oral mucositis with higher ulcer-free rates than placebo.	Ramezani *et al.*[153]
1% and 2% CUR Nanomicelle Gel	Recurrent Aphthous Stomatitis (RAS)	1% Curcumin nanomicelle gel:↑ efficacy in pain reduction 2% Curcumin gel: ↑ reduction in lesion size and overall healing	Bakhshi *et al.*[154]

(Continued)

Table 3. (Continued)

CUR formulation	Disease condition	Major findings	Ref
CUR-Containing Nanomicelles	COVID-19	↓ IFN-γ and IL-17 levels ↑ IL-4 and TGF-β levels, and accelerated recovery in COVID-19 patients	Hassaniazad *et al.*[155]
Nano-CUR capsule	Knee osteoarthritis	↑ overall symptoms, pain, stiffness, and physical activity	Hashemzadeh *et al.*[156]
Nano-CUR	Cystic fibrosis	↓ hs-CRP and fecal calprotectin levels ↑ IL-10 levels ↑ improved quality of life ↓ Pseudomonas colonies ↑ weight	Talebi *et al.*[157]
Nano-CUR supplementation	Mild and moderate acute pancreatitis	↓ GI ward length of stay ↓ need for analgesics ↑appetite score	Chegini *et al.*[158]
Nano-micellar CUR	Benign prostatic hyperplasia	↑ International Prostate Symptoms Score	Karami *et al.*[159]
Nano-CUR oral soft gels	COVID-19 (moderate-severe)	↑chest CT scores, oxygen saturation levels, and hospitalization duration	Sadeghizadeh *et al.*[160]
Nano-CUR capsule	Oral leukoplakia	↓ lesion size, number of lesions, and disease staging ↑ serum SOD levels.	Deb *et al.*[161]
Nano-CUR supplementation	Metabolic syndrome	↑ IL-10 and BDNF levels ↓ in IL-6 levels.	Osali[162]
Nano-CUR supplementation	Non-alcoholic fatty liver disease	↑ glucose indices, including fasting blood sugar and HbA1c.	Jazayeri-Tehrani *et al.*[77]

CNS: central nervous system; CUR: curcumin; PLGA: poly(lactic-co-glycolic acid); NP: nano particle; ↓: decreased/reduced; IL-6: interleukin-6; ↑: increased/improved; WBC: white blood cells; FBS: including fasting blood sugar; CRP: C-reactive protein; SOD: superoxide dismutase; TG: triglyceride; ESR: erythrocyte sedimentation rate; MCP-1: monocyte chemoattractant protein-1; SOFA: sequential organ failure assessment; ICAM-1: intercellular adhesion molecule 1; VCAM1: vascular cell adhesion molecule 1; TAC: total antioxidant capacity; CT: computed tomography; BDNF: brain-derived neurotrophic factor; GI: Gastrointestinal.

therapy may become more defined, offering a natural and accessible option for improving various treatment outcomes.

Extracellular vesicles-mediated curcumin delivery: advancing treatments

The use of extracellular vesicles (EVs), natural nanoparticles that are secreted from our cells into biofluids, as nanocarriers in non-neuronal conditions is also being investigated. EVs have been found to improve the delivery of therapeutic intervention, as well as, they serve as biomarkers in liver diseases. In a recent review, Wang *et al.*[78] found that EVs can serve as cautionary biomarkers, diagnostic and prognostic tools, and a possible mode for treating liver failure by encouraging hepatocyte regeneration and proliferation through various pathways. However, in the case of sepsis, Homma *et al.*[79] noted that in a sheep model of sepsis, EVs derived from bone marrow mesenchymal stem cells were not capable of lessening the "severity of multiorgan dysfunction" associated with sepsis. Osteoporosis is another condition in which the use of EVs as treatment being considered. In a recent review, He *et al.*[80] reported that, in mouse models, EVs derived from bone marrow can increase bone mass, enhance the microarchitecture of the bone matrix, and promote bone strength.

EVs loaded with curcumin are also being investigated in non-neuronal conditions, such as rheumatoid arthritis and hyperhomocysteinemia. In the case of rheumatoid arthritis, He *et al.*[81] found that loading curcumin onto EVs/exosomes helped stabilize curcumin. The curcumin-loaded exosomes (Curc-Exos) were found to aid in decreasing the production of anti-apoptotic proteins, such as IAP1 and IAP2. Curc-Exos was also noted to have anti-inflammatory properties, as it decreased inflammatory mediators, such as IL-6, TNF-α, MMP1, and PGE2. These findings indicated that Curc-Exos should be considered further as a treatment option for rheumatoid arthritis. Regarding hyperhomocysteinemia, Kalani *et al.*[82] used hyperhomocysteinemia in mouse models as a representation of a disrupted BBB. The results showed that cells treated with Curc-Exos had decreased oxidative stress and endothelial cell layer permeability.

EVs/exosomes are of particular interest to deliver curcumin for the treatment of CNS and other neuronal conditions, especially because EVs can cross the BBB.[83] In the case of PD, Upadhya and Shetty[84] showed that EVs can release pathologic miRNAs and/or proteins, which can cause the progression of the disease state. Liu *et al.*[85] investigated the use of curcumin as a part of the rabies virus glycoprotein (RVG) peptide–modified exosome (EXO) curcumin/phenylboronic acid-poly(2-(dimethylamino)ethyl acrylate) nanoparticle/small interfering RNA targeting SNCA (REXO-C/ANP/S). This delivery system can cross the BBB and deliver the drug to the neurons involved in the pathologic process. The study found that REXO-C/ANP/S serves as a "nano scavenger" to aid in diminishing alpha-synuclein aggregates. The study also found reduced motor deficits in the mouse models. A recent study by Mohabat *et al.*[86] investigated the use of curcumin-loaded exosomes derived from human endometrial stem cells (hEnSCs EXOs-Cur) and reported that hEnSCs EXOs-Cur can penetrate the BBB, reduce alpha-synuclein aggregates, and lessen neural cell death. These studies suggest that the anti-inflammatory and antioxidant effects of curcumin can attenuate the pathologic processes associated with PD.

