Curcumin-Based Nanomedicines and Neurodegenerative Diseases

Subjects: Integrative & Complementary Medicine

Contributor: Lucas Fornari Laurindo , Gabriel Magno de Carvalho , Bárbara de Oliveira Zanuso , Maria Eduardo Figueira , Rosa Direito , Ricardo de Alvares Goulart , Daiene Santos Buglio , Sandra Maria Barbalho

Curcumin (CUR) is a polyphenol extracted from the rhizome of *Curcuma longa* that possesses potent anti-inflammatory and antioxidant potential. Neurodegenerative diseases (ND) are brain disorders characterized mainly by progressive loss of selectivity in vulnerable populations of neurons, which contrasts with metabolic or toxic brain disorders due to the select static neuronal loss that occurs in these. Theoretically, ND can be classified according to primary clinical signals such as dementia, motor neuron disease or parkinsonism, anatomic distribution of neurodegeneration such as frontotemporal degenerations, extrapyramidal disorders or spinocerebellar degenerations or, principally, ND can be classified as their molecular abnormality.

curcumin delivery systems nanomedicines curcumin-based nanomedicines

1. Alzheimer’s Disease

Alzheimer’s disease (AD) is characterized by neuritic plaques and fibrillar tangles resulting from the accumulation of amyloid beta peptide (Aβ) and massive neuronal losses. It is considered a disease of multifactorial origin due to the action of several risk factors such as advanced age, genetic factors, head trauma, vascular diseases, infections, and other factors numerous environmental factors [1][2][3]. Pathologically, the production of soluble Aβ oligomers and the activation of inflammation are the two most essential steps in AD occurrence. While the oligomers are responsible for the neuronal dysfunction proper of the AD clinical features due to misfolding protein disorders, the evidenced neurodegeneration develops neuronal inflammation, and this process must be assessed in favor of a more direct role of glial cells activation during the synaptic functions alterations [4][5].

Tayor et al. [6] studied the effects of different nanoliposomes associated with CUR and lipid ligands on the aggregation of amyloid-β 1-42 (Aβ 1-42) peptide in vitro. The nanoliposome formulations involved nanosized liposomes composed of CUR, CUR derivative, or lipid ligands such as phosphatidic acid (PA), cardiolipin (CL), or GM1 ganglioside (GM1). Nanoliposomes containing PA, CL, and GM1 showed little or no inhibitory effect on amyloid fibril formation. CUR liposomes were the most effective, showing evident concentration-dependent inhibition of Aβ aggregation.

Mathew et al. [7] investigated the role of CUR-loaded polylactic-coglycolic acid copolymer (PLGA) nanoparticles on Aβ aggregation in vitro. These nanoparticles were conjugated to Tet-1 peptide due to its affinity for neurons, facilitating the targeting of nanoparticles to the central nervous system. After co-incubation, the breakdown of

amyloid aggregates was observed and breakdown into considerably smaller plaques after 48 h of coincubation. Nanoparticles conjugated to Tet-1 peptide showed similar anti-amyloid activity, although they were slower than nanoparticles without Tet-1 in formulating the same effect. Tet-1-conjugated PLGA-CUR nanoparticles also demonstrated 60% free radical scavenging activity, showing that PLGA and Tet-1 do not nullify the antioxidant property of CUR. Furthermore, the study showed that CUR-loaded PLGA nanoparticles conjugated to Tet-1 did not demonstrate in vitro cytotoxicity.

Tiwari et al. [8] analyzed the effects of PLGA nanoparticles encapsulated in CUR (Cur-PLGA-NPs) on the induction of neurogenesis and neuronal differentiation in vitro and in vivo and observed potent proliferation of endogenous neural stem cells (NSC) and neuronal differentiation in the hippocampus and subventricular zone compared to bulk CUR, increasing β-catenin nuclear translocation and increasing GSK-3β phosphorylation. These actions elevated the expression of pro-neurogenic genes. Furthermore, treatment with Cur-PLGA-NP increased proliferation even at very low doses and was not cytotoxic at high doses compared to free CUR.

Kuo & Lin et al. [9] evaluated liposomes conjugated with wheat germ agglutinin (WGA) and CL on the transport of nerve growth factor (NGF) and CUR across the blood-brain barrier and on the viability of SK-N-MC cells against apoptosis induced by Aβ 1-42 fibrils in vitro. Analyzes showed that increasing the molar percentage of CL in liposomes improved the trapping efficiency of NGF and CUR and accelerated the release of NGF from liposomes with WGA-CL-NGF-CUR. In contrast, the release of CUR from these liposomes was delayed. Furthermore, treatment with WGA-CL-NGF-CUR liposomes slightly increased the viability of SK-N-MC cells with Aβ 1-42, showing that WGA-CL-NGF-CUR liposomes can be potential colloidal delivery transporters in targeting the blood-brain barrier for AD treatment.

