Integrative Medicine Research 12 (2023) 100968

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Review Article

Curcumin, inflammation, and neurological disorders: How are they linked?

Prachi Garodia [a,*], Mangala Hegde [b], Ajaikumar B. Kunnumakkara [b], Bharat B. Aggarwal [c,*]

[a] Integrative Research Center, Miami, FL, USA
[b] Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Assam, India
[c] Inflammation Research Center, San Diego, CA, USA

ARTICLE INFO

Keywords:
Alzheimer's disease
Curcumin
Inflammation
Neurological disorders
Parkinson's disease

ABSTRACT

Background: Despite the extensive research in recent years, the current treatment modalities for neurological disorders are suboptimal. Curcumin, a polyphenol found in *Curcuma* genus, has been shown to mitigate the pathophysiology and clinical sequalae involved in neuroinflammation and neurodegenerative diseases.
Methods: We searched PubMed database for relevant publications on curcumin and its uses in treating neurological diseases. We also reviewed relevant clinical trials which appeared on searching PubMed database using 'Curcumin and clinical trials'.
Results: This review details the pleiotropic immunomodulatory functions and neuroprotective properties of curcumin, its derivatives and formulations in various preclinical and clinical investigations. The effects of curcumin on neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), brain tumors, epilepsy, Huntington's disorder (HD), ischemia, Parkinson's disease (PD), multiple sclerosis (MS), and traumatic brain injury (TBI) with a major focus on associated signalling pathways have been thoroughly discussed.
Conclusion: This review demonstrates curcumin can suppress spinal neuroinflammation by modulating diverse astroglia mediated cascades, ensuring the treatment of neurological disorders.

1. Introduction

Neurological diseases (NDs) are characterized by progressive deterioration of preferentially susceptible neurons in various regions of central nervous system (CNS).[1,2] Numerous factors, including the excessive accumulation of misfolded proteins, inadequate clearance by proteasomal complexes, oxidative stress, deficiency in endogenous antioxidant enzymes activity, mitochondrial dysfunction, depletion of neurotrophin, neuro-inflammation, and various genetic perturbations contribute to the development and progression of NDs.[3] Depending on the location, neuronal loss, gliosis, or demyelination can cause cognitive decline, behavioural issues, and motor abnormalities.[4] NDs can be mainly characterized as memory loss/dementia or personality disorders—AD, impaired mobility, motor functions and attention deficits—PD, progressive weakness and decline in cognitive functions—ALS, auto-immune mediated neuronal loss— MS.[4,2,5] NDs have a significant negative influence on quality of life (QoL), as evidenced by their high disability-adjusted life years (DALYs), which measures loss of years of healthy life due to illness. Epidemiological studies have indicated that incidence of these diseases including AD and PD is increasing globally with rising life expectancies.[6,7] Progressive neuronal loss, associated stroke, ischemia and immense pain due to NDs have been the major cause of disabilities and mortality in the aged-adults.[4,2,5] The majority of treatments for NDs now on the market are aimed at providing temporary symptom alleviation. Certain conventional pharmacological compounds used to treat NDs exhibit inevitable side effects.[4] Besides, most of these drugs are expensive. As a result, there is a great need for the development of innovative treatments and neuroprotective substances with higher efficacy and fewer off-target effects to prevent and halt the development of NDs.

Natural compounds from the plant origin have been extensively explored to obtain the more effective and safer alternate therapeutic agent against various chronic diseases including cardiovascular diseases, cancers, diabetes, and NDs.[4,8–13] In-depth investigations have provided the evidence that phytochemicals including alkaloids, flavonoids, polyphenols and terpenes have remarkable potential in alleviating NDs *in vitro, in vivo* and clinical studies. Suppression of oxidative stress, inflammatory responses, cell death, neuronal activation along with stimulation of angiogenesis and neurogenesis are the well-known NDs progression preventing processes that can be accomplished by the primary bioactive substances isolated from plants.[4,5] Considerable research conducted over the past fifty years have shown that curcumin, a potential bioactive compound isolated from turmeric, aid in the

* Corresponding authors at: Integrative Research Center, Miami, FL, USA (P. Garodia); Inflammation Research Center, San Diego, CA, USA (B. B. Aggarwal).
E-mail addresses: prachigarodia@hotmail.com (P. Garodia), bbaggarwal@gmail.com (B.B. Aggarwal).

https://doi.org/10.1016/j.imr.2023.100968
Received 24 February 2023; Received in revised form 14 May 2023; Accepted 7 June 2023
Available online 25 June 2023

treatment of practically most of the human diseases. This phytochemical is known to possess anti-arthritis, anti-atherosclerosis, anti-bacterial, anti-diabetic, anti-fungal, anti-hypertensive, anti-hyperlipidemic, anti-inflammatory, anti-tumor, antiphlogistic, anti-psoriasis, antithrombotic, and anti-hepatotoxic effects.[5,14–16] In addition to its organ protective properties such as cardioprotective, hepatoprotective, nephron protective, and pulmonary protective effects, this phytochemical is also known to have neuroprotective activities.[17–28] Curcumin has been shown in animal experiments to accelerate adult hippocampus neurogenesis by augmenting the density of newly formed cells in the dentate gyrus areas of the brain.[29] Additionally, it is a strong inhibitor of reactive astrocyte and glial cells activation, preventing the death of hippocampus cells driven by kainic acid.[30] Moreover, curcumin was found to be potential in the treatment of AD due to its ability to disaggregate β-amyloid and prevent the production of fibrils and oligomers.[5,31] Curcumin has been proven to be neuroprotective in animal models of seizures, migraine, ALS, PD, MS and neuroinflammation in a number of experimental studies.[5] With all of this background information, the current review aims to describe the potential of curcumin in various cell lines, animal models of NDs and in clinical trials. We have also illustrated the molecular mechanisms behind the protective activities of curcumin. Further, the safety, adverse side effects, disadvantages and future prospective have been thoroughly discussed.

2. Methods

This is a review article which provide the update on uses of curcumin in treating various chronic neurological diseases. Publications that provide the evidence of effectiveness of curcumin in preventing and reducing the symptoms of neurological diseases were collected from PubMed database by searching the keyword of curcumin plus name of the diseases, for instance, 'curcumin and Alzheimer's disease', 'curcumin and amyotrophic lateral sclerosis', 'curcumin and epilepsy', etc. The review articles, retracted manuscripts, short notes and editorial communications and manuscripts on turmeric were considered irrelevant articles for the current study. The remaining research articles were further thoroughly screened for dose, time and effects in both *in vitro* and *in vivo* studies. In addition, we also conducted the search for clinical trials on curcumin using 'curcumin and clinical trials' as a keyword. The number of articles screened and criteria for considering relevant articles are provided in the supplementary figure.

3. Effect of curcumin on various NDs

NDs occur primarily due to inflammation, oxidative stress, aging, trauma, vascular dysfunction, mitochondrial dysfunction, metabolic and genetic perturbations. Damaged mitochondria at the location of injury generate a huge amount of reactive oxygen species (ROS).[32] To reduce this oxidative load and provide some protection for the neurons, autophagy plays a key role and destroys these dysfunctional mitochondria.[33,34] By preventing mitochondrial apoptosis and neuroinflammation, autophagy has restorative benefits and plays a crucial role in re-establishing neuronal homeostasis. Controlled stimulation of the PI3K/Akt/mTOR signalling pathway can prevent post-injury mediated apoptosis as well as help regulate neuronal degeneration.[35] Both endogenous and exogenous ligands can activate NF-κB, and activated protein is reported to be involved in neuronal and glial cells functional deregulation under a variety of inflammatory circumstances. Additionally, activated NF-κB promotes the release of inflammatory substances including IL-6, which leads to secondary brain injury.[32,36] Increasing lines of evidence suggest that neurodegenerative processes are initiated by oxidative damage and free radicals. Nuclear factor erythroid 2 (Nrf2) controls the expression of genes linked to oxidative stress. It activates antioxidant enzymes including glutathione peroxidase (GSH-Px), heme oxygenase-1 (HO-1), malondialdehyde (MDA), nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase-1 (NQO1), and superoxide dismutase (SOD).[34] Curcumin has been shown to cross BBB and activate Nrf2 and its associated genes, inhibit NF-κB and inflammatory cytokines thereby reducing the neuroinflammation. Moreover, curcumin is a known free radical and ROS scavenger.[32] This section details the major pathways which are dysregulated in NDs. The potential of curcumin in reversing the events have also been highlighted (Fig. 1). Anti-NDs effect of curcumin *in vitro* and *in vivo* models (Table 1) and the effect of various curcumin and its derivatives in clinical trials (Table 2) have been explained.

Curcumin has shown to be a potential candidate in treating various disorders including AD, ALS, MS, migraine, and HD, PD etc. (Figs. 2 and 3). The efficacy of curcumin in treating these disease and associated inflammatory pathways have been discussed in detail.

3.1. Alzheimer's disease (AD)

AD is the most prevalent chronic neurodegenerative disorder characterized by dementia and cognitive impairment mainly due to the accumulation of amyloid β (Aβ) protein plaques. Even though the etiology of AD is largely unknown, however, both environmental and genetic factors have been shown to play a crucial role in the disease development.[191–193] Growing lines of evidence suggest that environmental toxins including aluminium toxicity could act as causative factor by altering neuronal structure, blood brain barrier (BBB) and neurotransmission.[193]

Despite the various efforts since decades, there are no satisfactory preventive and curative medicines for AD. For instance, the drugs which are approved to treat AD such as acetyl choline esterase (AChE) inhibitors including donepezil and non-competitive N-methyl D-aspartate (NMDA) receptor antagonists, are unable to decelerate the AD progression. These drugs were also found to cause side effects such as nausea, diarrhea, and insomnia.[193] Hence, it is imperative to develop novel efficacious medicines with least or no side effects for AD. Indeed, recent researches have shown that curcumin inhibits oxidative stress, inflammatory response and provides cytoprotective environment in AD *in vitro* and animal models. Curcumin treatment was found to inhibit the thapsigargin (TG)-induced cell toxicity and death in SH-SY5Y cells.[38] TG is a guaianolide-type sesquiterpene lactone commonly found in *Thapsia garganica* plant.[194,195] It is an inhibitor of endoplasmic reticulum (ER) Ca^{+}-ATPase pump and is a known inducer of ER stress (ERS).[195–197] ERS is one of the major contributor for AD development and progression.[198] The experiments aim to uncover mechanistic insights revealed that curcumin reduced ROS by inhibiting TG-induced ERS and mitochondrial stress as evidenced by the downregulation of GRP78, pSer981-PERK, pSer51-eIF2α, and MFN2 in SH-SY5Y cells.[38] Recently, another chemical 1,2-diacetylbenzene (DAB), a metabolite of 1,2-diethylbenzene, found in petrol and vehicle oils has gained the attention due to its harmful effects on CNS.[199–201] This chemical has been shown to activate microglia, inflammation, oxidative stress, impede hippocampal neurogenesis, and cause the cognitive impairment similar to AD.[200,202–204] Interestingly, a recent research showed that curcumin treatment prevented DAB associated neuronal toxicity *in vitro* by promoting NRF2 and interleukin 10 (IL-10) expression and inhibiting triggering receptor expressed on myeloid receptor 1 (TREM1), DNAX activation protein 12 (DAP12), nuclear factor kappa B (NF-κB), cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), complement 3A (C3A), complement 5A (C5A), toll-like receptor 4 (TLR4), myeloid differentiation primary response protein 88 (MYD88), interleukin-6 (IL-6), nod-like receptor protein 3 (NLRP3), caspase-1, interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), phospho-Tau, β-amyloid, glycogen synthase kinase-3 beta (GSK-3β), reactive ROS, and advanced glycation end-products (AGEs).[39] In another study, curcumin rescued cell viability of amyloid beta 42 (Aβ_{42}) treated primary hippocampal neurons isolated from mice by upregulating sirtuin 3 (SIRT3) deacetylation, nicotine adenine dinucleotide (NAD)$^{+}$/NADH ratio, adenosine triphosphate (ATP), and thyroid hormone receptor beta (Thrb).[37] This study also validated the changes in SIRT3, NAD/NADH ratio and Thrb in transgenic AD mice

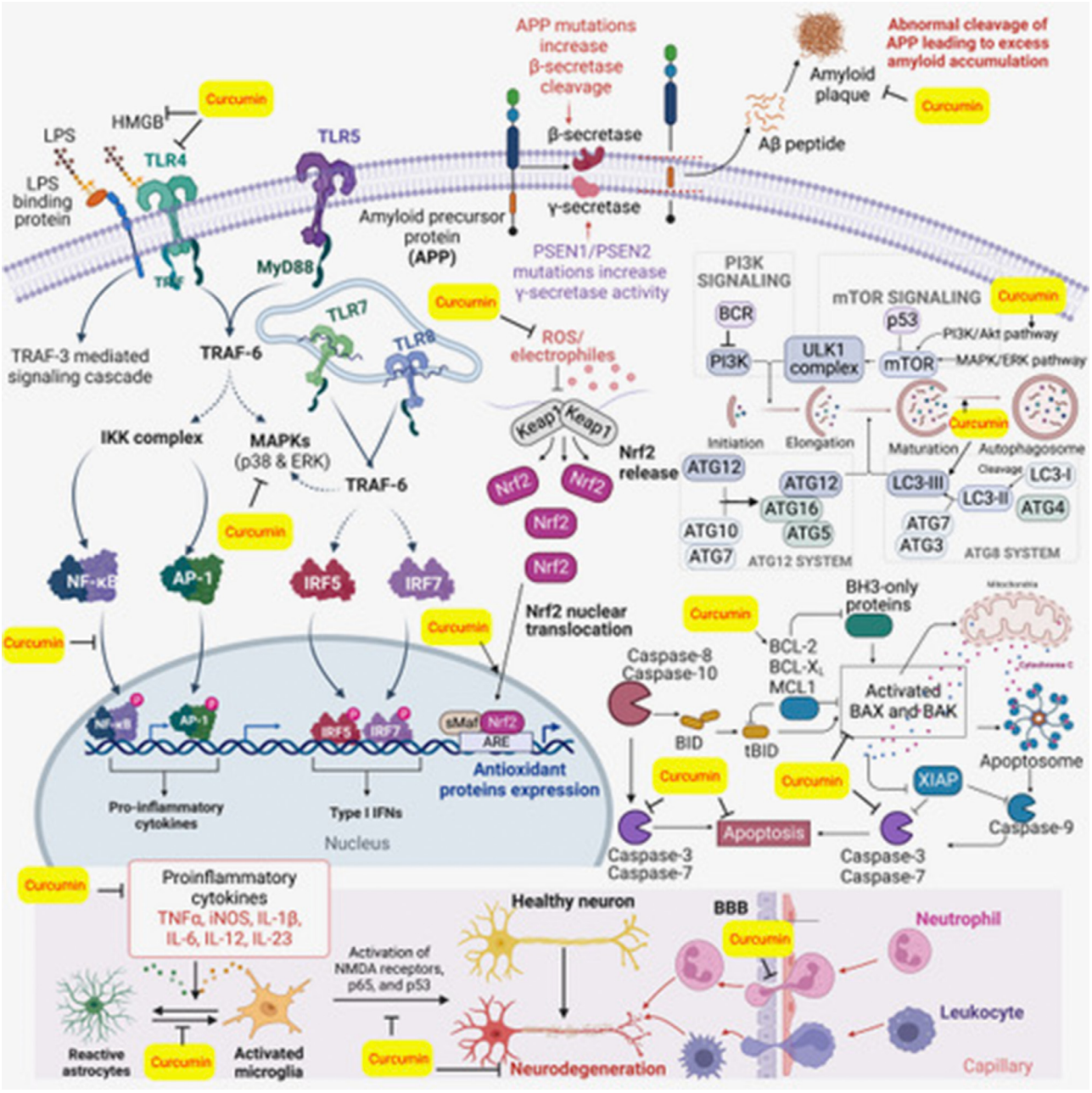

Fig. 1. Major inflammatory pathways associated with neurological disorders and potential of curcumin in restoring these deregulated pathways have been shown.