In the AD model, Wang *et al*.[87] noted that curcumin-loaded exosomes effectively crossed the BBB via transcytosis and increased its bioavailability in the target tissues. The curcumin-loaded exosomes reduced neuronal death and Tau phosphorylation by activating the AKT/GSK-3β pathway. Similarly, Fernandes *et al*.[88] proposed a new concept for the delivery of curcumin in AD. Using a zebrafish model, they investigated the use of an exosome-like liposome to deliver curcumin to the target tissue. The study found that this novel delivery system shared the benefits of exosomes in crossing the BBB.

In the case of ischemic injuries, He *et al*.[89] used exosomes derived from macrophages and loaded with curcumin, which decreased the ROS generation in the regions with ischemic damage. The decrease in the accumulation of ROS aids in reducing damage to the BBB and neuronal apoptosis. Furthermore, Tian *et al*.[90] found that curcumin-loaded exosomes also initiated a suppression of the inflammatory processes in the ischemic brain.

Taken together, these studies show that EV-based curcumin formulations have therapeutic potential for CNS diseases such as AD, PD, ischemic injuries, and rheumatoid arthritis. The therapeutic outcomes of EV-curcumin formulations largely occur by overcoming curcumin limitations of low bioavailability and suboptimal BBB permeability.

Exploring the potential of intranasal curcumin delivery for efficient treatment of neurological disorders

The emergence of intranasal (IN) administration has introduced a paradigm shift in targeted drug delivery to the CNS, presenting a novel and non-invasive approach for effective therapeutic intervention. This approach capitalizes on the distinctive histological attributes of the nasal cavity, facilitating direct access of approx. 50% of the therapeutic agents to the brain.[91] A key advantage of IN delivery lies in its ability to significantly circumvent liver metabolism, systemic circulation, and BBB permeability, leading to high bioavailability in the CNS.[91,92] Pharmacokinetic investigations have revealed that despite potential bioavailability reductions attributed to the nasal epithelium, drug concentrations within various CNS regions post-IN administration can exhibit up to a 10-fold increment compared to systemic injection.[93,94] Strikingly, dose escalation of IN-administered drugs elicits proportionate enhancements in drug concentration across diverse CNS territories. The non-invasive nature of IN administration, complemented by user-friendly delivery devices such as sprays or atomizers, not only fosters patient acceptance but also accommodates frequent dosing. Clinical trials corroborate the feasibility of repeated IN delivery within brief intervals, even daily, highlighting the adaptability of this approach for versatile treatment regimens.[95,96]

Leveraging the potential of IN drug delivery, contemporary research has harnessed its capabilities to surmount therapeutic challenges associated with curcumin. IN delivery of curcumin emerges as a promising strategy to enhance its brain bioavailability. Multiple studies have explored the efficacy of IN curcumin delivery employing diverse formulations and carriers, striving to maximize its therapeutic potential for neurological disorders. Strategies such as mucoadhesive microemulsion systems (MMESs) have demonstrated heightened brain uptake relative to intravenous administration, with implications for targeted brain delivery.[97] Microemulsions (MEs) incorporating docosahexaenoic acid (DHA)-rich oil have showcased superior brain penetration, potentially mediated by DHA-induced BBB transport. Furthermore, the development of thermosensitive hydrogels and innovative nanoparticles exhibits promise in augmenting curcumin's brain delivery, reinforcing the potential of IN administration as a transformative avenue for curcumin's therapeutic application in CNS disorders.[98] These strategies circumvent the constraints associated with curcumin's physicochemical attributes, paving the way for enhanced treatments of neurological conditions.

Conclusions

The intricate nature of CNS diseases, often accompanied by a spectrum of comorbidities, requires a comprehensive therapeutic approach. Curcumin's multifaceted actions as an antioxidant, anti-inflammatory, and immunomodulatory make it an appealing adjuvant therapy by targeting various inflammatory signaling pathways implicated in the pathogenesis of CNS disorders. Innovative strategies, such as combining curcumin with existing medications, show promise in enhancing therapeutic outcomes in CNS diseases. Collaborative efforts to optimize dosing regimens and identify optimal drug combinations and effective delivery systems can reshape the treatment landscape for these conditions. To this end, nanoformulations, especially using natural nanoparticle EVs for curcumin delivery, hold great potential for improving curcumin's bioavailability and facilitating its passage through the BBB. Furthermore, IN delivery methods of curcumin nanoformulations offer opportunities to enhance direct brain targeting while minimizing the peripheral side effects in the other parts of the body. Thus, the combined efforts in unraveling curcumin's therapeutic potential and harnessing innovative delivery systems including EVs as nanocarriers and IN method hold the promise of improving the outcomes and management of CNS diseases.

AUTHORS' CONTRIBUTIONS

SG contributed to the initial drafting of the manuscript, review of literature, preparation of tables, and overall editing. LZ contributed to the initial drafting of the manuscript and prepared the figure. SS contributed to the initial drafting of the manuscript. BS and UPS provided critical overall manuscript editing and revision. SK contributed to conceptualization, funding, overall supervision, and supported review development and overall editing.

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