Fan et al. [10] analyzed the effects of CUR-loaded PLGA- polyethylene glycol (PEG) nanoparticles conjugated with B6 peptide in vitro and in vivo. In vitro results showed that all particles studied did not affect cell viability and had relatively low toxicity profiles. In vivo analyses showed that treatment with PLGA-PEG-B6/CUR improved mice's spatial learning and memory capacity, as they spent less time finding the platform. Furthermore, treatment with PLGA-PEG-B6/CUR reduced Aβ production in the hippocampus and decreased tau phosphorylation in mice.

SoukhakLari et al. [11] experimented with the effect of bovine serum albumin (BSA) -based CUR nanoparticles on memory and concentration of MMP-2, MMP-9, and MAPKs in the hippocampus in NMRI mice. The treatment significantly optimized the performance of the mice in the passive avoidance memory test, which did not occur with the treatment with the same doses of natural CUR, showing the effectiveness of CUR nanoparticles.

Huo et al. [12] evaluated the role of selenium nanoparticles encapsulated PLGA nanospheres with CUR (Se/Cur-PLGA) on Aβ aggregation in vivo and showed that in the treated groups, the selenium nanoparticles on the surface of the nanospheres helped in the penetration of CUR through blood–brain barrier (BBB) and, consequently, in the realization of its effects. Se/Cur-PLGA nanospheres were located mainly on amyloid β plaques and completely crossed the BBB, showing that these nanospheres bound exactly to amyloid β plaques.

Zhang et al. [13] analyzed the effects of intranasally administered CUR-encapsulated chitosan-coated PLGA acid nanoparticles and CUR/hydroxypropyl-β-cyclodextrin inclusion complexes on CUR transport in AD. In vitro analysis involved human neuroblastoma cells (SH-SY5Y) and mice microglia cells (BV-2) used to evaluate cytotoxicity, cell uptake, and anti-inflammatory and antioxidant activities, while in vivo studies involved C57BL/6 mice who received CUR solution, CUR-CSPLGA-NPs or CUR/HP-β-CD inclusion complexes intranasally. The in vitro study showed that both CUR-CS-PLGA-NPs and CUR/HP-β-CD inclusion complexes showed high stability, did not alter CUR release under different conditions, and did not impair the antioxidant and anti-inflammatory activity of CUR as well as could facilitate the internalization of CUR in SH-SY5Y cells and BV-2 cells and demonstrated low cytotoxicity. The in vivo study indicated that the CUR/HP-β-CD inclusion complexes demonstrated the highest bioavailability and highest peak CUR concentration (Cmax) among the three groups, which may produce therapeutic improvement concerning the CUR solution and CUR-CS -PLGA-NPs in the long-term treatment of AD.

Lin et al. [14] evaluated the combination of PLGA-PEG-PLGA thermo-sensitive hydrogel with CUR (PGC) in preventing and decreasing the progression of AD. In vitro studies demonstrated that PGC did not exert cytotoxicity but had excellent anti-inflammatory and antioxidant properties and microglial modulation. In vivo studies demonstrated better performance of animals with AD treated with PGC injection. In addition, PGC reduced the aggregation and deposition of β-amyloid proteins in the neurons of treated mice and significantly increased hippocampal activity.

Campisi et al. [15] studied the effects of systemic administration of C-SLN on the delivery of CUR to neuronal cells and the levels of expression of the tissue transglutaminase isoform (TG2) in an experimental model of AD. After the interventions, the animals underwent a behavioral descent test to assess memory and learning. The results showed that treatment with SLNs loaded with CUR improved cognitive and memory performance, especially in Tg mice compared to WT mice. Furthermore, the different TG2 isoforms were modulated differently with systemic administration of SLNs-CUR in Tg and WT mice. TG2-L expression increased with SLNs-CUR in Tg and WT mice, whereas TG2-S expression decreased with SLNs-CUR in Tg and WT.

The study performed by Ruan et al. [16] investigated the effects of a highly-sensitive CUR-conjugated nanotheranostic platform on the reversal of cognitive deficits in AD and on the detection of Aβ plaques by magnetic resonance imaging in vivo. After treatment, all rats were evaluated for spatial reference memory by the Morris water maze (MWM) test. The results showed that this multifunctional nanomaterial efficiently reduced the Aβ plaque burden, indicating that this nanomaterial has great potential to be applied to the early diagnosis and treatment of AD.