models.[37] Similar study was also conducted by He et al., and found that curcumin effectively reduced the toxicity induced by Aβ 25–35 in microglial cells by downregulating high-mobility group box 1 (HMGB1), receptor for advanced glycation end products (RAGE), TLR4, IL-1β, and TNF-α levels.[40] Further, curcumin treatment significantly reduced high molecular weight (HMW) Aβ_{42}O-induced neurite damage and neuronal cell death and suppressed IL-1β and TNF-α release in rat microglial cells and neurons.[41] Also, derivatives of curcumin has been shown to be effective in regulating HSP90, HSP70, Akt, caspase-3, glutathione (GSH), phospho Tau, ROS, nitrites and prevents aggregation of Aβ in to oligomers oxidative stress, and inflammation thereby providing the neuroprotection and rescuing neuronal cells from Aβ neurotoxicity and okadaic acid induced cytotoxicity *in vitro* and *in vivo*.[48,49,205] Another study demonstrated that curcumin diethyl gamma amino butyrate (Cur-2GE) reduced nitric oxide (NO) production, TNF-α, and IL-6 levels to a greater extent than curcumin in lipopolysaccharide (LPS) stimulated BV-2 microglial cells.[50] Further, bisdemethoxycurcumin treatment was found to ameliorate cell survival, phospho AMPK, anti-oxidative stress ability, SIRT1, SOD, and GSH levels in SK-N-SH neuronal cells treated with Aβ_{1-42} oligomers.[58] Furthermore, tetrahydrocurcumin (THC) was reported to alleviate Aβ_{42}/Aβ_{40} levels and Aβ-induced G1/S arrest and apoptosis in BV2 glial cells. This study also revealed that THC induced Gab2, K-Ras and inhibited caspase 3 levels leading to increased cell viability.[63]

The major feature of AD is the deposition of Aβ plaque results from the cleavage of amyloid precursor protein (APP), a transmembrane protein, or due to mutations in APP and presenilin genes (PSEN1 and PSEN2). Hence, the APP/PS1 transgenic mice with increased amount of Aβ plaque have been one among the best suitable model for studying pathophysiology of AD.[42,206] In the APP/PS1 mouse models curcumin remarkably inhibited the formation of amyloid protein plaques and improved time spent in target quadrant, short term working mem-

Table 1
In vitro/in vivo studies that show the effect of curcumin on various neurological diseases.

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
Alzheimer's disease						
	Curcumin	Primary hippocampal neurons	1, 5, 10 μM	–	↑Cell viability in presence of Aβ_{42}, ↑SIRT3 deacetylation, ↑NAD/NADH, ↑ATP, ↑Thrb	37
		SH-SY5Y cells	0.625–5μmol/L	4 hours	↓TG-induced cell toxicity, ↓TG-induced apoptosis, ↓TG-induced ROS, ↓GRP78, ↓pSer981-PERK, ↓pSer51-eIF2α, ↓TG induced MFN2, ↓TG-induced mitochondrial stress, ↓TG-induced ERS	38
		BV2, SH-SY5Y cells	1, 2.5, 5, 10, 20 μM	24 hours	No cytotoxicity, No effect on cell viability, ↑Nrf2, ↑IL-10, ↓TREM1, ↓DAP12, ↓NF-κB, ↓COX-2, ↓iNOS, ↓TNF-α, ↓IL-1, ↓C3A, ↓C5A, ↓TLR4, ↓MYD88, ↓IL-6, ↓NLRP3, ↓Caspase-1, ↓IL-1α, ↓IL-1β, ↓ROS, ↓AGE, ↓p-Tau, ↓β-amyloid, ↓GSK-3β	39
		Microglia	10 μM	1 hour before Aβ 25–35 treatment	↓HMGB1, ↓RAGE, ↓TLR4, ↓IL-1β, ↓TNF-α, ↓Cytotoxicity of Aβ 25–35	40
		Rat microglia cells & primary cortical neurons	1-50 μM	0–30 days	↓HMW Aβ_{42}O-induced IL-1β & TNF-α release, ↓Neurite damage, ↓Neuronal cell death	41
		APP/PS1 mice	100 mg/kg/day	5 months	↑Time spent in target quadrant, ↑Short term working memory, ↓Escape latency, ↓GFAP, ↓COX-2, ↓CD68, ↓HMGB1, ↓TLR4, ↓RAGE, ↓NF-κB	42
		APP/PS1 mice	0.16, 1 g/kg	6 months	↑Spatial memory retention, ↑ABCA1, ↑HDL, ↑ApoA1, ↑RXR-α, ↑LXR-β, ↓TC, ↓Platform crossing frequency, ↓Amyloid protein plaques	43
		APP/PS1 mice	100, 200, 300 mg/kg/day	2 weeks	↑JMJD3, ↑BDNF, ↑Time spent in target quadrant, ↑Swimming speed, ↑No. of platform crossings, ↓H3K27me3 BDNF, ↓Escape latency	44
		APP_{TG} mice	100 mg/kg/day	3 months	↑SIRT3 deacetylation, ↑NAD/NADH, ↑Thrb, ↑Time spent in the target quadrant, ↓Escape latency	37
		Wistar Albino rats	200 mg/kg/day	7 days	↓Length to reach the platform, ↓Time to reach the platform, ↓IL-6	45
		ApoE4 transgenic mice	40 mg/kg/day	3 weeks	↑Time spent in the platform, ↑Number of times mice crossed the platform, ↑Improvement in neuronal morphology, ↓ApoE4, ↓TNF-α, ↓IL-1β, ↓Spatial learning deficits, ↓Neuronal cell death, ↓Nuclear translocation of NF-κB, ↓Number of $GRP78^+$ cells, ↓Number of IRE1α^+ cells	46
	Curcumin α- and β-D-glucoside	Wistar rats	12.5, 25 mg/kg	10 days	↑GSH, ↑FRAP, ↓Memory impairment, ↓Protein carbonyls	47
	Curcumin, THC	SH-SY5Y cells	1 μM	24-48 hours	↑HSP90, ↑HSP70, ↑Akt, ↓Caspase-3	48
	Curcumin derivatives	SH-SY5Y cells	0.1–10 μM	–	↑Neuroprotection, ↑GSH, ↓Inflammation, ↓Oxidative stress, ↓p-Tau, ↓ROS, ↓ Nitrites	49
	Curcumin, Cur-2GE	BV2	10 μM	24 hours	↓NO production, ↓TNF-α, ↓IL-6	50
	Curcugreen	3xTg, 5xFAD mice	100 mg/kg	2 months	Restored spleen & liver cytoarchitecture, ↓Spleen size, ↓Bronchiolar degeneration, ↓Granulomatous inflammation, ↓Apoptotic death, ↓Amyloid deposits, ↓p-Tau	51
	Cur ME, CurDHA ME	Acute oAβ_{25-35} C57B1/6 J, J20 transgenic mice	2 mg/kg	4 days, 4 weeks (3 times/week)	Restored spatial memory deficits, anxiety & depression, ↑Short-term memory, ↓GFAP, ↓p-Tau, ↓p-JNK2	52
	Cur-MNPs	APP/PS1 mice	25mg/kg	4 days for 3 consecutive months	↑Memory, ↑Spatial learning, ↓Escape latency, ↑BDNF, ↑DCX, ↑Neuron generation, ↓Finding the blind platform time, ↓Aβ in brain, ↓Microglia, ↓Inflammation, ↓NLRP3 inflammasome, ↓IL-18, ↓CD68	53
	Curcumin nanoparticles	Wistar rats	10, 50 mg/kg	6 weeks	↑GST, ↑CAT, ↑GPx, ↑SOD, ↑IDE, ↑BDNF, ↑ADAM-10, ↑Bcl-2, ↑Normal architecture of pyramidal cells, ↓Memory deficits, ↓NO, ↓Swim time & distance, ↓AGEs, ↓TBARS, ↓TNF-α, ↓IL-1β, ↓Aβ−42, ↓AChE, ↓Bax, ↓p-p38 MAPK, ↓p-ERK, ↓p-MEK, ↓p-Tau, ↓Pyknotic pyramidal cells	54

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
		Wistar Albino rats	50 mg/kg/day	15 days	↑GSH, ↑Restoration of NO, ↑Na^+-K^+-ATPase, ↑Restoration of glutamate, glycine, taurine & GABA, ↓Latency to locate the platform, ↓MDA, ↓TNF-α, ↓AChE, ↓Tau, ↓Pyknotic neurons	55
	Curcumin lipid core NPs	Swiss mice	10 mg/kg	Alternate days for 12 days	↓Non-aversive memory impairment, ↓Inflammation, ↓COX-2	56
	Curcumin loaded T807/RPCNP	Primary astrocytes, HT22	5 μg/mL	12 hours	↑p-PKB, ↓p-Tau, ↓Mitochondrial ROS, ↓Apoptosis, ↓GSK-3β, ↓Astrocytes activation	57
		OA treated mice	2 mg/kg, every two days	10 days	↑Spatial learning & memory, ↓p-Tau, ↓Cognitive impairment, ↓Neuronal cell death, ↓Abnormal activation of microglia	57
	Bisdemethoxycurcumin	SK-N-SH cells	15 μM	30 min	↑Cell survival, ↑p-AMPK, ↑Anti-oxidative stress ability, ↑SIRT1, ↑SOD, ↑GSH	58
		C57BL/6, APP/PS	5 μg/kg/day	1 month	↑Improvement in cognitive function, ↑Number of neurons, ↑SIRT1, ↓Oxidative stress, ↓Aβ deposition	59
	PGC	N2a cells, BV2	1, 10, 25 μM	–	↓Aβ aggregation, ↓Aβ-induced neurotoxicity, ↓β-secretase, ↓Aβ-induced ROS, ↓Aβ-induced inflammation	60
		aluminium-induced AD rats	16.5 mg/kg	4 weeks	↑Hippocampal activity, ↓Abnormal cells with nuclear condensation, ↓Aβ deposition & aggregation, ↓Neurodegeneration	60
	pHDL/Cur-siBACE1	BV2, SH-SY5Y	–	–	↑IκBα, ↓Aβ, ↓Inflammatory cytokine release, ↓TNF-α, ↓IL-6, ↓IL-1β	61
		APP/PS1 mice	200 μL (curcumin, 5.6 mg/kg & siBACE1, 0.71mg/kg)	Every 4 days for 7 times	↑Focused search strategies, ↓Aβ burden, ↓NF-κB, ↓Escape latency, ↓Memory deficits, ↓Neuronal inflammation	61
	Solid-lipid curcumin NPs	5xFAD mice	100 mg/kg	2 months	↑Discrimination index, ↑Exploration index, ↑Synaptophysin, ↑PSD95, ↑CREB, ↑p-CREB, ↓Spatial memory deficits, ↓Pyknotic cells, ↓Neurodegeneration, ↓Aβ plaque load, ↓Loss in dendritic branching & sprouting, ↓Loss in dendritic spines	62
	THC	BV2	0.1, 5, 20 μM	24 hours	↑Gab2, ↑K-Ras, ↑Cell viability in presence of Aβ, ↓Aβ-induced G1/S arrest, ↓Aβ -induced apoptosis, ↓Caspase-3	63
		APP/PS1 mice	400 mg/kg/day	5 months	↑Gab2, ↑K-Ras, ↑Learning & memory, ↓Escape latency, ↓Aβ burden, ↓$A\beta_{42}/A\beta_{40}$, ↓TNF-α, ↓TGF-β1	63
Amyotrophic lateral sclerosis (ALS)						
ALS	Curcumin	THP-1 cells	0.5, 1, 5, 10, 20, 30 μM	6, 24, 72 hours	↓SOD1 aggregates, ↓Cell death	64
	Curcumin NP	THP-1 cells	0.5, 1, 5, 10, 20, 30 μM	6, 24, 72 hours	↓SOD1 aggregates, ↓Cell death	64
	DMC	NSC-34 with TDP-43 mutation	15 μM	3 days	↑Complex I activity, ↑MMPo, ↑UCP2, ↓Mitochondrial swelling, ↓Cristal dilation	65
	DMC	NSC-34	15 μM	24 hours	↓WT & Q331K TDP-43-induced abnormal inactivation of Na_v current, ↓Abnormal APs	66
	Monocarbonyl dimethoxy curcumin C	NSC-34	10 μM	24 hours	↑HO-1, ↓Insoluble TDP-43 fragments, ↓TDP-25, ↓Size of TDP-25 aggregates, ↓LDH, ↓MDA	67
Canine DM	Curcumin	Dogs (PWC breed)	13 mg	1 to 2 divided doses	↑Survival, ↓Non-weight bearing of hind/ thoracic limb	68
Epilepsy and Seizures						
	Curcumin	Organotypic slice culture model of hippocampus & entorhinal cortex obtained from Sprague-Dawley rats	10 μmol/L	Every day from day 2 culture	↑HMOX1, ↓Average AP frequency, ↓Seizure-like events, ↓pS6, ↓p-$pS6^{Ser240/244}$, ↓p-MAPK, ↓IL-6, ↓IL-1β, ↓TGF-β	69
		Swiss albino inbred mice	50, 100, 200 mg/kg	21 days	↑Seizure threshold, ↑Locomotor activity, ↑Protection against post-ictal mortality	70