Patil et al. [17] evaluated the applicability of a nanoimaging agent (NIA) based on poly[b-L-malic acid] (PMLA) containing gadolinium–DOTA (Gd–DOTA) and derived CUR in detecting images of Aβ plaques in human samples. Magnetic resonance imaging in the presence of NIA showed a high-contrast enhancement. At the same time, no contrast was obtained with plates incubated with free CUR and free Gd-DOTA, evidencing that NIA could bind to Aβ plates by CUR, which may be a promising method for the safe and non-invasive diagnosis of AD.

Giacomeli et al. [18] compared the effects of CUR lipid-core nanocapsules (LNC) and free CUR (FC) in a model of induced AD in aged Swiss Albino mice. After 14 days, treatment with FC and LNC reduced the cognitive deficit induced by Aβ 1-42 in the MWM test. Furthermore, the administration of Aβ 1-42 increased the mRNA expression of TNF-α, IL-1β and IL-6, IFN-γ and NF-κB in the hippocampus and prefrontal cortex of control mice, while treatment with FC and LNC decreased expression of TNF-α, IL-1β, IL-6, IFN-γ, and NF-κB mRNA.

The above information shows that CUR-based nanomedicines such as liposomes, nanoparticles, nanocapsules, and nanospheres can promote anti-dementia effects and protect against AD. The results of the included studies evidenced that CUR in the form of nanomedicines decreased Aβ aggregation, amyloid fibril formation and TG2 expression, upregulated Aβ aggregates breakdown, neurogenesis, neuronal differentiation, the proliferation of endogenous NSC, β-catenin nuclear translocation, GSK-3β phosphorylation, expression of pro-neurogenic genes, neuronal cells viability, spatial learning, memory capacity, and microglial modulation, as well as reduced Tau protein phosphorylation, mRNA expression of TNF-α, IL-1β and IL-6, IFN-γ and NF-κB and brain oxidative stress.

2. Parkinson’s Disease

In turn, Parkinson’s disease (PD) causes movement disorders. The pathological hallmark of PD consists of neural inclusions in the form of Lewy bodies and Lewy neurites, with selective degeneration of dopamine neurons in the substantia nigra, with decreased levels of dopamine in the striatum and other areas of the brain, which leads to impaired motor control [19][20][21]. In PD, inflammation is also part of its pathogenesis. During PD, principally, the neuronal death of dopaminergic neurons from the substantia nigra *pars compacta*, and the consequent microglial cell activation leads to the expression of several pro-inflammatory cytokines that implicates degeneration on even more dopaminergic neurons. Different from other ND, the gut–brain axis and the possible contribution of dysbiotic-bowel peripheral inflammation could also contribute to the brain’s neuroinflammation and, therefore, to the death of neurons [22][23].

Bollimpelli et al. [24] studied the neuroprotective effects of CUR-loaded lactoferrin nanoparticles on rotenone-induced PD in dopaminergic cell line SK-NSH pretreated with CUR in solution, nanoCUR equivalent or lactoferrin nanoparticles (deprived of CUR), in addition to being subsequently treated with rotenone for induction of neurotoxicity. The assays showed that pretreatment with CUR or nanoCUR solution rescued cells from rotenone-induced neurotoxicity but more substantially in pretreatment with nanoCUR, while lactoferrin nanoparticles devoid of CUR showed no significant effect in attenuating neurotoxicity. In addition, ROS levels were reduced with pretreatment with CUR and nanoCUR solution. The expression of Tyrosine Hydroxylase (TH), an enzymatic marker of dopaminergic cell injury, was efficiently retained with nanoCUR pretreatment. In contrast, the expression of α-synuclein, a critical component in Lewy body formation, was also deleted.

Zhang et al. [25] evaluated the role of CUR-loaded modified polysorbate 80 cerassome (CPC) nanoparticles (NPs) in the localized delivery of CUR to targeted brain nuclei through an adequate opening of the BBB by ultrasound-targeted microbubble destruction (UTMD). The results showed that treatment with CPC NPs combined with UTMD in MPTP-induced PD mice notably improved behavioral disturbance, dopamine depletion, and TH expression, as

well as reduced α-synuclein (AS) expression, showing that the delivery of CUR with this treatment was efficient, as well as its therapeutic effects against PD.

Sookhaklari et al. [26] evaluated the effect of BSA-based nanoCUR against 6-OHDA-induced cell death in vitro. SH-SY5Y cells were treated with OHDA and subsequently with different doses of nanoCUR and CUR free. Treatment with nanoCURA at doses of 400 and 500 nM prevented cell death. Furthermore, this CUR nanoformulation restored the 6-OHDA-induced p-Akt/t-Akt decrease. This neuroprotective effect of CUR was four times higher with CUR in nanoformulation compared to CUR free.

Liu et al. [27] experimented with a peptide-modified exosome chemical complex (EXO) CURa/phenylboronic acid-poly(2-(dimethylamino)ethyl acrylate) nanoparticle/small interfering RNA targeting SNCA (REXO-C/ANP/S) as a nano scavenger to remove aggregates of α-synuclein and reduce its cytotoxicity in PD neurons. C57BL/6 mice received MPTP for PD induction, and then REXO-C/ANP/S treatment and other control NPs were administered. After treatment, mice from the NP groups showed a trend toward improvement in exercise, especially the REXO-C/ANP/S group. The neuronal repair was also superior in PD mice injected with REXO-C/ANP/S compared to the other groups. Furthermore, treatment with REXO-C/ANP/S was more effective in clearing α-synuclein, reduced IL-2 and IL-17 expression, and increased IL-10 expression.

Yan et al. [28] studied the role of PLGA-lipid nanobubbles (NBs) in the delivery of CUR and BBB opening induced by low-intensity focused ultrasound (LIFU) in C57BL/6 mice. After treatment, the rats were subjected to behavioral tests to assess the remission of PD symptoms. Performance on the behavioral test among mice-induced PD was superior in mice treated with Cur-NBs combined with LIFU. Furthermore, Cur-NBs combined with LIFU improved the local delivery of CUa to deep brain nuclei, significantly potentiating the effectiveness of CUR compared to groups that were treated with either Cur-NBs alone or LIFU alone.

Furthermore Guzman et al. [29] analyzed the effect of CUR-loaded human serum albumin nanoparticles (CUHNP) on the prevention of PD-like symptoms in *Caenorhabditis elegans*. Treatment with CUHNP effectively delayed the deterioration of nematode movement. Ultimately, CUHNP could enhance the activity of dopamine transporters at the end of presynaptic neurons, resulting in enhanced dopamine transport to synaptic neurons.

Due to the above information, CUR-based nanomedicines are effectively more efficient as an adjuvant treatment against PD than free CUR. CUR in the form of NPs, exosomes, and NBs exerted reduction in α-synuclein expression, brain OS, TH expression, Lewy body formation, behavioral disturbances, dopamine depletion, neuronal cells death and IL-2 and IL-17 levels, as well as increases in neuronal repair, IL-10 levels and dopamine transport to synaptic neurons. These actions can contribute highly to anti-PD treatment clinically.

3. Multiple Sclerosis

Multiple sclerosis (MS) is a complex neurodegenerative disease characterized to be an inflammatory process with the production and release of pro-inflammatory cytokines that also lead to oxidative burden. This

pathophysiological inflammation and OS result in demyelination, reduced remyelination, and decreased axonal survival, together with massive activation of microglial cells. As a substantial share of patients suffering from MS present deterioration of neurological functions slowly and considering the silent progression of the disease, the use of anti-inflammatory and antioxidants compounds is gaining interest towards its easy manipulation, many benefits, and pleiotropic activity with few cytotoxicity as adjuvants in MS treatment [30][31].

Motavaf et al. [32] investigated the effects of dendrosomal CUR nanoparticles (DNCur) on oligodendrogenesis and remyelination both in vitro and in vivo using models of MS demyelination. The results indicated that DNCur effectively enhanced oligodendrogenesis from NSC and oligodendrocyte progenitor cells in a dose-dependent manner in vitro. The CUR-based nanomedicine also promoted remyelination via promoting oligodendrogenesis in vitro. On the other hand, in vivo, DNCur had a significant impact in enhancing the remyelination capacity of transplanted NSC through the promotion of not only their survival but also oligodendrogenesis enhancement.

Motavaf et al. [33] also conducted an in vivo study to evaluate the protective effects of DNCur against cuprizone-induced (CPZ) demyelination in the mouse corpus callosum. The results showed that the use of DNCur protected the oligodendrocyte lineage cells against CPZ-derived demyelination, as well as suppressed the accumulation of astrocytes and microglia cells in the *corpus callosum* of the CPZ-fed mice. In addition, the DNCur treatment also increased the index of luxol fast bluefast blue and myelin-specific proteins as an indicator of myelin content, as these are myelin-specific proteins. The authors, therefore, suggested an efficient pleiotropic therapeutic strategy for DNCur in the myelinating protection of cells via possibly suppressing astrocytes and microglia.