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
		Wistar rats	1500 ppm	5 weeks	↑Prevention of grade III seizures, ↑Na-K ATPase activity, ↓DPH anisotropy, ↑Ambulatory activity, ↑Normal cellular architecture, ↓Onset & progression of seizures, ↓Lipid peroxidation, ↓Protein oxidation, ↓PKC activity, ↓Defecation, ↓Epilepsy-related memory decline	71
		Sprague-Dawley rats	10, 30, 100, 300 mg/kg	Throughout the kindling days	↑After discharge threshold, ↑Stimulation current intensity required to evoke after discharge, ↓Behavioural seizure development	72
		Albino Wistar rats	50, 100, 200 mg/kg	30 mins before KA treatment	↑Mean latency of convulsion, ↓Percentage of convulsions, ↓MDA, ↓fall in GSH	73
		Wistar rats	100, 200, 300 mg/kg	30 mins prior to PTZ treatment	↑Delay in kindling development, ↑Latency to myoclonic jerks, ↑Latency to GTCS, ↑GSH, ↑Latency to clonic seizures, ↓Seizure severity, ↓Number of myoclonic jerks, ↓Duration of GTCS, ↓Retention transfer latency, ↓MDA	74
		Wistar rats	300 mg/kg	Prior to PTZ or MES	↑Latency to myoclonic jerks, ↑Protection against GTCS, ↑GSH, ↓Retention transfer latency, ↓MDA	75
		Sprague-Dawley rats	30, 100, 300 mg/kg/day	5 days	↑Delayed onset of seizures, ↑SOD, ↑GSH, ↓Occurrence of seizures, ↓LDH	76
		Wistar albino rats	80 mg/kg	21 days	↑GSH, ↑Na-K ATPase activity, ↓AChE, ↓MDA, ↓NO, ↓CAT	77
		Swiss albino mice	50, 100, 200 mg/kg/p.o.	–	↑GSH, ↓Incidence & seizure score, ↓MDA	78
		Sprague-Dawley rats	50, 100, 200 mg/kg	3 days prior to Li & Pc administration	↑Latency to seizure & SE, ↑Time spent in target quadrant, ↑Cognitive performance, ↑GSH, ↓Percentage of seizure & SE, ↓Frequency of seizure, PCS & STM episodes, ↓TBARS, ↓Mortality	79
		Swiss albino mice	50, 100, 200 mg/kg	15 days after the last dose of PTZ	↑Step down latency, ↑Brain norepinephrine, ↑Brain serotonin, ↓Seizure severity score, ↓Immobility period, ↓Number of mistakes, ↓Nitrite, ↓AChE	80
		Wistar rats	100 mg/kg/day	1 week prior to surgery	↓Seizure score, ↓SE, ↓MDA, ↓Nitrite & nitrate, ↓Neurodegeneration, ↓MFS width & staining density	81
		Wistar rats	100 mg/kg/day	40 days	↑GSH, ↑Cell devoid of pyknosis, ↑Entering safe compartment, ↑Latency to enter dark compartment, ↑Long term memory, ↓ROS, ↓Mitochondrial swelling, ↓MDA, ↓Mitochondrial structural abnormality	82
		Wistar rats	100 mg/kg	40 days	↓GFAP, ↓Iba-1, ↓Astrocyte & microglia activation, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓MCP-1, ↓Escape latency	83
		Wistar rats	50, 100, 200 mg/kg	24 days	↑Protection against seizures, ↓Mean frequency of interictal discharge, ↓Mean frequency of epileptiform discharge	84
		Wistar rats	100 mg/kg	14 days	↑Time spent in target quadrant, ↓TNF-α, ↓IL-1β, ↓GFAP positive cells, ↓Activation of astrocytes, ↓Neuronal loss, ↓Severity of MFS, ↓Frequency of abnormal spikes, ↓Degree of SRS, ↓Escape latency	85
		Wistar rats	100, 200, 300 mg/kg	1 hour prior to PTZ injection	↑Latency to myoclonic jerks, ↑Latency to clonic seizures, ↑Latency to tonic-clonic seizures, ↓Seizure severity, ↓Oxidative stress, ↓Neuronal injury	86
		Sprague-Dawley rats	200, 300 mg/kg	2 weeks	↑Surviving neurons, ↑Beclin-1, ↑LC3BII/I, ↑Autophagosomes, ↓RIP-1, ↓Apoptotic neurons, ↓MLKL	87
		Mice	150 mg/kg	25 mins prior to PTZ injection	↑Seizure latency, ↑Tonic-clonic latency, ↑HTR7, ↓Duration of tonic & tonic-clonic seizures, ↓Death & falling parameters	88

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
		Wistar rats	100 mg/kg	5 months before induction of epilepsy & 1 after induction of epilepsy	↓Epileptiform activity, ↓$Na_v1.1$, ↓$Na_v1.6$, ↓Development & occurrence of seizures, ↓Epilepsy-associated MUA	89
		Sprague-Dawley rats	40, 80 μM	4 days prior to PTZ injection	↑Number of stimulations required to reach Racine stage IV seizures, ↑Delay in onset of seizures	90
		Wistar rats	80 mg/kg	4 days	↑Latency to onset of spasms & isolated clonic seizures ↓Duration of seizures, ↓Damage to hippocampus, ↓Seizure severity, ↓Muscle contraction, ↓Apoptosis	91
	Curcuminoids	Wistar rats	100 mg/kg	7 days	↑IL10RB, ↑CXCL16, ↑CXCL17, ↑NCSTN, ↑CX3CL1, ↑CX3CR1, ↑C3AR1, ↑CTSA, ↑CTSD	92
	Curcumin + Diazepam	Wistar rats	80 mg/kg + 5 mg/kg	4 days prior to PTZ injection	↑Latency to onset of spasms & isolated clonic seizures ↓Duration of seizures, ↓Damage to hippocampus, ↓Seizure severity, ↓Muscle contraction, ↓Apoptosis	91
	Curcumin + Piperine	Wistar rats (pregnant)	60 mg/kg + 10 mg/kg	Day 0 of gestation until parturition	↑Working memory, ↑Correct entries to goal box, ↓TLR4 in pups, ↓Hyperthermia, ↓TNF-α, ↓IL-10, ↓IL-1β, ↓MDA	93
	Curcumin Nanoparticles	Wistar rats	50 mg/kg	4 days prior to atropine & pilocarpine administration	↑AChE activity, ↑GSH, ↑ NO, ↓Oxidative stress, ↓Hippocampal TNF-α, ↓Caspase-3	94
	Liposomal curcumin	Swiss albino mice	25, 50 mg/kg	–	↑Seizure threshold, ↑Latency to myoclonic jerk, ↑Latency to clonic seizures, ↓Duration of clonic seizure	95
	Micronized curcumin	Zebra fish (adult & larvae)	0.5 mg/kg & 1 μM	–	↓Locomotion, ↓Seizure occurrence, ↓Occurrence of tonic-clonic seizures, ↓Occurrence of stage III seizures	96
Huntington's disease						
	Curcumin	CAG140 mice	555 ppm	23 weeks	↑DARPP-32, ↑D1 receptor, ↑Rearing, ↓D1, ↓CB1, ↓Huntingtin stained nuclei & aggregates, ↓Neuropil aggregates	97
		Drosophila	3, 5, 10, 15, 20 μM	1, 7, 14 days post-eclosion	↑Improvement in crawling ability, ↓Photoreceptor neuron degeneration, ↓Internal eye morphological defects, ↓Eye roughness, ↓Loss of pigmentation in eye, ↓Progressive loss of locomotion, ↓AO-positive cells, ↓Apoptotic cell death in eye discs, ↓Poly-Q-induced cytotoxicity	98
		Drosophila	10 μM	12 hours, 1, 7, 13 days after eclosion	↑Per, ↑Tim, ↓Motor deficits	99
		Drosophila	10, 15, 20 μM	From larval stage to till day 15 post eclosion	↑Improvement in motor activity, ↑Median survival, ↑dSREBP, ↓Abnormal body weight, ↓Abnormal dry weight, ↓Elevation in H_2O content, ↓Trehalose levels, ↓Dysregulation in total lipid content, ↓Lipid droplet size, ↓ROS, ↓Free radicals	100
	Curcumin, Bioperine	R6/2 line of transgenic mice	25 mg/kg, 1 mg/ kg	Entire gestation period, 3 weeks after offspring birth	↑DARPP-32, ↑p-Akt, ↑p-ERK, ↑Preserved normal levels of BDNF, ↑Normal intestinal function, ↑Intestinal emptying, ↑Intestinal contractility, ↑Claudin-2, ↑ZO-1, ↑Occludin, ↓Motor deficit ↓Hind clasping behavior, ↓Brain weight loss, ↓Number of $EM48^+$mHtt aggregates, ↓Body weight loss, ↓Villi loss and atrophy, ↓PAS^+ globet cells	101
	C-SLN	Wistar rats	40 mg/kg/day	7 days	↑SDH, ↑MTT reduction rate, ↑NADH dehydrogenase, ↑Cytochrome c oxidase, ↑Mitochondrial F_1F_0 synthase activity, ↑Cytochrome *a*, b, c1 & c, ↑GSH, ↑SOD, ↑Cytosolic & nuclear Nrf2, ↑Locomotor activity, ↑Average velocity to traverse the beam, ↑Stride length, ↓Mitochondrial swelling, ↓MDA, ↓Protein carbonyl, ↓ROS, ↓Total time to traverse the beam, ↓Distance between the two paws, ↓Stride width, ↓Gait angle	102

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
	SLCPs	YAC128 transgenic mice	100 mg/kg/day	Alternate days for 8 weeks	↑Length of dendrites, ↑Dendritic spine density, ↓Learning memory deficits, ↓Latency to escape, ↓PSD-95	103
Migraine						
	Curcumin	HUVECs	10, 20, 30, 40, 50 μM	12 hours	↑Cell viability after H_2O_2 treatment, ↑GSH, ↑SOD, ↑Bcl-2, ↓LDH, ↓ROS, ↓MDA, ↓p21, ↓Bax, ↓p53, ↓Caspase-3	104
		Wistar-Bratislava albino rats	100 mg/kg	14 days	↓MDA, ↓NO, ↓TOS, ↓Flinches, ↓Shakes	105
		Wistar-Bratislava albino rats	10, 20 mg/kg	30 mins after NTG injection	↑Total anti-oxidant capacity, ↑Thiols, ↓MDA, ↓TOS, ↓Flinches, ↓Shakes	106
		Wistar rats	10, 20 mg/kg	60 mins before NTG administration	↑Total anti-oxidant capacity, ↓Flinches, ↓Shakes, ↓Biphasic response to nociceptive receptors	107
	Liposomal curcumin	Wistar-Bratislava albino rats	10, 20 mg/kg	30 mins after NTG injection	↑Total anti-oxidant capacity, ↑Thiols, ↓MDA, ↓TOS, ↓Flinches, ↓Shakes	106
		Wistar rats	10, 20 mg/kg	60 mins before NTG administration	↑Total anti-oxidant capacity, ↓Flinches, ↓Shakes, ↓Biphasic response to nociceptive receptors	107
Multiple sclerosis						
	Curcumin	T cells	0.5-10 μg/mL	48 hours	↓IL-12, ↓p-JAK2, ↓p-TK2, ↓STAT3, ↓STAT4, ↓T cell proliferation	108
		$CD4^+$ T cells	5, 10, 20, 40, 60 μM	24, 48, 72 hours	↑Apoptosis, ↑Bax, ↓Cell proliferation, ↑Caspase-3, ↓Colony formation, ↓Bcl-2, ↓CD25, ↓CD44	109
		BV-2 cells	1–500 μM	24 hours	↑IL-10, ↓NO, ↓IL-6, ↓TNF-α, ↓iNOS, ↓AXL, ↓p-JAK2, ↓p-STAT3	110
		C8-D1A cells	10, 20, 50 μM	20, 24, 72 hours	↑Cell proliferation at low concentration, ↓IL-2, ↓IL-6, ↓TNF-α, ↓IL-17A, ↓IFNγ	111
		SJL/J mice	50, 100 μg	Every other day for 25 days	↓Clinical severity & duration, ↓IFNγ, ↓Inflammation, ↓Demyelination, ↓IL-12	108
		Lewis rats	100, 200 mg/kg	14 days	↓MMCS, ↓Disease severity, ↓Immune cell infiltration, ↓Th17 cell proliferation, ↓IL-17	112
		C57BL/6 mice	100 μg/day	14 days (alternate day)	↑T-bet, ↑IL-4, ↑IL-10, ↓Mean clinical score, ↓IFNγ, ↓IL-17, ↓$CD4^+$IFNγ^+ & $CD4^+$IL-17^+ T cells, ↓IL-12, ↓IL-23	113
		C57BL/6 mice	20 mg/kg	21 days	↑Forelimb strength, ↑TGF-β, ↑SOD, ↓Disease severity, ↓Disease onset scores, ↓Weight loss, ↓IL-6, ↓TNF-α, ↓IL-17A, ↓IFNγ, ↓Demyelination	114
		C57BL/6 mice	10 mg/kg/day	15 days	↑LC3II, ↑Beclin, ↑Atg5, ↓p-Akt, ↓p-mTOR, ↓Infiltrated immune cells, ↓Demyelination, ↓p62, ↓IL-17, ↓IFNγ	115
		Wistar rats	20, 40 μg/kg	5 days	↑Distance travelled, ↓TAC, ↓CAT, ↓Escape latency, ↓SOD, ↓MDA	116
		Wistar rats	100 mg/kg/day	From 12th day for 24 days	↑MBP, ↑Reduction in weight loss, ↓iNOS, ↓Cumulative disease disability, ↓NOGO-A	117
		C56BL/6 mice	100 mg/kg	2 days prior to immunization to 21 days post immunization	↓Infiltrated immune cells, ↓Demyelination, ↑Arg-I, ↑IL-10, ↑TGF-β, ↓COX-2, ↓IL-1β, ↓iNOS, ↓Activation of microglia, ↓AXL, ↓TMEM119	110
		C56BL/6 mice	100 mg/kg	15 days	↑Sniffing of the novel object, ↑GSH, ↑SOD, ↑MBP, ↓Neurological severity, ↓Paralysis with neurological score, ↓Infiltration of immune cells, ↓Demyelination in spinal cord, ↓LTCD3, ↓LTCD4, ↓Behavioral abnormality, ↓MDA	111
	Curcumin-linoleic acid conjugate	Wistar rats	20, 40 μg/kg	5 days	↑Distance travelled, ↑TAC, ↓CAT, ↓Escape latency, ↓SOD, ↓MDA	116
	Dendrosomal nanocurcumin	NSCs	1, 5 μM	24 hours	↑NSCs proliferation, ↑$MAP2^+$ cells, ↑MBP^+ cells, ↑NeuN, ↑Olig2, ↑Remyelination, ↑Differentiation of NSCs into oligodendroglial cells, ↓Differentiation of NSCs into astrocytes	118
		C57BL/6 mice	12.5 mg/kg	3 weeks	↑Remyelination, ↑MBP, ↑$CC1^+$/$Olig2^+$ cells	118