Lu et al. [34] conducted an in vivo study with a mice model of experimental autoimmune encephalomyelitis and found that targeted immunomodulation of inflammatory monocytes across the blood-brain barrier by CUR-NPs was an effective strategy to not only augment CUR bioavailability but also delay the progression of that MS model. The authors used a high-density lipoprotein-mimicking peptide-phospholipid scaffold (HPPS) as a way to ameliorate CUR bioavailability and to create CUR-loaded HPPS (CUR-HPPS) NPs that were taken specifically and efficiently by inflammatory monocytes through their scavenger receptor B type 1 (SR-B1). After this taking, the monocytes were infiltrated across the blood-brain barrier of the encephalomyelitis mice. The liberation of CUR resulted in decreased microglia proliferation, restricted immune cell infiltration in the neuronal areas, and reduced morbidity of the experimental model from 100% to 30%. Molecularly, CUR attenuated NF-kB activation and inhibited the expression of adhesion and migration-related molecules in the mice's brain.

Dolati et al. [35] conducted a clinical study and found that the use of nanoCUR improved regulatory T-cell (Treg) frequency and function in patients with MS. In all, 50 patients were enrolled in this trial, and 25 of them were treated at least for six months with preparations of nanoCUR capsules while the others received placebo. The results revealed a decrease in the proportion of peripheral Treg cell frequency and the levels of TGF-β, IL-10, and forkhead box protein 3 (FoxP3) expression. It has been discovered that the disturbance in the development and function of Treg subpopulations could be associated with disabilities in most patients with MS. The use of nanoCUR, therefore, can be a pathway in the restore of the frequency and function of Treg cells in these patients.

Dolati et al. [36] also evaluated in what appears to be the same population as of the previous study the effects of nanoCUR as a potent anti-inflammatory treatment or adjuvant against MS. The authors found that nanoCUR was able to decrease the expression levels of the inflammatory miR-145, miR-132, and miR-16. In addition, nanoCUR decreased signal transducer and activator of transcription (STAT) 1, NF-kB, and AP-1 activation and signaling in MS patients, as well as increased STAT5 mRNA expression levels. The use of nanoCUR also reduced the levels of IL-1β, IL-6, chemokine (C-C motif) ligand (CCL) 2, CCL5, IFN-γ, and TNF-α mRNA expression levels.

Due to the above results, it is possible to say that CUR-based nanomedicines are effective agents against demyelination during MS treatment. CUR in the forms of dendrosomal CUR NPs, CUR-HPPS, and simple nanoCUR were able to increase oligodendrogenesis, remyelination, neuronal myelin content and STAT5 mRNA expression levels in patients and models with MS. Additionally, the nano formulations with CUR decreased astrocytes and microglia cells accumulation and actions, microglial proliferation, disease's morbidity, NF-kB activation and signaling, adhesion and migration-related proteins, peripheral Treg cell frequency and function, TGF-β, IL-10 and FoxP3 expression levels, inflammatory miR-145, miR-132, and miR-16 expression levels and STAT1 activation and signaling, as well as the expression levels of IL-1β, IL-6, CCL2, CCL5, IFN-γ and TNF-α mRNA.

4. Huntington's Disease

Huntington's disease (HD) is a neurodegenerative condition caused mainly by an abnormal expansion of polyglutamine replicated in the first exon of the huntingtin gene. The disease is characterized by neurodegeneration, particularly in the brain's striatum and cortex. The mutation in the huntingtin causes abnormalities in the functioning of the codified protein, which leads to deleterious effects, ultimately to the demise of specific neurons and other neuronal cells. The first HD symptoms and signals appear in mid-life and include cognitive deficits and motor disturbances in a progressive timeline. Although this disease is inherited, treatments have been proposed over the years, and many of them significantly improve HD patients' quality of life [37][38]. Despite synthetic approaches, CUR-based therapies have been proposed against HD due to the anti-aging and anti-neurodegeneration effects of this polyphenol [39][40][41]. However, CUR-based nanotherapies usually obtain better results against HD as well.

Traditionally, researchers focused on brain changes as the cause of progressive motor and cognitive dysfunction during HD. However, the discovery of huntingtin protein and its mutated form being expressed in different organs and tissues than the brain corroborated the hypothesis that other mechanisms could be involved in HD disease, like an inflammatory response. New research evidenced that inflammatory states can be evaluated since the onset of classical HD signals and symptoms as inflammation can adjuvantly cause systemic suppression of energy metabolism, failure of transcription, and mitochondrial dysfunction, as well as contributes to abnormalities of neurons' cytoskeleton, microglial disruption, and impairments to the axonal neuron transport [42][43][44][45].

Sandhir et al. [46] discussed in an in vivo study with a mouse model of HD the effects of CURNPs in neurochemical and neurobehavioral deficits encountered during the disease. Truly, the authors wanted to explore the effects of the CUR-based nanotherapy against the typical HD mitochondrial dysfunction. CUR was encapsulated in C-SLNs and

was used to ameliorate 3-nitropropionic acid (3-NP)-induced HD in rats. The results showed that CUR significantly penetrated the animals' brain and decreased the striatum's Complex II activity. However, the treated animals also presented elevated mitochondrial complexes activity, as well as increased cytochrome levels. Molecularly, CUR diminished the oxidative stress imposed on the rats' brains due to a significant increase in GSH and SOD levels and decreased mitochondrial swelling, lipid peroxidation, protein carbonyl formation, and ROS production. At least, the mice presented significant improvements in neuromotor coordination. These effects were attributed to the activation of the Nrf2 by CUR.

References

1. Soria Lopez, J.A.; González, H.M.; Léger, G.C. Alzheimer's disease. Handb. Clin. Neurol. 2019, 167, 231–255.
2. Breijyeh, Z.; Karaman, R.J.M. Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules 2020, 25, 5789.
3. Zhang, H.; Zheng, Y. β Amyloid Hypothesis in Alzheimer's Disease: Pathogenesis, Prevention, and Management. Zhongguo yi xue ke xue yuan xue bao Acta Acad. Med. Sin. 2019, 41, 702–708.
4. Ozben, T.; Ozben, S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. Clin. Biochem. 2019, 72, 87–89.
5. Forloni, G.; Balducci, C. Alzheimer's Disease, Oligomers, and Inflammation. J. Alzheimers Dis. 2018, 62, 1261–1276.
6. Taylor, M.; Moore, S.; Mourtas, S.; Niarakis, A.; Re, F.; Zona, C.; La Ferla, B.; Nicotra, F.; Masserini, M.; Antimisiaris, S.G.; et al. Effect of curcumin-associated and lipid ligand-functionalized nanoliposomes on aggregation of the Alzheimer's Aβ peptide. Nanomedicine 2011, 7, 541–550.
7. Mathew, A.; Fukuda, T.; Nagaoka, Y.; Hasumura, T.; Morimoto, H.; Yoshida, Y.; Maekawa, T.; Venugopal, K.; Kumar, D.S. Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide for potential use in Alzheimer's disease. PLoS ONE 2012, 7, e32616.
8. Tiwari, S.K.; Agarwal, S.; Seth, B.; Yadav, A.; Nair, S.; Bhatnagar, P.; Karmakar, M.; Kumari, M.; Chauhan, L.K.; Patel, D.K.; et al. Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway. ACS Nano 2014, 8, 76–103.
9. Kuo, Y.C.; Lin, C.C. Rescuing apoptotic neurons in Alzheimer's disease using wheat germ agglutinin-conjugated and cardiolipin-conjugated liposomes with encapsulated nerve growth factor and curcumin. Int. J. Nanomed. 2015, 10, 2653–2672.

10. Fan, S.; Zheng, Y.; Liu, X.; Fang, W.; Chen, X.; Liao, W.; Jing, X.; Lei, M.; Tao, E.; Ma, Q.; et al. Curcumin-loaded PLGA-PEG nanoparticles conjugated with B6 peptide for potential use in Alzheimer's disease. Drug Deliv. 2018, 25, 1091–1102.
11. SoukhakLari, R.; Moezi, L.; Pirsalami, F.; Moosavi, M. The Effect of BSA-Based Curcumin Nanoparticles on Memory and Hippocampal MMP-2, MMP-9, and MAPKs in Adult Mice. J. Mol. Neurosci. 2018, 65, 319–326.
12. Huo, X.; Zhang, Y.; Jin, X.; Li, Y.; Zhang, L. A novel synthesis of selenium nanoparticles encapsulated PLGA nanospheres with curcumin molecules for the inhibition of amyloid β aggregation in Alzheimer's disease. J. Photochem. Photobiol. B 2019, 190, 98–102.
13. Zhang, L.; Yang, S.; Wong, L.R.; Xie, H.; Ho, P.C. In Vitro and In Vivo Comparison of Curcumin-Encapsulated Chitosan-Coated Poly(lactic-co-glycolic acid) Nanoparticles and Curcumin/Hydroxypropyl-β-Cyclodextrin Inclusion Complexes Administered Intranasally as Therapeutic Strategies for Alzheimer's Disease. Mol. Pharm. 2020, 17, 4256–4269.
14. Lin, Y.W.; Fang, C.H.; Yang, C.Y.; Liang, Y.J.; Lin, F.H. Investigating a Curcumin-Loaded PLGA-PEG-PLGA Thermo-Sensitive Hydrogel for the Prevention of Alzheimer's Disease. Antioxidants 2022, 11, 727.
15. Campisi, A.; Sposito, G.; Pellitteri, R.; Santonocito, D.; Bisicchia, J.; Raciti, G.; Russo, C.; Nardiello, P.; Pignatello, R.; Casamenti, F.; et al. Effect of Unloaded and Curcumin-Loaded Solid Lipid Nanoparticles on Tissue Transglutaminase Isoforms Expression Levels in an Experimental Model of Alzheimer's Disease. Antioxidants 2022, 11, 1863.
16. Ruan, Y.; Xiong, Y.; Fang, W.; Yu, Q.; Mai, Y.; Cao, Z.; Wang, K.; Lei, M.; Xu, J.; Liu, Y.; et al. Highly sensitive Curcumin-conjugated nanotheranostic platform for detecting amyloid-beta plaques by magnetic resonance imaging and reversing cognitive deficits of Alzheimer's disease via NLRP3-inhibition. J. Nanobiotechnology 2022, 20, 322.
17. Patil, R.; Gangalum, P.R.; Wagner, S.; Portilla-Arias, J.; Ding, H.; Rekechenetskiy, A.; Konda, B.; Inoue, S.; Black, K.L.; Ljubimova, J.Y.; et al. Curcumin Targeted, Polymalic Acid-Based MRI Contrast Agent for the Detection of Aβ Plaques in Alzheimer's Disease. Macromol. Biosci. 2015, 15, 1212–1217.
18. Giacomeli, R.; Izoton, J.C.; Dos Santos, R.B.; Boeira, S.P.; Jesse, C.R.; Haas, S.E. Neuroprotective effects of curcumin lipid-core nanocapsules in a model Alzheimer's disease induced by β-amyloid 1-42 peptide in aged female mice. Brain Res. 2019, 1721, 146325.
19. Radhakrishnan, D.M.; Goyal, V. Parkinson's disease: A review. Neurol. India 2018, 66, S26–S35.
20. Tolosa, E.; Garrido, A.; Scholz, S.W.; Poewe, W. Challenges in the diagnosis of Parkinson's disease. Lancet. Neurol. 2021, 20, 385–397.