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
		C57BL/6 mice	12.5 mg/kg	6 weeks	↑Olig2$^+$ cells, ↑LFB staining, ↑MBP, ↓Number of microglial cells, ↓GFAP$^+$ cells, ↓Astrocyte activation	119
	Curcumin loaded HDL mimicking peptide-phospholipid scaffold	C57BL/6 mice	1.8 mg/kg	4 alternate days from 8th day (i.e. 8th, 10th, 12th, and 14th day)	↑Delay in disease progression, ↓Morbidity, ↓Immune cell infiltration, ↓CD45$^+$ cells, ↓CD45$^+$CD11b$^+$Ly6C$^+$CCR2$^+$ monocytes infiltration, ↓CD11b$^+$ cells, ↓CD3$^+$ T cells, ↓Th1 cells, ↓Th17 cells, ↓DC maturation, ↓DIR-BOA$^+$ monocytes	120
	Polymerized nanocurcumin	Lewis rats	12.5 mg/kg/day	Day 12–29 post-immunization	↑Myelination, ↑IL-4, ↑IL-10, ↑HO-1, ↑NGF, ↑MBP, ↑Nestin, ↑Olig2, ↑PDGFR-α, ↓Peak & cumulative EAE scores, ↓MCP-1, ↓IL-1, ↓Demyelination, ↓iNOS, ↓EAE score, ↓TNF-α receptor, ↓IL-17, ↓CD8	121
Neuroblastoma						
	Curcumin	SH-SY5Y	2.5, 5, 10, 20, 40, 80 μM	2–24 hours	↑Nuclear translocation of TFEB, ↑HO-1, ↑LAMP-1, ↑LC3II, ↑Nrf2 translocation, ↑MCOLN1, ↓GSK-3β, ↓p62, ↓ROS, ↓Aggregation of APP	122
		SH-SY5Y	1, 2.5, 5, 10, 15 μM	24 hours	↓p-JNK/JNK ratio, ↓p-ERK, ↓p-Tau, ↓LC3BII/I, ↓H_2O_2-induced oxidative stress, ↓UBC9, ↓SUMO-1ylation	123
	Curcumin, Curcumin-Mn complexes	NG108–15	1–50 μg/mL	-	↑Cell viability, ↓H_2O_2, ↓Oxidative stress	124
Neurotoxicity						
aluminium- induced toxicity	curcumin	wistar rats	100 mg/kg/day	60 days	↑Mg^{2+}, ↑CAT, ↑Na^+-K^+-ATPase activity, ↑Mg^{2+} ATPase activity, ↑Improvement in hippocampal structure, ↓Ca^{2+}	125
	Curcumin	Wistar albino rats	100 mg/Kg	60, 90 days	↑Body weight, ↑Memory recognition, ↑SOD, ↑CAT, ↑Hippocampal cell viability, ↑Normal morphology of neuronal cells, ↓Memory deficit, ↓Absolute hippocampus weight, ↓Time spent in the dark room, ↓Hippocampal AChE, ↓MDA, ↓Oxidative stress, ↓IFNγ, ↓IL-4, ↓Karyopyknotic neuronal cells, ↓Neutrophil infiltration, ↓Neurofibrillary tangles, ↓Hippocampal cell apoptosis	126
Parkinson disease						
	Curcumin	PC12 cells	20, 40 μmol/L	24 hours	↑Bcl-2, ↓MPP$^+$-induced cytotoxicity & apoptosis, ↓Loss of MMPo, ↑Attenuation of ROS increase, ↓iNOS	127
		SH-SY5Y cells	5, 10, 50 μM	24, 48 hours	↑α-Synuclein solubility, ↓α-Synuclein aggregation	128
		MES23.5 cells	10, 15 μmol/L	–	↑Restoration of MMPo, ↑SOD, ↓6-OHDA-induced cytotoxicity, ↓ROS, ↓6-OHDA-induced NF-κB translocation	129
		Rat mesencephalic cells	10 nM	3, 6, 12, 24 hours	↑LRRK2	130
		SH-SY5Y cells	0.5, 1, 5, 10, 25, 50 μM	18 hours	↑Cell viability, ↓MPP$^+$-induced cell death, ↓MPP$^+$-induced nuclear condensation, ↓MPP$^+$-induced cleaved caspase-3, p-JNK, MKK4 activation, & p-c-Jun	131
		SH-SY5Y cells	4 μM	2-24 hours	↓α-Synuclein-induced toxicity, ROS, caspase-3 activity, & apoptosis	132
		SH-SY5Y cells	5, 10, 20 μM	30 mins prior to 6-OHDA treatment	↑Cell viability, ↓6-OHDA-induced cytotoxicity, ↓6-OHDA-induced cell death, ↓6-OHDA-induced ROS, ↓Bax/Bcl-2 ratio, ↓p-p53	133
		PC12 cells	500 nM	–	↓α-Synuclein-induced toxicity, cell death, ROS, mitochondrial depolarization, cytochrome c release, caspase-3 activity, caspase-9 activity	134
		Deutocerebrum primary cells	5, 10, 15 μmol/L	6 days	↑Cell viability, ↑Cell adhesion, ↑Normal cell morphology, ↑SOD, ↑GSH-Px, ↑Wnt3a, ↑β-catenin, ↑c-MYC, ↑Cyclin D1, ↓MDA, ↓Apoptosis, ↓MMPo	135

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
		SH-SY5Y PD cells	1, 2.5, 5, 10, 20, 25 μmol/L	24, 48 hours	↑Cell proliferation, ↑MAP2 cells, ↑TH-positive cells, ↓Apoptosis	136
		PC12 cells	0.5, 1, 2, 5, 10 μM	6 hours	↑Beclin-1, ↓6-OHDA-induced apoptosis, ↓ROS, ↓MDA, ↓p-Akt, ↓p-mTOR	137
		Sprague-Dawley rats	50 mg/kg	Daily for 4 days prior to 6-OHDA injection	↓Mean percentage of TH-positive cell loss, ↓Loss of DOPAC, ↓Loss of HVA	138
		Swiss albino mice	80 mg/kg	7 days	↑SOD, ↑CAT, ↑GSH, ↓Lipid peroxidation	139
		C57BL/6 mice	50 mg/kg/day	7 days	↑Locomotion frequencies, ↑Traction scores, ↑Rearing frequencies, ↓MPTP-induced impairment in dopamine nervous system, ↓Activated astrocytes, ↓p-JNK1/2, ↓c-Jun, ↓Cleaved caspase-3	131
		Wistar rats	50 mg/kg/day	10 days	↑Locomotion, ↑Number of Nissl neurons, ↓Bax/Bcl-2	140
		Wistar rats	50 mg/kg	24 days	↑DOPAC, ↑TH-positive cells, ↓Iron stained cells	141
		ICR mice	200 mg/kg	7 days	↑TH-positive cells, ↓Microglia activation, ↓Astrocyte activation	142
		ICR mice	200 mg/kg/day	7 days	↑TH-positive cells, ↓Loss of DA neurons, ↓Microglia activation, ↓GFAP	143
		Sprague-Dawley rats	5, 10, 20 mg/kg/day	30 days	↑SOD, ↑GSH-Px, ↑AChE, ↑Improvement in neuroethological condition, ↑DA, ↑ SN cell mass, ↑SN cell cytoarchitecture, ↑bFGF, ↑NGF, ↑TrkA, ↑Hsp70, ↓Aberrated alteration in behaviour, ↓MDA	144
		Sprague-Dawley rats	10 μmol/L	One each day for 3 consecutive days	↑Motor latency, ↑SOD, ↑Residence time on rotarod, ↑GSH-Px, ↑TH-positive cells, ↑Wnt3a, ↑β-catenin, ↑c-MYC, ↑Cyclin D1, ↓Rotation numbers, ↓Dopaminergic neuron death, ↓GFAP astrocytes activation, ↓MDA	135
		Swiss albino mice	80 mg/kg/day	12 days	↑Time spent on wire, ↑NE level, ↑DA level, ↑GSH, ↑SOD, ↑ATP, ↑SDH, ↓CRP, ↓IL-6, ↓A_{2A}R expression, ↓α-synuclein, ↓MDA, ↓Ang-II, ↓Caspase-3, ↓DNA fragmentation, ↓Neurodegeneration changes in cells	145
		C57BL mice transplanted with hUC- MSCs-CUR	–	–	↑Improvement in rearing, ↑TH-positive cells, ↑Bcl-2, ↑DA levels, ↑IL-10, ↑HGF, ↑NGF, ↑VEGF, ↑G-CSF, ↓NADPH-d, ↓Bax, ↓Caspase-3, ↓Drop frequency	136
		6-OHDA lesioned Parkinsonian rats	200 mg/kg	2 weeks pre- and post- surgery	↑TH-positive cells, ↑Neuroprotective effect, ↑Neuronal count	146
		6-OHDA lesioned Parkinsonian rats	50 mg/kg/day	2 weeks	↑Parkinsonian disability score, ↑Autophagy score, ↓α-Synuclein, ↓TH, ↓p62	137
	Curcumin, Curcumin-Mn complexes	ICR mice	6.25, 25, 50 mg/kg	Three times at 1, 3, 7 hours post MPTP injection	↑Cognitive functions, ↓Learning memory impairment, ↓MPTP-induced striatal dopamine depletion, ↓Oxidative stress, ↓Dopaminergic neuronal damage	124
	Curcumin, Rotenone	Swiss albino mice	50, 100, 200 mg/kg, 1 mg/kg	3 weeks	↑Improvement in rotarod activity, ↑Recovery of retention time on rotarod, ↑Improvement in locomotor activity, ↑Improvement in rearing, ↑Immobility time, ↑Grooming behaviour, ↑SOD, ↑GSH, ↑CAT, ↑SDH, ↑MTT reduction activity, ↓MDA, ↓Nitrite, ↓AChE	147
	Curcumin, THC	Swiss albino mice	20, 40, 80, 160 mg/kg, 60 mg/kg	7 days	↑DA, ↑DOPAC, ↓MAO-B activity	148
	Curcumin monoglucoside	N27 cells	0.25, 0.5, 1, 2.5 5 μM	24 hours	↑Cell viability, ↑GSH, ↑NQO1, ↑Complex I & complex IV activities, ↓LDH release, ↓ROS, ↓Hydroperoxides, ↓MDA, ↓NOS2, ↓DNA damage, ↓p-JNK, ↓p-c-Jun, ↓Cleaved procaspase-3	149
		D. melanogaster	10, 100, 500, 1000 μM	14 days	↑Free radicals scavenging, ↑GSH, ↓Mortality, ↓Locomotor deficits, ↓Turnover of DA, ↓(DOPAC+HVA)/DA	149

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
	Curcumin nano emulsions	Swiss mice	25, 50 mg/kg/day	30 days	↑Total distance travelled, ↑Number of rearings, ↑CAT, ↑Exploratory activity, ↑Improvement in balance, ↑GR activity, ↓Number of slip steps, ↓Bradykinesia, ↓TBARS, ↓GSH-Px, ↓Complex I inhibition by ROT	150
	Curcumin loaded HSA NPs	C. elegans	10, 30 μg/mL	24, 72, 120 hours	↑Delay in age-related deterioration of movement, ↑Alcohol avoidance, ↑DA, transportation, ↓Movement speed	151
	hEnSCs-EXOs-CUR	PC12 cells	–	–	↑Cell viability	152
		C57BL/6 mice	1 mg/mL	10 times every other day for 28 days	↑TH-positive cells, ↑Motor latency, ↑Bcl-2, ↓Rotational numbers, ↓α-Synuclein, ↓Bax, ↓Caspase-3	152
	PR-EXO/PP@CUR nanocarrier	C57BL/6 mice	9, 12 μg/mL curcumin	6 h	↑Improvement in movement, ↑Improvement in coordination ability, ↑DA, ↑DOPAC, ↓α-Synuclein aggregates, ↓TNF-α, ↓IL-1β, ↓IL-6	153
	Soluplus-curcumin formulation	C57BL/6 mice	48 mg/kg	8 weeks (from 2 weeks after the LPS injection until the end of the study)	↓Parkin protein, ↓p-Rab-10, ↓PINK1	154
Traumatic brain injury						
	Curcumin	Microglia	0.5, 1, 2, 5, 10 μM	–	↑IκB-α, ↓Cleaved caspase-3, ↓Neuronal damage, ↓Microglia activation, ↓IL-6, ↓IL-1β, ↓p-IκB-α, ↓NF-κB, ↓RANTES	155
		Sprague-Dawley rats	500 ppm	4 weeks	↑BDNF, ↑p-Synapsin I, ↑Swimming timing in the target zone, ↓Oxidized proteins, ↓Escape latency	156
		Sprague-Dawley rats	500 ppm	4 weeks	↑p-AMPK/AMPK, ↑uMtCK, ↑UCP2, ↑Sir2, ↑COX-2	157
		CD-1 mice	75, 150, 300 mg/kg	15 mins prior to TBI or 30 mins to 1hr prior to TBI	↑Overall locomotion, ↑Time spent on exploring a novel object, ↓Brain water content, ↓Cerebral edema, ↓AQP4, ↓IL-1β, ↓GFAP, ↓p-NF-κB	158
		Wistar rats	50, 100 mg/kg	5 days before TBI	↑Motor performance, ↑Recovery of balance, ↓Lesion volume, ↓MDA	159
		C57BL/6 mice	50, 100, 200 mg/kg	15 mins post TBI	↑IκB-α, ↓TLR4, ↓Cerebral edema, ↓Brain water content, ↓MCP-1, ↓IL-1β, ↓IL-6, ↓TLR4$^+$ microglia/macrophages, ↓TNF-α, ↓RANTES, ↓NF-κB, ↓p-IκB-α, ↓MyD88	155
		ICR mice	50, 100 mg/kg	30 mins post TBI	↑Bcl-2, ↑GSH-Px, ↑SOD, ↑HO-1, ↑NQO-1, ↑Nuclear Nrf2, ↓NSS score, ↓Brain water content, ↓Cerebral edema, ↓Neuronal apoptosis, ↓Cleaved caspase-3	160
		C57BL/6 mice	50 mg/kg	15 mins post TBI	↑Nuclear Nrf2, ↑HO-1, ↑NQO-1, ↑Bcl-2, ↓Cleaved caspase-3, ↓MPO$^+$ cells, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓MDA	161
		Sprague-Dawley rats	100 mg/kg/day	Every other day for 7 days	↑Body weight, ↑Liver weight, ↑T3, ↑T4, ↑TSH, ↑SOD, ↑Tg, ↑FOXE1, ↑TSHR, ↑TSHβ, ↓Thyroid weight, ↓MDA, ↓TRHR, ↓TTR, ↓GSH-Px, ↓Infiltration of immune cells, ↓ROS, ↓NF-κB, ↓Follicular cavity size, ↓PAX8, ↓TTF1, ↓NIS, ↓TPO	162
	CNB-001	Sprague-Dawley rats	500 ppm	2 weeks	↑BDNF, ↑Synapsin I, ↑CREB, ↑SOD, ↑Learning ability, ↓Foot faults, ↓Oxidized protein levels	163
	THC	Sprague-Dawley rats	10, 25, 50 mg/kg	30 mins post TBI	↑Nrf2 nuclear translocation, ↑Bcl-2, ↑SOD, ↑GSH-Px, ↓Cerebral edema, ↓Brain water content, ↓Neuronal degeneration, ↓Bax, ↓Cleaved caspase-3, ↓MDA	164
		Sprague-Dawley rats	25, 50 mg/kg	30 mins post TBI	↑LC3II, ↑Beclin, ↑p-Akt, ↓Neurological deficits, ↓Brain water content, ↓Number of damaged neurons, ↓Neuronal apoptosis, ↓Cleaved caspase-3, ↓p62	165

(*continued on next page*)

Table 1 (*continued*)

Disease/Condition	Curcumin formulation	Cell line / Animal model	Dose	Duration	Effects	Refs.
	CM-NPs	Wistar rats	50 mg/kg	Post TBI for 10 days	↓mNSS score, ↓Brain water content, ↓Cerebral edema, ↓Iba-1$^+$ cells, ↓GFAP$^+$ cells, ↓TLR4$^+$ cells, ↓NF-κB^+ cells	[166]

Abbreviations.
6-OHDA, 6-hydroxy dopamine; $A_{2A}R$, Adenosine 2A receptor; ABCA1, ATP-binding cassette subfamily A member 1; $A\beta_{42,}$ Amyloid beta 42; AChE, Acetylcholinesterase; ADAM10, ADAM metallopeptidase domain 10; AGE, Advanced glycation end products; ALS, Amyotrophic lateral sclerosis; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; Ang-II, Angiotensin II; AO, Acridine orange; ApoA1, Apolipoprotein A1; ApoE4, Apolipoprotein E4; APP, Amyloid beta precursor protein; Aps, Action potentials; AQP4, Aquaporin 4; Arg-I, Arginase 1; Atg5; Autophagy related gene 5; ATP, Adenosine triphosphate; Bax, Bcl-2 associated X-protein; Bcl-2, B cell lymphoma 2; BDNF, Brain-derived neurotrophic factor; bFGF, Basic fibroblast growth factor; bmm, brummer gene encodes for triglyceride lipase in *Drosophila*; C3A, Complement 3A; C3AR1, Complement 3A receptor 1; C5A, Complement 5A; CAT, Catalase; CCR2; C–C motif chemokine receptor 2; CD25, Cluster of differentiation 25; CD44, Cluster of differentiation 44; CD68, Cluster of differentiation 68; COX-2, Cyclooxygenase-2; CREB, Cyclic AMP response element binding protein; CTSA, Cathepsin A; CTSD, Cathepsin D; CX3CL1, Chemokine (C-X-C motif) ligand 1; CXCL16, Chemokine (C-X-C motif) ligand 16; CXCL17, Chemokine (C-X-C motif) ligand 17; CX3CR1, Chemokine (C-X3-C motif) receptor 1; D1, Dopaminergic receptor 1; DA, Dopamine; DAB, 1,2-Diacetylbenzene; DAP12, DNAX activation protein 12; DARPP-32, Dopamine- and cAMP-regulated phosphoprotein 32 kDa; DC, Dendritic cells; DCX, Doublecortin; DiR-BOA, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide bisoleate; DOPAC, Dihydroxyphenyl acetic acid; DPH, Diphenylhexatriene; EAE, Experimental autoimmune encephalomyelitis; eIF2, Eukaryotic translation initiation factor alpha; ER, Endoplasmic reticulum; ERK, Extracellular signal-regulated kinase; ERS, Endoplasmic reticulum stress; FOXE1, Forkhead box E1; FRAP, Ferric reducing antioxidant power; Gab2, Growth factor receptor bound protein 2-associated protein 2; GABA, Gamma amino-butyric acid; G-CSF, Granulocyte colony stimulating factor; GFAP, Glial fibrillary acidic protein; GPx, Glutathione peroxidase; GSH, Glutathione reduced; GSK-3β, Glycogen synthase kinase 3 beta; GST, Glutathione S transferase; GRP78, Glucose-regulated protein 78 kDa; GTCS, Generalized tonic-clonic seizure; H_2O, Water; H_2O_2, Hydrogen peroxide; HDL, HGF, Hepatocyte growth factor; High density lipoprotein; HMGB1, High mobility group box 1; HMW, High molecular weight; HO-1/HMOX1, Heme oxygenase 1; HSP70, Heat shock protein 70; HSP90, Heat shock protein 90; HTR, Hydroxy tryptamine receptor; HVA, Homovanilic acid; Iba-1, Ionized calcium binding adapter molecule 1; IDE, Insulin degrading enzyme; IFNγ, Interferon gamma; IL-1; Interleukin 1; IL-1α, Interleukin 1 alpha; IL-1β, Interleukin 1 beta; IL-4, Interleukin 4; IL-6, Interleukin 6; IL-10, Interleukin 10; IL10RB, Interleukin 10 receptor beta; IL-12; Interleukin 12; IL-17, Interleukin 17; IL-23, Interleukin 23; iNOS, Inducible nitric oxide synthase; IRE1-α, Inositol requiring enzyme 1 alpha; JAK2, Janus kinase 2; JMJD3, Jumonji domain containing protein 3; JNK, c-Jun N-terminal kinase; KRAS, Kristen rat sarcoma virus; LAMP-1; Lysosomal associated protein 1; LC3B, Light chain 3B; LDH, Lactate dehydrogenase; LFB, Luxol fast blue; LTCD3; Lymphocyte cluster of differentiation 3; LTCD4; Lymphocyte cluster of differentiation 4; LXR-β, Liver X receptor beta; MAP2; Microtubule associated protein 2; MAPK, Mitogen-activated protein kinase; MAO-B, Monoamine oxidase B; MBP, Myelin basic protein; MCOLN1, Mucolipin 1; MCP-1, Monocyte chemoattractant protein 1; MDA, Malondialdehyde; Mfn2, Mitofusin 2; MFS, Mossy fiber sprouting; MKK4, Mitogen activated protein kinase 4; MLKL, Mixed lineage kinase domain-like; MMP, Matrix metalloprotease; MMPo, Mitochondrial membrane potential; MPO, Myeloperoxidase; MPP, 1-Methyl-4-phenylpyridinium ion; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR, Mammalian target of rapamycin; MTT, 3-(4,5-dimethylthiozolyly-2)−2,5-diphenyltetrazolium bromide; MUA, Multiple-unit activity; MYD88, Myeloid differentiation primary response 88; NAD, Nicotinamide adenine dinucleotide; NA_v current, Voltage-gated sodium current; NCSTN, Nicastrin; NF-κB, Nuclear factor kappa B; NGF, Nerve growth factor; NIS, Sodium iodide symporter; NLRP3, NACHT, LRR, and PYD domain containing protein 3; NO, Nitric oxide; NOS2, Nitric oxide synthase 2; NQO1, NADPH quinone dehydrogenase 1; NSC, Neural stem cells; Nrf2, Nuclear factor erythroid 2-related factor 2; NSS, Neurologic severity score; NTG, Nitroglycerin; Olig2; Oligodendrocyte transcription factor 2; PAS$^+$, Periodic acid-Schiff positive; PAX8, Paired box 8; PCS, Peripheral cholinergic signs; PDGRF-α, Platelet-derived growth factor alpha; Per, Period; PERK, Pancreatic EIF-2 alpha kinase; PKB, Protein kinase B; PKC, Protein kinase C; PSD-95, Postsynaptic density protein 95; RAGE, Receptor for advanced glycation end products; RANTES, Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; RIP-1, Receptor interaction protein kinase 1; ROS, Reactive oxygen species; RXR-α, Retinoid X receptor alpha; ROT, Rotenone; SDH, Succinate dehydrogenase; SE, Status epilepticus; SREBP, Steroid regulatory proteins; Sir2, Silent information regulator 2; SIRT1, Sirtuin 1; SIRT3, Sirtuin 3; SN, Substantia nigra; SOD, Superoxide dismutase; SRS, Spontaneous recurrent seizures; STAT3, Signal transducer and activator of transcription 3; STAT4, Signal transducer and activator of transcription 4; STM, Stereotyped movements; TAC, Total antioxidant capacity; TBARS, Thiobarbituric acid-relative substances; TC, Total cholesterol; TDP-25, TAR DNA binding protein 25; TDP-43, TAR DNA binding protein 43; TFEB, Translocation of transcription factor EB; Tg, Thyroglobulin; TG, Thapsigargin; TGF-β, Transforming growth factor beta; TH, Tyrosine hydroxylase; Th17 cells, T helper 17 cells; THC, Tetrahydrocurcumin; Thrb, Thyroid hormone receptor beta; Tim, Timeless; TK2; Tyrosine kinase 2; TLR4, Toll-like receptor 4; TMEM119, Transmembrane protein 119; TNF-α, Tumor necrosis factor alpha; TOS, Total oxidative status; TPO, Thyroid peroxides; TREM1, Triggering receptor expressed on myeloid cells 1; TRHR, Thyrotropin-releasing hormone receptor; TrkA, Tyrosine kinase A; TSH, Thyroid stimulating hormone; TSHβ, Thyroid stimulating hormone beta;TSHR, Thyroid stimulating hormone receptor; TTF1, Thyroid transcription factor 1; TTR, Transthyretin; UBC9, Ubiquitin conjugating enzyme 2-homologus to yeast UBC9; UCP2, Uncoupling protein 2; uMtCK, Ubiquitous mitochondrial creatinine kinase; VEGF, Vascular endothelial growth factor; WT, Wild type; ZO-1, Zonula occludens 1.

ory, escape latency, spatial memory retention, platform crossing frequency, amyloid protein plaques, and swimming speed. Curcumin was also shown to augment the expression of ABCA1, ApoA1, RXR-α, LXR-β, BDNF, JMJD3, and high density lipoprotein (HDL) levels and down-regulated glial fibrillary acidic protein (GFAP), COX-2, cluster of differentiation (CD68), HMGB1, TLR4, advanced glycation end product-specific receptor (RAGE), NF-κB, H3K27me3 BDNF and total cholesterol (TC) levels.[42,43,44] Another study demonstrated that bisdemethoxycurcumin treatment for 1 month resulted in improved cognitive function, number of neurons, SIRT1, oxidative stress and markedly alleviated Aβ deposition.[59] Besides, THC was found to ameliorate learning capabilities, memory, escape latency and inhibit Aβ burden, $A\beta_{42}/A\beta_{40}$ levels in APP/PS1 mice. THC was also shown to enhance the expression of Gab2 and K-Ras levels and suppress TNF-α and TGF-β1 levels in these mice models.[63] In addition, curcumin magnetic nanoparticles (Cur-MNPs) have been shown to ameliorate memory, spatial learning, escape latency, finding the blind platform time, amyloid plaques, neuron generation, Aβ in brain, microglia activation, inflammation, BDNF levels, doublecortin (DCX) levels, NLRP3 inflammasome formation, IL-18 levels, and CD68 levels in APP/PS1 mice.[53] Recently, Lin et al., synthesized novel poly(lactic-co-glycolic acid) (PLGA)-poly(ethylene glycol) (PEG) combined thermo-sensitive hydrogel loaded with curcumin (PGC) and reported that PGCs reduce β-secretase, Aβ aggregation, Aβ-induced neurotoxicity, and ROS levels in neuronal cell lines.[60] HDL-inspired nano scavenger that contains curcumin, β-site APP cleavage enzyme 1 (BACE1) siRNA, and phosphatidic acid functionalized HDL (pHDL) (pHDL/Cur-siBACE1) treatment was shown to improve focused search strategies, Aβ burden, NF-κB, neuronal inflammation, escape latency, and memory deficits in APP/PS1 mice. Mechanistic studies have revealed that pHDL/Cur-siBACE1 nano scavengers eliminate Aβ plaque and suppress IκB-α, and inflammatory cytokines including TNF-α, IL-6 and IL-1β levels *in vitro*.[61]

Several studies have revealed that scopolamine, a nonselective and competitive inhibitor of muscarinic acetylcholine receptor, causes

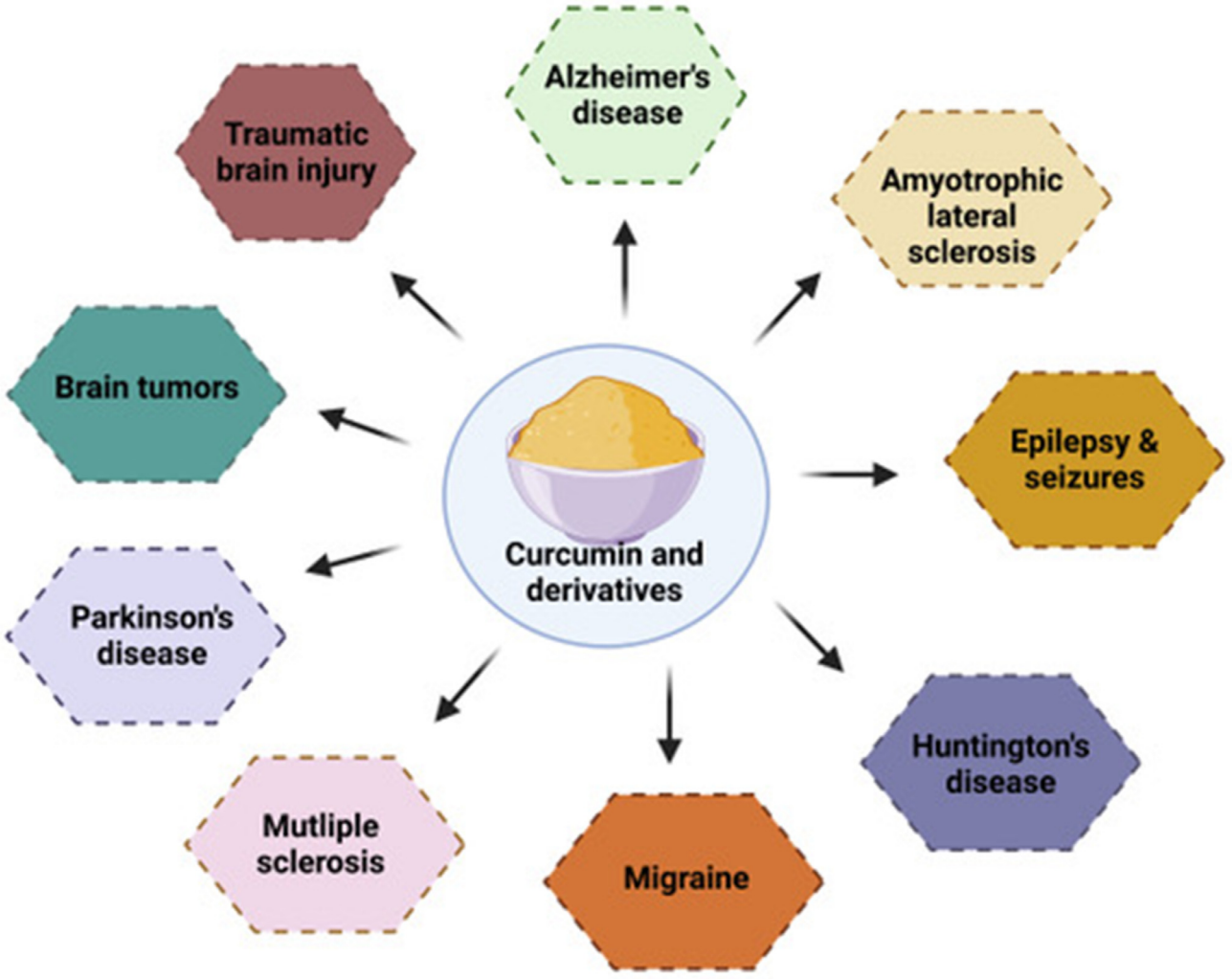

Fig. 2. Illustrates the curcumin activity against various NDs.

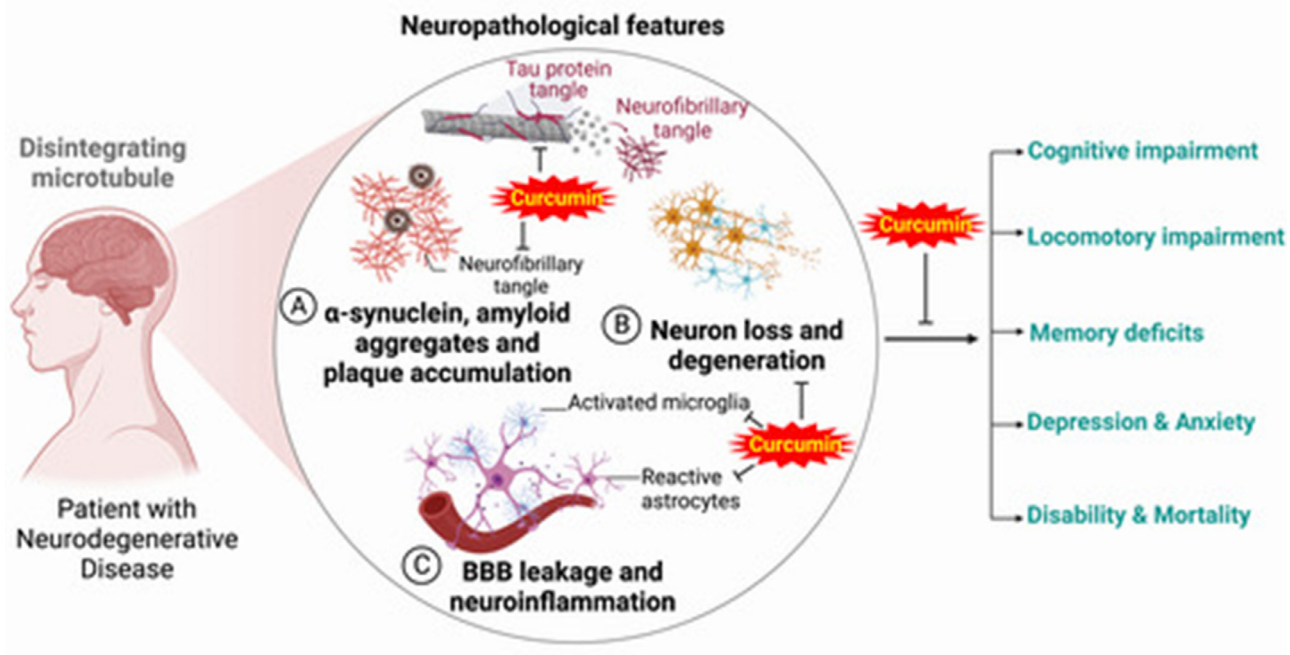

Fig. 3. Neuropathological features associated with commonly occurring NDs and their outcomes.