21. Chia, S.J.; Tan, E.K.; Chao, Y.X. Historical Perspective: Models of Parkinson's Disease. Int. J. Mol. Sci. 2020, 21, 2464.
22. Pajares, M.; Rojo, I.A.; Manda, G.; Boscá, L.; Cuadrado, A. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells 2020, 9, 1687.
23. Marogianni, C.; Sokratous, M.; Dardiotis, E.; Hadjigeorgiou, G.M.; Bogdanos, D.; Xiromerisiou, G. Neurodegeneration and Inflammation-An Interesting Interplay in Parkinson's Disease. Int. J. Mol. Sci. 2020, 21, 8421.
24. Bollimpelli, V.S.; Kumar, P.; Kumari, S.; Kondapi, A.K. Neuroprotective effect of curcumin-loaded lactoferrin nano particles against rotenone induced neurotoxicity. Neurochem. Int. 2016, 95, 37–45.
25. Zhang, N.; Yan, F.; Liang, X.; Wu, M.; Shen, Y.; Chen, M.; Xu, Y.; Zou, G.; Jiang, P.; Tang, C.; et al. Localized delivery of curcumin into brain with polysorbate 80-modified cerasomes by ultrasound-targeted microbubble destruction for improved Parkinson's disease therapy. Theranostics 2018, 8, 2264–2277.
26. Sookhaklari, R.; Geramizadeh, B.; Abkar, M.; Moosavi, M. The neuroprotective effect of BSA-based nanocurcumin against 6-OHDA-induced cell death in SH-SY5Y cells. Avicenna J. Phytomed. 2019, 9, 92–100.
27. Liu, L.; Li, Y.; Peng, H.; Liu, R.; Ji, W.; Shi, Z.; Shen, J.; Ma, G.; Zhang, X. Targeted exosome coating gene-chem nanocomplex as "nanoscavenger" for clearing α-synuclein and immune activation of Parkinson's disease. Sci. Adv. 2020, 6, eaba3967.
28. Yan, Y.; Chen, Y.; Liu, Z.; Cai, F.; Niu, W.; Song, L.; Liang, H.; Su, Z.; Yu, B.; Yan, F. Brain Delivery of Curcumin Through Low-Intensity Ultrasound-Induced Blood-Brain Barrier Opening via Lipid-PLGA Nanobubbles. Int. J. Nanomed. 2021, 16, 7433–7447.
29. de Guzman, A.C.V.; Razzak, M.A.; Cho, J.H.; Kim, J.Y.; Choi, S.S. Curcumin-Loaded Human Serum Albumin Nanoparticles Prevent Parkinson's Disease-like Symptoms in C. elegans. Nanomaterials 2022, 12, 758.
30. Theodosis-Nobelos, P.; Rekka, E.A. The Multiple Sclerosis Modulatory Potential of Natural Multi-Targeting Antioxidants. Molecules 2022, 27, 8402.
31. Nataf, S.; Guillen, M.; Pays, L. Irrespective of Plaque Activity, Multiple Sclerosis Brain Periplaques Exhibit Alterations of Myelin Genes and a TGF-Beta Signature. Int. J. Mol. Sci. 2022, 23, 14993.
32. Motavaf, M.; Sadeghizadeh, M.; Babashah, S.; Zare, L.; Javan, M. Dendrosomal nanocurcumin promotes remyelination through induction of oligodendrogenesis in experimental demyelination animal model. J. Tissue Eng. Regen. Med. 2020, 14, 1449–1464.