Table 2
Effect of Curcumin on Various Neurological Diseases in Humans.

Disease	Curcumin & its formulation	Dose	Duration	Effects	Refs.
Alzheimer's disease					
	C3 complex	2 g/day, 4 g/day	24 weeks	↑Glucose, ↓Hematocrit	167
	Longvida	40 g/day	2 days	↑Detection of amyloid spots (aided in diagnosis)	168
	Theracurmin	180 mg/day	18 months	↑Improvement in memory, ↓Tau, ↓Amyloid	169
ALS					
	Curcumin	600 mg/day	6 months	Stable score of ALS-FRS-r, Stable FRAP values, ↓Lactate, ↓AOPPs	170
	Nanocurcumin	80 mg/day	12 months	↑Survival	171
Migraine					
	Curcumin	1000 mg/day	8 weeks	↓CGRP, ↓IL-6, ↓Severity, ↓Headache frequency, ↓Duration of headache	172
	Nanocurcumin	80 mg/day	2 months	↓Frequency of headache attack	173
		80 mg (1 capsule/day)	2 months	↓IL-6 mRNA, ↓IL-6, ↓hs-CRP	174
		80 mg (1 capsule/day)	2 months	↓COX-2, ↓Frequency of attack, ↓Severity of pain	175
		80 mg	2 months	↓Pentraxin-3	176
		80 mg	2 months	↓IL-17 mRNA and serum levels	177
		80 mg/day	8 weeks	↓Headache frequency, severity, & duration	178
		80 mg/day	2 months	↓Headache frequency	179
		80 mg/day	2 months	↓MCP-1, ↓Headache attack frequency, ↓Headache severity & duration	180
	Nanocurcumin + Coenzyme Q10	80 mg/day +300 mg/day	8 weeks	↓Headache frequency, severity, & duration	178
	Nanocurcumin + ω−3 FA		2 months	↓Frequency of headache attack, ↓TNF-α	173
		80 mg/day + 2500 mg/day			
			2 months	↓ Frequency of headache attack, ↓Serum ICAM-1 levels	181
		80 mg (1 capsule /day) + 2500 mg (1 capsule/day)	2 months	↓IL-6 mRNA, ↓IL-6, ↓hs-CRP	174
		80 mg (1 capsule/day) + 1800 mg (2 capsules/day)	2 months	↓COX-2, ↓iNOS, ↓Frequency of attack, ↓Headache duration	175
		80 mg	2 months	↓VCAM	182
		80 mg/day	2 months	↓Headache frequency, ↓IL-1β	179
Multiple sclerosis					
	Nanocurcumin	–	6 months	↑miR-145, ↑SOX2, ↑Sirtulin 1, ↑FOXP3, ↑PDCD1, ↑STAT5, ↓miR-132, ↓miR-16, ↓STAT1, ↓NF-κB, ↓AP-1, ↓IL-6, ↓TNF-α, ↓IL-1β, ↓IFNγ, ↓CCL2, ↓CCL5	183
		80 mg/day	6 months	↓Th17 cells, RORγt, IL-17	184
		–	6 months	↑Restoration of dysregulated miRNAs, ↓Demyelinating inflammation	185
		80 mg/day	6 months	↑Frequency of T-reg cells, ↑FoxP3, ↑TGF-β, ↑IL-10	186
Parkinson's disease					
	Curcumin	80 mg/day	9 months	↓MDS-UPDRS part III score	187
Spinal cord injury					
	Curcumin	110 mg/kg/day	6 months	↑BMD indicators of lumbar, femoral neck, & hip	188
	Curcumin + anti-inflammatory diet	1200 mg/day	12 weeks	↑TRP/LNAA ratio, ↓IL-6, ↓IL-1β, ↓IFN-γ, ↓CRP, ↓Proinflammatory composite score	189
Traumatic brain injury					
	Curcuminoids (C3 complex) +piperine	500 mg/day + 5 mg/day	7 days	↓Leptin	190

Abbreviations.
ALS, Amyotrophic lateral sclerosis; ALS-FRS-r, Revised ALS Functional rate scaling; AOPPs, Advanced oxidative protein products; AP-1, Activator protein 1; CCL2, C–C motif chemokine ligand 2; CCL5, C–C motif chemokine ligand 5; CGRP: Calcitonin gene related peptide; CRP, C-reactive protein; FOXP3: Forkhead box P3; FRAP, Ferric reducing antioxidant power; COX-2, Cyclooxygenase 2; hs-CRP, Heat-sensitive C-reactive protein; ICAM, Intracellular adhesion molecule; IFNγ, Interferon gamma; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-17, Interleukin 17; LNAA, Large neutral amino acids; MCP-1, Monocyte chemoattractant protein-1; MDS-UPDRS, Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale; mRNA, Messenger ribonucleic acid; NF-κB: Nuclear factor kappa B; PDCD1, Programmed cell death 1; RORγt, Retinoic-acid-receptor-related orphan nuclear receptor gamma; SOX2, SRY-box transcription factor 2; STAT1, Signal transducer and activator of transcription 1; STAT5, Signal transducer and activator of transcription 5; TGF-β, Transforming growth factor-beta; Th17 cells, T helper 17 cells; TNF-α, Tumor necrosis factor alpha; TRP, Tryptophan.

oxidative stress, neuronal inflammation, mitochondrial dysfunction, and apoptosis. The scopolamine lesioned animal models were shown to display the similarity with cholinergic hypothesis of aging and AD.[45,207–209] Treatment of scopolamine lesioned rat models with curcumin (200 mg/kg/day) for 7 days has been reported to remarkably reduce the length and time taken to reach the platform. Curcumin treatment was also shown to reduce the IL-6 levels significantly in these rats.[45] A novel curcumin derivative, curcumin glucoside has been found to enhance GSH, FRAP and reduce protein carbonyls and memory impairments in scopolamine induced AD Wistar rats.[47]

Another chemical streptozotocin (STZ), a glucosamine derivative, is known to preferentially damage the pancreatic β cells and is often used

to induce diabetes in animal models. Substantial amount of literature provide the evidence that STZ injected intracerebroventricularly at a sub diabetic level cause cognitive impairment, oxidative stress, Aβ deposition, neuronal inflammation, and memory deficits similar to manifestations in sporadic AD.[55,210] The nanocurcumin administration was reported to alleviate the oxidative stress in STZ AD rat models by inducing GST, CAT, GSH-Px, SOD, insulin degrading enzymes (IDE), a disintegrin and metalloproteinase domain 10 (ADAM 10), and BDNF levels.[54] The regimen was also found to enhance the Bcl-2 and suppress Aβ−42, AGEs, thiobarbituric acid reactive substances (TBARS), NO, TNF-α, IL-1β, AChE, Bax, phospho p38MAPK, phospho ERK, phospho MEK and phospho Tau levels in these models and thereby improving the normal architecture of pyramidal cells, memory deficits, swim time and distance and reducing the pyknotic pyramidal cells.[54] Similarly, Noor et al. demonstrated that nanocurcumin supplementation resulted in increased GSH, Na^+-K^+- ATPases, restoration of NO, glutamine, glycine, GABA, and reduced latency to locate the platform, MDA, TNF-α, AChE, Tau, and pyknotic neurons in STZ lesioned AD rats.[55]

Apolipoprotein E (ApoE), a 34 kDa protein containing 299 amino acids play a crucial role in lipid transportation and lipoprotein metabolism.[46] Among the three alleles *i.e.* ε2, ε3, and ε4 of ApoE, ε4 (ApoE4) has been shown to be involved in AD pathology. ApoE4 has been shown to be a risk factor for the development of various chronic diseases including atherosclerosis, diabetes, and AD.[46,211–214] Curcumin has also been reported to be effective in ApoE4 transgenic AD mice models in which administration of 40 mg/kg/day curcumin for 3 weeks showed reduction in ApoE4, TNF-α, IL-1β, and nuclear translocation of NF-κB and improved time spent in the platform, number of times mice crossed the platform, spatial learning deficits, neuronal morphology, number of $GRP78^+$ cells, number of IRE1-α^+ cells and rescued neuronal cells from degenerative death.[46]

A novel highly bioavailable curcumin formulation called curcugreen treatment was found to restore spleen size, spleen and liver cytoarchitecture and inhibited bronchiolar degeneration, granulomatous inflammation, apoptotic death, amyloid deposits and phospho Tau levels in 3xTg, 5xFAD mice, AD mice models.[51] In another study, treatment of oAβ25–35 induced acute C57B1/6 J AD mice and J20 transgenic mice with curcumin microemulsions (Cur ME) and curcumin conjugated to docosahexanoic acid (DHA) microemulsions (CurDHA ME) effectively restored spatial memory deficits, anxiety, depression, short-term memory and suppressed GFAP, phospho Tau, and phospho JNK2 levels.[52] In addition, supplementation with lipid core co-encapsulated meloxicam and curcumin NPs showed reduced non-aversive memory impairment, inflammation, and COX-2 expression in Aβ peptide-induced AD Swiss mice.[56] Recently, Gao et al., developed curcumin loaded red blood cell (RBC) membrane coated with PLGA bearing T807 (imaging agent) (curcumin loaded T807/RPCNP) biomimetic nanoparticles and tested their efficacy against AD both *in vitro* and *in vivo*.[57] These nanoparticles showed to increase phospho protein kinase B (PKB), phospho Tau, mitochondrial ROS, GSK-3β and apoptosis in HT 22 neuronal cells. This study also showed Curcumin loaded T807/RPCNP reduces the activation of primary astrocytes *in vitro*.[57] Additionally, supplementation of curcumin loaded T807/RPCNP (2 mg/kg, every 2 days) for 10 days showed enhanced spatial learning memory, and suppressed phospho Tau, cognitive impairment, neuronal cell death, and abnormal activation of microglia in okadaic acid lesioned AD mice.[57] In Wistar rats curcumin was shown to mitigate aluminium induced neuronal cytotoxicity (symptoms similar to AD) as evidenced by increased Mg^{2+}, CAT, SOD, Na^+-K^+ ATPase activity, Mg^{2+}ATPase activity, improvement in hippocampal structure, normal morphology of neuronal cells, hippocampal cell viability body weight, memory recognition, and reduced Ca^{2+}, hippocampal AChE, MDA, IFNγ, IL-4 levels, oxidative stress, memory deficit, absolute hippocampus weight, time spent in the dark room, karyopyknotic neuronal cells, neutrophil infiltration, neurofibrillary tangles, hippocampal cell apoptosis.[125,126] Moreover, aluminium-induced AD rat models when treated with PGC improved hippocampal activity, and mitigated Aβ deposition and aggregation, nuclear condensation, and neurodegeneration.[60] Another study explored the effect of solid-lipid curcumin nanoparticles on 5xFAD AD mice models and found that treatment with these nanoparticles significantly improved discrimination index, exploration index, synaptophysin, PSD95, CREB, phospho CREB, spatial memory deficits, pyknotic cells, neurodegeneration, Aβ plaque load, loss in dendritic branching and sprouting of dendritic cells and loss in dendritic spines.[62]

Taken together, these *in vitro* and *in vivo* evidences suggest that curcumin is effective in treating AD irrespective of the disease etiology and alleviated associated neuroinflammation. However, further investigation is reqiured to bring curcumin to bedside.[167–169]

3.2. Amyotrophic lateral sclerosis (ALS)

ALS is a rare devastating paralytic neurodegenerative disease principally affecting upper and lower motor neurons and frontotemporal system with a lifetime risk of 1 in 350 people.[215,216] While cause of sporadic ALS is largely unknown, 10–20% of patients display familial ALS with a clear genetic etiology.[215,216] Genetic makeup of ALS is extremely complex with greater than 40 associated genes have been identified till date which vary in mode of inheritance, frequency and penetrance.[215] The most prevalent mutations being *C9orf72* repeat expansions, missense mutation in *SOD1* followed by mutations in TAR DNA binding protein (*TARDBP*) and fused in sarcoma (*FUS*) genes.[215,217,218] Despite the extensive research, the current disease management of ALS is unsatisfactory. Increasing lines of evidence suggests that curcumin has the potential to treat ALS. For instance, monocytes (THP-1) cells treated with curcumin have shown reduced cell death upon treatment of SOD1 aggregates.[64] Monocytes/macrophages, in general, produce higher amounts of SOD1, thus making them suitable model to study the ALS etiology.[64,219] This study also showed that curcumin in solution inhibits DTT-induced aggregation of SOD1.[64] Besides, curcumin treatment has been shown to improve the survival and non-weight bearing of hind/ thoracic limb in dogs of Pembroke Welsh Corgis (PWC) breed with canine degenerative myelopathy, a spontaneous ALS models.[68] In addition, curcumin derivative dimethoxy curcumin (DMC) treatment was found to enhance complex I activity, MMPo, mitochondrial uncoupling protein 2 (UCP2), and alleviate mitochondrial swelling, cristal dilation, WT & Q331K TAR DNA binding protein 43 (TDP-43)-induced abnormal inactivation of voltage gated sodium channel current, abnormal action potentials in neuroblastoma spinal cord-34 (NSC-34) cells, that expresses several features of ALS motor neurons without inducing agents, *in vitro*.[65,66] In another *in vitro* study, monocarbonyl DMC was shown to reduce insoluble TDP-43 fragments, TAR DNA binding protein 25 (TDP-25) and size of TDP-25 aggregates by upregulating hemeoxygenase-1 (HO-1) levels and was found to reduce oxidative stress by downregulating LDH and MDA levels in NSC-34 cells.[67] Moreover, supplementation with 600 mg/day of curcumin for 6 months improved stable disease scores and ferric reducing antioxidant power (FRAP) values with reduced lactate and advanced oxidative protein products (AOPPs) values in ALS patients.[170] In another clinical trial nanocurcumin treatment (80 mg/day) for an year showed to increase the survival rate in ALS patients.[171] Hence, both preclinical and clinical studies support that curcumin treatment can significantly reduce oxidative stress and prevent neuronal degeneration in ALS.

3.3. Epilepsy and seizures

Epilepsy, one among the most prevalent CNS disorders affecting over 50 million individuals worldwide, poses enormous healthcare and socioeconomic burden.[220–222] The spontaneous and abrupt onset of a seizure has become a serious medical emergency since it may result in additional difficulties.[223] It is primarily identified by aberrant electrical activity in various brain areas. The sudden massive entry of Ca2+ into neurons is the principal neurotoxic process that results in cell death

and progressively leads to neurodegeneration.[222] The electric shocks due to seizure outbreak can affect either a portion of the body (partial) or the entire body (generalised). They are accompanied by a loss of consciousness and control over bowel movements.[222] Due to the narrow therapeutic margin and hazardous side effects of prescribed pharmaceutical medications to treat epilepsy and the progressive development of treatment resistant refractory epilepsy, medicinal plants have gained increasing attention in recent years.[220,222] Drion and colleagues have proved that curcumin enhanced HMOX1 levels and suppressed average action potential frequency, seizure-like events, pS6, phospho $pS6^{Ser240/244}$, phospho MAPK, IL-6, IL-1β, and TGF-β levels in organotypic slice culture model of hippocampus & entorhinal cortex obtained from Sprague-Dawley rats.[69] Curcumin administration was shown to attenuate electric shock induced seizures and provide protection against post-ictal mortality in Swiss albino inbred mice.[70] In another study, curcumin was shown to protect against electro behavioral seizures as evidenced by increased prevention of grade III seizures, Na-K ATPase activity, ambulatory activity, normal cellular architecture, and reduced onset & progression of seizures, DPH anisotropy, lipid peroxidation, protein oxidation, PKC activity, defecation, and epilepsy-related memory decline in Wistar rats.[71] Besides, curcumin administration throughout the kindling days were found to enhance after discharge threshold, stimulation of current intensity required to evoke after discharge and inhibit behavioural seizure development in Sprague-Dawley rats.[72] Yet, another study showed that curcumin protects the Wistar rats against kainic acid (analogue of glutamic acid, produce convulsions by activating kainite excitatory neurons) induced seizures as observed by increased mean latency of convulsion, GSH levels, and time spent in target quadrant, and reduced percentage of convulsions, mossy fiber sprouting (MFS) intensity, activation of astrocytes and microglia, frequency of abnormal spikes, degree of spontaneous recurrent seizures (SRS), TNF-α, IL-1β, MDA, nitrite and nitrate levels.[73,81,85] Curcumin was also shown to effectively attenuate seizures and cognitive impairment in pentylenetetrazole (PTZ) kindling models, widely accepted epileptogenic animal models. In these models curcumin was shown to enhance the delay in kindling development, latency to myoclonic jerks, latency to generalized tonic-clonic seizures (GTCS), latency to myoclonic jerks, latency to enter dark compartment, latency to onset of spasms, step down latency, brain norepinephrine, serotonin, 5-hydroxytryptamine receptor 7 (HTR7) and GSH levels and decreased number of myoclonic jerks, mean frequency of interictal discharge, mean frequency of epileptiform discharge, seizure severity scores, duration of GTCS, muscle contractions, retention transfer latency, mitochondrial swelling, mitochondrial structural abnormality, pyknotic cells, damage to hippocampus, nitrite, neuronal injury, oxidative stress, AChE, ROS and MDA levels.[74,75,78,80,82,84,86,88,91] Kaur et al., deduced that curcumin administration alleviate inflammatory responses in PTZ induced epileptic rat models by suppressing GFAP, Iba-1, astrocyte and microglia activation, activation, TNF-α, IL-1β, IL-6 and MCP-1 levels.[83] Studies have also recorded the beneficial effects of curcumin in treating pilocarpine (cholinergic agonist) induced epileptic rat models where curcumin administration was found to delay the onset of seizures, and augment SOD, Na-K ATPase activity and GSH levels and reduced occurrence of seizures, MDA, AChE, NO, and CAT levels.[76,77] In another study curcumin was shown to protect the rat brain from lithium-pilocarpine induced status epilepticus (SE) by improving latency to seizure and SE, time spent in target quadrant, cognitive performance, beclin, LC3BII, receptor interaction protein kinase 1 (RIP-1), mixed lineage kinase domain-like (MLKL), and GSH levels, and reducing the percentage frequency of seizure and SE, peripheral cholinergic signs (PCS) and stereotyped movements (STM) episodes, TBARS, and mortality.[79,87] In the iron induced epileptic rat models curcumin has been shown to inhibit epileptic activity, multiunit activity (MUA) and seizures.[89] In another study, curcumin was found to increase number of stimulations required to reach Racine stage IV seizures and delayed in onset of seizures in Sprague-Dawley rats.[90] Moreover, curcuminoids were shown to reduce inflammation in rat epileptic models. This study also reported that curcumin induced the expression of anti-inflammatory molecules including IL10RB, CXCL16, CXCL17, NCSTN, CX3CL1, CX3CR1, C3AR1, cathepsin A (CTSA), and cathepsin D (CTSD).[92] Curcumin formulations such as curcumin plus piperine, curcumin plus diazepam, curcumin nanoparticles, liposomal curcumin and micronized curcumin have also been shown to be effective in treating epilepsy in animal models.[91,93–96] These curcumin formulations have shown to improve latency to onset of spasms & isolated clonic seizures, duration of seizures, damage to hippocampus, seizure severity, occurrence of stage III seizures, muscle contraction, working memory, correct entries to goal box, GSH, and NO levels, and reduce TLR4 in pups, hyperthermia, TNF-α, IL-10, IL-1β, MDA, AChE activity, oxidative stress, and caspase-3 expression.[91,93–96] Hence, curcumin and its derivatives can be used as potential candidates to treat epilepsy and associated diseases.

3.4. Huntington's disease (HD)

HD is a neurological disorder with autosomal dominant inheritance pattern and is characterized by massive neuronal degeneration, motor and cognitive impairments with psychiatric symptoms.[224–227] It arises from the mutation in Huntingtin gene as expansion of cytosine-adenosine-guanine repeats which results in elongation of polyglutamine (polyQ) segment in the Huntingtin protein.[228,103] HD is generally a mid-life disease with certain exceptional cases of early onset in childhood (as early as 2 years) and late onset in mid-80 s.[229] There is no approved-disease curing/modifying drugs at present for HD.[227,230] Besides, the treatment modalities include anti-sense oligonucleotides, splicing modulators, and small molecule inhibitors generally provide marginal-relief to symptoms of HD and many of them possess severe adverse side effects.[227,231,100] Interestingly, natural compounds are an alternative to these synthetic drugs with minimum or no side effects. Growing line of evidence indicate that curcumin and its formulation could be an effective therapy against HD.[103,97–102] Transgenic *Drosophila* models have established as a highly effective model system for studying HD since they mimic the majority of the characteristics of neurodegenerative diseases, including late onset, neurodegeneration, motor dysfunction, progressive accumulation of aggregates in the cytoplasm and neurites and shortened lifespan.[98,232–235] Treatment of transgenic *Drosophila* adult and larvae with various concentration of curcumin has been shown to be beneficial in reversing HD symptoms. Chontham and Agrawal treated transgenic HD models of *Drosophila* larvae with 3, 5, 10, 15, and 20 μM of curcumin for 1, 7, and 14 days post eclosion period and observed that curcumin effectively improved crawling ability and inhibited photoreceptor neuron degeneration, morphological defects in the internal part of the eye, eye roughness, loss of pigmentation in eye, acridine orange (AO)-positive cells, polyQ-induced cytotoxicity and apoptotic cell death in eye discs and progressive loss of locomotion in these flies.[98] In another study, curcumin (10 μM) treatment for 1, 7, and 13 days after eclosion has been shown to reduce motor defects and increased mid-night levels of circadian genes Per and Tim miRNAs than mid-day levels.[99] Moreover, curcumin (10, 15, and 20 μM) fed flies (from larvae to till 15 days after eclosion) exhibited improvement in motor activity and median survival rate, with induced mRNA expression of *Drosophila* sterol regulatory element binding protein (dSREBP) and brummer (bmm) that encodes triglyceride lipase.[100] The treatment also reduced abnormal high body weight, abnormal high dry weight with elevation in H_2O content, trehalose levels, dysregulation in total lipid content, lipid droplet size, ROS, free radicals, and mRNA expression of lipin.[100] These studies also reported that curcumin of 10 μM shows the best effect against HD compared to higher and lower doses.[100,98,99] Transgenic HD mice and rats also have been shown to recapitulates human HD pathology *in vivo* and are the suitable models for novel drug discovery.[101,236–238] Curcumin treatment was also observed to be effective in these models. For example, dietary curcumin of 92 mg/kg for 23 weeks was shown to enhance striatal dopamine- and cAMP-regulated

phosphoprotein 32 kDa (DARPP-32) and dopaminergic receptor 1 mRNAs and rearing and decrease cannabinoid receptor 1 (CB1) mRNAs neuropil aggregates, Huntingtin stained nuclei and aggregates in CAG140 mice (knock-in model of HD).[97] Another study showed that dietary supplementation of curcumin (25 mg/kg) with Bioperine (1 mg/kg) in R6/2 line of transgenic mice for entire gestation period and 3 weeks after birth ameliorated HD severity by enhancing DARPP-32, phosphoAkt, phosphoERK, Claudin-2, ZO-1, occludin, and preserving normal levels of BDNF.[101] The treatment also augmented normal intestinal functions including intestinal emptying and contractility.[101] This study also showed that curcumin/Bioperine treatment remarkably inhibited motor deficits, hind clasping behaviour, brain and body weight loss, number of $EM48^+$ mHtt aggregates, villi loss and atrophy and PAS^+ globet cells.[101] In another study, curcumin solid lipid particle formulation (SLCPs) in 100 mg/kg doses (alternate days for 8 weeks) increased the length of dendrites and density of dendritic spines and alleviated learning memory deficits, latency to escape and post-synaptic density protein-95 (PSD-95) levels in YAC128 transgenic mice.[103] Another curcumin solid-lipid nanoparticle formulation (40 mg/kg for 7 days) when given orally to 3-nitropropionic acid induced HD models of wistar rats significantly upregulated SDH activity, NADH dehydrogenase activity, cytochrome c oxidase activity, mitochondrial F_1F_0 synthase activity, cytochrome *a*, b, c1 & c levels, GSH levels, SOD levels, cytosolic & nuclear Nrf2 levels and 3-(4,5-dimethylthiazolyl-2)−2,5-diphenyltetrazolium bromide (MTT) reduction rate.[102] This treatment also resulted in improved locomotor activity, average velocity to traverse the beam, stride length, and reduced mitochondrial swelling, MDA levels, protein carbonyl levels, ROS, total time to traverse the beam, distance between the two paws, stride width and gait angle in these rat HD models.[102] Collectively these studies indicated that curcumin reduces the HD symptoms severity via modulating multiple pathways including Akt pathway, ERK pathway, dopamine and cannabinoid receptor mediated pathway, ROS, mitochondrial respiratory chain and inflammatory pathways.

3.5. Migraine

Migraine is a neurovascular disorder, ranked second most prevalent disorder and sixth cause of disability in the world with typical symptom of recurrent headache.[104,106,107,239–241] Migraine associated pain disability reduces work capacity and productivity leading to considerable economic burden on society.[104,242] Although there is an armamentarium of migraine-specific medications, the long-term usage of these drugs cause dependency, habituation, and addiction.[243,244] The use of non-migraine specific drugs to relive migraine associated pain is also alarming and is a key risk factor for transformation into chronic migraine.[243–245] Hence, there is an urgent need for scientists to develop adequate preventive and curative medicines for migraine. Various preclinical and clinical studies have been reported curcumin to be beneficial in treating migraine. For instance, Ouyang and colleagues demonstrated that curcumin (10, 20, 30, 40, and 50 μM) increases viability of endothelial cells treated with H_2O_2 by upregulating GSH, SOD, Bcl-2, and downregulating LDH, ROS, MDA, p21, Bax, p53, and caspase-3 levels.[104] This study showed that curcumin mitigates H_2O_2-induced oxidative stress and cell death in vascular cells indicating the potential in treating migraine.[104] Besides, several studies have shown that curcumin and/or liposomal curcumin formulations effectively reduced MDA, nitric oxide, total oxidative stress, flinches, shakes, and biphasic response to nociceptive receptors and enhance TAC and thiols levels in nitro-glycerine (a vasodilator) induced experimental rat migraine models.[107,106,105] In addition, curcumin at 1 g/day dose for 8 weeks has been effectively shown to reduce headache attack frequency, duration and severity in migraine patients.[172] This study also showed that curcumin remarkably reduced inflammatory marker IL-6 and calcitonin-gene related peptide (CGRP).[172] Several randomized clinical trials have shown that nanocurcumin (80–160 mg/day) with or without omega-3 FA for 2 months alleviated frequency of headache attack, severity of pain, duration of headache with simultaneous downregulation of inflammatory molecules such as IL-6, IL-17, hs-CRP, COX-2, MCP-1, ICAM1, TNF-α, VCAM, and pentraxin 3.[173–182] In another study, administration of curcumin along with coenzyme Q10 was shown to diminish headache frequency, severity, and duration in migraine patients.[178] Therefore, curcumin can effectively alleviate the symptoms by regulating inflammatory markers in migraine patients and can be a potential drug candidate to treat these patients.

3.6. Multiple sclerosis (MS)

MS is an autoimmune disease of CNS affected over 2 million people globally and is characterized by progressive demyelination, neuroinflammation, axonal damage, breakdown of BBB, oligodendrocyte loss, and neuronal death.[109,111,246–251] It primarily affects individuals between the 20 to 40 years old, with females being more at risk than males.[252] Despite the fact that more than 10 disease-modifying medications are clinically available for MS treatment, the majority of MS patients continue to have varied degrees of impairment and ongoing clinical symptoms.[115] Besides, the long term usage of these drugs have shown several adverse side effects.[117,253] Hence, it is important to research and understand how natural substances affect the pathophysiology of disease. Fortunately, experimental autoimmune encephalomyelitis (EAE) has given researchers a great chance to explore substances in-depth for potential therapeutic applications for MS since EAE and MS are both auto-inflammatory diseases.[250,117,254] Accumulating evidences suggest that curcumin prevents the onset and progression of MS and associated autoimmune encephalitis *in vitro* by increasing Bax, IL-10, caspase-3, and reducing T cell proliferation, IL-12, phosphoJAK2, phospho TK2, STAT3 STAT4, NO, IL-6, TNF-α, iNOS, Bcl-2, CD25, CD44, AXL, IL-2, IL-17A, and IFNγ levels.[109,111,108,110] In the autoimmune MS mice models, treatment of curcumin significantly alleviated clinical severity and duration, inflammation, disease severity, behavioural abnormality demyelination, disease onset scores, weight loss, paralysis, IL-12, mean clinical score, IFNγ, IL-17, IL-6, TNF-α, phospho Akt, phospho mTOR, IFNγ , p62, $CD4^+IFN\gamma^+$ and $CD4^+IL\text{-}17^+$ T cells, infiltrated immune cells, iNOS, IL-1β, IL-12, IL-23, COX-2, TMEM119, AXL, MDA, LTCD3, and LTCD4, and improved sniffing of the novel object, TGF-β, SOD, LC3II, Beclin, Atg5, IL-10, Arg-I, GSH, SOD and MBP levels.[111,115,108,110,113,114] In addition, in autoimmune rat models curcumin was found to be effective in increasing distance travelled, TAC, and MBP levels and inhibited CAT, MMCS, disease severity, immune cell infiltration, Th17 cell proliferation, IL-17, latency, SOD, MDA, weight loss, iNOS, cumulative disease disability, and NOGO-A levels.[117,112,116] In another study, treatment of curcumin-linoleic acid conjugate improved distance travelled, TAC, CAT, escape latency, SOD, and suppressed MDA in autoimmune Wistar rats.[116] Moreover, dendrosomal curcumin treatment resulted in NSCs proliferation, increased $MAP2^+$ cells, MBP^+ cells, NeuN, Olig2, remyelination, differentiation of NSCs into oligodendroglial cells,$CC1^+/Olig2^+$ cells, $Olig2^+$ cells, and LFB staining, and reduced $GFAP^+$ cells, astrocyte activation, and differentiation of NSCs into astrocytes both *in vitro* and *in vivo* models.[118,119] Further, curcumin loaded HDL mimicking peptide-phospholipid complex delay in disease progression, morbidity, immune cell infiltration, $CD45^+$ cells, $CD45^+CD11b^+Ly6C^+CCR2^+$ monocytes infiltration, $CD11b^+$ cells, $CD3^+$ T cells, TH1 cells, TH17 cells, DC maturation, and $DIR\text{-}BOA^+$ monocytes.[120] Furthermore, bioavailable polymerized nanoparticle increased myelination, IL-4, IL-10, HO-1, NGF MBP, Nestin, Olig2, PDGRF-α, and reduced peak and cumulative EAE scores, MCP-1, IL-1, demyelination, iNOS, EAE score, TNF-α receptor, IL-17, CD8 in MS animal models.[121]

In the clinical settings nanocurcumin administration has been shown to improve disease condition and alleviate inflammation by upregulating miR-145, SOX2, sirtulin 1, FOXP3, PDCD1, STAT5, and downregulating miR-132, miR-16, STAT1, NF-κB, AP-1, IL-6, TNF-α, IL-1β, IFNγ, CCL2, CCL5 in MS patients.[183] Besides, in a randomized clinical trial

nanocurcumin supplementation inhibited Th17 cells, RORγt, IL-17 levels in MS patients.[184] Nanocurcumin treatment was also found to increase the frequency of T-reg cells, FoxP3, TGF-β, and IL-10.[186] Another study compared the miRNAs expressed in MS patients with normal healthy subjects and identified putative dysregulated miRNAs in MS patients. These dysregulated miRNAs were found to be restored after 6 months of nanocurcumin treatment in MS patients.[185]

These evidences suggest that curcumin ameliorate autoimmune encephalitis and MS in animal models.