33. Motavaf, M.; Sadeghizadeh, M.; Babashah, S.; Zare, L.; Javan, M. Protective Effects of a Nano-Formulation of Curcumin against Cuprizone-Induced Demyelination in the Mouse Corpus Callosum. Iran. J. Pharm. Res. 2020, 19, 310–320.
34. Lu, L.; Qi, S.; Chen, Y.; Luo, H.; Huang, S.; Yu, X.; Luo, Q.; Zhang, Z. Targeted immunomodulation of inflammatory monocytes across the blood-brain barrier by curcumin-loaded nanoparticles delays the progression of experimental autoimmune encephalomyelitis. Biomaterials 2020, 245, 119987.
35. Dolati, S.; Babaloo, Z.; Ayromlou, H.; Ahmadi, M.; Rikhtegar, R.; Rostamzadeh, D.; Roshangar, L.; Nouri, M.; Mehdizadeh, A.; Younesi, V.; et al. Nanocurcumin improves regulatory T-cell frequency and function in patients with multiple sclerosis. J. Neuroimmunol. 2019, 327, 15–21.
36. Dolati, S.; Ahmadi, M.; Aghebti-Maleki, L.; Nikmaram, A.; Marofi, F.; Rikhtegar, R.; Ayromlou, H.; Yousefi, M. Nanocurcumin is a potential novel therapy for multiple sclerosis by influencing inflammatory mediators. Pharmacol. Rep. 2018, 70, 1158–1167.
37. Pandey, M.; Rajamma, U. Huntington's disease: The coming of age. J. Genet. 2018, 97, 649–664.
38. Kim, A.; Lalonde, K.; Truesdell, A.; Gomes Welter, P.; Brocardo, P.S.; Rosenstock, T.R.; Gil-Mohapel, J. New Avenues for the Treatment of Huntington's Disease. Int. J. Mol. Sci. 2021, 22, 8363.
39. Stacchiotti, A.; Corsetti, G. Natural Compounds and Autophagy: Allies Against Neurodegeneration. Front. Cell Dev. Biol. 2020, 8, 555409.
40. Mahjoob, M.; Stochaj, U. Curcumin nanoformulations to combat aging-related diseases. Ageing Res. Rev. 2021, 69, 101364.
41. Abrahams, S.; Haylett, W.L.; Johnson, G.; Carr, J.A.; Bardien, S. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. Neuroscience 2019, 406, 1–21.
42. Valadão, P.A.C.; Santos, K.B.S.; Ferreira, E.V.T.H.; Macedo, E.C.T.; Teixeira, A.L.; Guatimosim, C.; de Miranda, A.S. Inflammation in Huntington's disease: A few new twists on an old tale. J. Neuroimmunol. 2020, 348, 577380.
43. Tabrizi, S.J.; Estevez-Fraga, C.; van Roon-Mom, W.M.C.; Flower, M.D.; Scahill, R.I.; Wild, E.J.; Muñoz-Sanjuan, I.; Sampaio, C.; Rosser, A.E.; Leavitt, B.R. Potential disease-modifying therapies for Huntington's disease: Lessons learned and future opportunities. Lancet Neurol. 2022, 21, 645–658.
44. Illarioshkin, S.N.; Klyushnikov, S.A.; Vigont, V.A.; Seliverstov, Y.A.; Kaznacheyeva, E.V. Molecular Pathogenesis in Huntington's Disease. Biochemistry 2018, 83, 1030–1039.

45. Stephenson, J.; Nutma, E.; van der Valk, P.; Amor, S. Inflammation in CNS neurodegenerative diseases. Immunology 2018, 154, 204–219.
46. Sandhir, R.; Yadav, A.; Mehrotra, A.; Sunkaria, A.; Singh, A.; Sharma, S. Curcumin nanoparticles attenuate neurochemical and neurobehavioral deficits in experimental model of Huntington's disease. Neuromolecular. Med. 2014, 16, 106–118.