3.7. Parkinson's disease (PD)

PD is the second most prevalent neurodegenerative disease with an estimated 10 million patients suffering worldwide in 2020.[255] The disease predominantly results in the degeneration of dopamine-producing neurons in the substantia nigra of brain leading to defects in locomotor and cognitive functions. The pathophysiological mechanism underlying the disease development include increased aggregation and reduced degradation of α-synuclein and mitochondrial dysfunction affecting majorly complex I.[255–258] The currently available treatment modalities only provide symptomatic relief, for example, supplement with dopamine temporarily control motor deficits.[256] Deep brain simulation is generally used in patients with drug resistance.[255] Natural antioxidants such as curcumin remains a promising alternative therapy to prevent or inhibit oxidative stress and disease progression. Study conducted by Chen et al., used PD recapitulating 1-methyl-4-phenylpyridinium ions (MPP^+) treated PC12 *in vitro* models to demonstrate positive effects of curcumin.[127] MPP^+ is an active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) which has shown to cause Parkinsonism in primates including humans by inducing oxidative stress, mitochondrial dysfunction, and neuronal cell death.[127,259,260] Curcumin was demonstrated to protect PC12 cells from MPP^+-induced damage by upregulating Bcl-2 and downregulating iNOS. It was also shown to prevent the loss of MMPo and attenuate increase in ROS upon MPP^+ treatment in these cells.[127] Curcumin was also shown to enhance SH-SY5Y cell viability, proliferation, tyrosine hydroxylase (TH) positive cells and microtubular-associated protein 2 (MAP2) positive cells upon MPP treatment and reduce MPP^+-induced nuclear condensation and cell death by inhibiting cleaved caspase-3, phosphoJNK, phosphoJun and MKK4 activation.[131,136] MPP^+-induced Swiss albino mice Parkinson model showed reduced oxidative stress and lipid peroxidation when treated with curcumin as evidenced by upregulation of SOD, CAT and GSH.[139] MPP^+-induced dopamine neurotoxicity in C57BL/6 mice was also found to be reduced when curcumin was administered.[131] This study also showed that curcumin increased locomotion frequencies, traction scores, and rearing frequencies and inhibited activation of astrocytes, phospho-JNK1/2, c-Jun, and cleaved caspase-3 in these models.[131] Interestingly, another study demonstrated that MPTP-lesioned C57BL mice transplanted with curcumin activated mesenchymal stem cells (MSCs) derived from human umbilical cord exhibited improved rearing, dopamine levels, drop frequency and TH-positive cells. This study also showed that transplantation of curcumin activated MSCs modulated IL-10, HGF, NGF, VEGF, G-CSF, NADPH dehydrogenase, Bcl-2, Bax, and caspase-3 expression in these models.[136] MPTP-induced neurodegeneration was also shown to be inhibited by curcumin and its derivative tetrahydro curcumin in Swiss albino mice models by inducing dopamine, DOPAC and inhibiting MAO-B activity.[148] Curcumin and curcumin-manganese complexes improved cognitive functions, learning memory, dopaminergic neuronal damage and oxidative stress in MPTP-induced ICR mice Parkinson models.[124] Another study revealed that treatment of novel curcumin nanocarrier formulation, PR-EXO/PP@CUR, markedly improved movement, coordination ability, dopamine levels, DOPAC and impeded α-synuclein aggregates, TNF-α, IL-1β, and IL-6 levels in MPTP-induced PD mice models.[153]

Similarly, 6-hydroxydopamine (6-OHDA) is another chemical used to induce PD symptoms in various models.[129] Curcumin treatment was shown to inhibit 6-OHDA-induced cytotoxicity and NF-κB translocation in mesencephalon hybrid dopaminergic cell line MES23.5.[129] It was also shown to inhibit 6-OHDA-induced cytotoxicity and cell death of SH-SY5Y cells by downregulating p53 and Bax/Bcl-2 ratio.[133] Curcumin also restored MMPo and upregulated SOD levels and inhibited ROS production in these cells.[129] Another study demonstrated that curcumin rescued 6-OHDA lesioned PC12 cell models by upregulating Beclin-1, and inhibiting phospho Akt, phospho mTOR, ROS, and MDA production.[137] Moreover, curcumin inhibited α-synuclein aggregation and augmented α-synuclein solubility in A53T-mutant α-synuclein expressing SH-SY5Y cells.[128] Additionally, curcumin also inhibited α-synuclein-induced toxicity, mitochondrial depolarization, ROS, caspase-3 activity, caspase-9 activity, and apoptosis in PC12 cells expressing inducible A53T-mutant α-synuclein.[132,134] In another study, treatment of curcumin resulted in overexpression of leucine-rich repeat kinase 2 (LRRK2), mutation in which was reported in familial PD, in rat mesenchymal cells.[130] In line with these, curcumin was also found to augment cell viability, adhesion, normal cell architecture of deutocerebrum primary cells compared to cells treated with 6-OHDA by upregulating SOD, GSH-Px, Wnt3a, β-catenin, c-MYC, and cyclin D1 and inhibiting MDA, apoptosis, and MMPo.[135] Besides, curcumin administration enhanced TH-positive cells inhibited microglia and astrocytes activation seen as reduced GFAP in these cells, and prevented the degeneration of dopaminergic neurons in 6-OHDA lesioned ICR mice.[142,143] Also, curcumin treatment induced SOD, GSH-Px, AChE, DA, FGF, NGF, TrkA, Hsp70, Wnt3a, β-catenin, c-MYC, cyclin D1, TH-positive cells, substantia nigra (SN) cells mass, SN cell cytoarchitecture, and reduced mean percentage of TH-positive cell loss, loss of dihydroxyphenyl acetic acid (DOPAC), loss of homovanilic acid (HVA), aberrated alteration in behaviour, rotation numbers, dopaminergic neuron death, GFAP astrocytes activation, and MDA levels in 6-OHDA-induced PD Sprague-Dawley rat models and thereby improved motor latency and neuroethological conditions.[135,138,144] In the 6-OHDA lesioned Wistar rats curcumin increased DOPAC, TH-positive cells and decreased iron-stained cells.[141] Further, curcumin supplementation also prevented TH-positive cell loss as evidenced by enhanced TH expression and neuronal count via upregulating autophagy score and reduced p62 and α-synuclein expression in 6-OHDA-induced Parkinsonian rats.[137,146] Curcumin-loaded human endometrial stem cell derived exosomes (hEnSCs-EXOs-CUR) was found to effectively increased the 6-OHDA treated PC12 cell viability *in vitro*.[152] This study also found that hEnSCs-EXOs-CUR treatment enhanced TH-positive cells, motor latency, rotational numbers and Bcl-2 expression and suppressed α-synuclein, Bax and caspase-3 in 6-OHDA lesioned mice.[152] Another chemical rotenone (ROT), a pesticide and fish poison, has shown to be neurotoxic and several studies have used this chemical to generate animal models of PD.[147,261,262] Curcumin was also shown to be effective in treating ROT-induced PD in Swiss albino mice models. In these models, curcumin treatment enhanced time spent on wire, locomotor activity, rearing, rotarod activity, retention time on rotarod, grooming behaviour, norepinephrine level, dopamine level, GSH, SOD, ATP, SDH, CAT, and MTT reduction activity and impeded CRP, IL-6, adenosine $A_{2A}R$ expression, α-synuclein, MDA, nitrite, AChE, angiotensin-II, caspase-3, DNA fragmentation, and neurodegeneration changes.[147,145] A novel curcumin formulation, curcumin monoglucoside was also found to mitigate ROT-lesioned Parkinsonism by increasing cell viability, GSH, NQO1, complex I and complex IV activities, LDH release, and diminished ROS, hydroperoxides, MDA, NOS2, phospho JNK, phospho c-Jun, cleaved procaspase-3 and DNA damage, in N27 dopaminergic neuronal cells *in vitro*.[149] This study also showed that curcumin monoglucoside supplementation ameliorated free radicals scavenging, GSH, and reduced mortality, locomotor deficits, dopamine turnover, and (DOPAC+HVA)/DA ratio in ROT-induced Parkinson's *Drosophila* flies.[149] In another study, administration of curcumin nanoparticles was found to augment total body balance, distance travelled, number of rearings, CAT, and reduced number of slip steps, bradykinesia, TBARS, GSH-Px, GSH reductase activity, complex I

inhibition in ROT-induced Parkinson's Swiss mice.[150] Furthermore, supplementation with Soluplus (a polycarrier)-curcumin formulation significantly reduced Parkin protein, phospho Rab-10, and PINK1 in LPS model of Parkinson's C57BL/6 mice.[154] Another study showed that curcumin is also beneficial in treating homocysteine Wistar rat model of Parkinson where it improved locomotory functions, neurons with Nissl bodies and Bax/Bcl-2 ratio.[140] Also, curcumin loaded human serum albumin nanoparticles have been found to alleviate symptoms in PD *in vivo*. In this study, curcumin induced delay in age-related deterioration of movement, increased alcohol avoidance and dopamine transportation and reduced movement speed.[151] Clinical trials aimed to understand the effect of curcumin on PD are scarce which is mainly due to the difficulty in obtaining desired number of patients samples. Recently, Ghodsi et al., showed that administration of curcumin (80 mg/day) reduced disease progression score *i.e.* Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III score in PD patients ($n = 60$) compared to those who received gelatin capsule as placebo.[187] However, the post hoc analysis did not show significant difference between two groups.[187] Although, several studies suggest that curcumin remarkably inhibit PD symptoms and alleviate inflammation *in vivo,* further clinical trials are imperative to establish its potential in treating PD.

3.8. Brain tumors

The prevalence of primary CNS cancers is drastically increasing with a current incidence rate of 27.86 per 100,000 individuals. Glioblastoma (GBM) is a most frequently occurring tumor among malignant primary CNS tumors, with an annual incidence of 3.19 per 100,000. GBM accounts for nearly 15.4% of all primary brain tumours and 45.6% of all primary malignant brain tumours.[263–265] At present, surgical resection followed by the adjuvant chemo and radiation therapy is the standard care regimen for GBM and this practice is in use for more than ten years with no progress.[266–268] The median overall survival of GBM patients is increased by this rigorous multimodal therapy to 15 months.[266–268] Due to the poor prognosis and side effects of existing therapeutics, it is imperative to develop the novel therapeutics to enhance the survival rate and QoL of patients.[265] Contemporary medications and plant chemicals have been widely explored as anti-brain cancer agents due to their minimal toxicity profiles. Curcumin treatment has been shown to augment cell viability, nuclear translocation of TFEB, HO-1, LAMP-1, LC3II, Nrf2 translocation, MCOLN1, and modulate GSK-3β, p62, ROS, phosphoJNK/JNK ratio, phospho ERK, phospho Tau, LC3BII/I, H_2O_2-induced oxidative stress, UBC9, and SUMO-ylation in SH-SY5Y neuroblastoma cells.[124,122,123]

3.9. Traumatic brain injury (TBI)

Traumatic brain injury (TBI) is a serious CNS damage often known as a sudden insult brought on by falls, sports, auto accidents and neuronal inflammation.[32,269,270] TBI affects more than 10 million young and old people annually worldwide.[269,271] Localized brain damage results from primary TBI, whereas secondary TBI commences with inflammatory activity and progresses to disruption of the BBB, CNS edema, enhanced peripheral immune cell infiltration and the release of a myriad of immune mediators, such as chemokines and interleukins. TBI changes neuronal cell architecture, integrity, molecular signalling and functioning.[272] TBI generally disrupts brain physiology, impairs cognition, decision-making capability, memory, attention, and speaking abilities in addition to tissue damage like axonal damage, hemorrhage and contusions.[272] Due to the underlying complex pathophysiological mechanism, effective pharmaceutical treatment for TBI is still elusive.[32] Several studies indicate that curcumin attenuates cerebral edema, promote energy homeostasis and inhibit oxidative stress followed by TBI. For example, curcumin was found to reduce inflammatory markers including TLR4, MCP-1, IL-1β, IL-6, TNF-α, regulated upon activation, normal T-cell expressed and presumably secreted (RANTES), NF-κB, phospho IκB-α, myeloid differentiation primary response gene 88 (MYD88), and infiltration of TLR4$^+$ microglia/macrophages followed by cerebral edema, and brain water content in craniotomy-induced TBI mice. This study also reported that curcumin enhanced IκB-α levels in these mice TBI models.[155] The experiments aimed to identify molecular mechanisms also have shown that curcumin treatment effectively increase IκB-α levels and inhibit cleaved caspase-3, neuronal damage, microglia activation, IL-6, IL-1β, phospho IκB-a, NF-κB, and RANTES in LPS treated microglia cells *in vitro*.[155] In another study curcumin was reported to improve overall locomotion, time spent on exploring a novel object, and suppress IL-1β, GFAP, and phospho NF-κB levels.[158] Curcumin treatment was shown to profoundly reduce brain water content and cerebral edema via downregulating aquaporin 4 (AQP4) levels.[158] Administration of curcumin was also shown to improve motor performance, recovery balance, lesion healing and inhibit MDA levels in surgically-induced TBI rat models.[159] Besides, dietary supplement of curcumin promoted BDNF, phospho synapsin I, swimming timing in the target zone, and suppressed oxidized proteins, escape latency in Sprague-Dawley rats with post fluid percussion injury (FPI) induced TBI.[156] Similar study conducted on Sprague-Dawley rats with FPI-induced TBI showed that curcumin treatment efficiently upregulated phospho AMPK/AMPK ratio, ubiquitous mitochondrial creatinine kinase (uMtCK), UCP2, silent information regulator 2 (Sir2) and COX-2 levels.[157] In addition, in the surgery-induced TBI ICR-mice models curcumin supplementation was shown to reduce neurological severity scoring (NSS) score, brain water content, cerebral edema, and neuronal apoptosis.[160] Studies have also proven that at the molecular level curcumin upregulated Bcl-2, GSH-Px, SOD, HO-1, NQO-1, and nuclear translocation of Nrf2, and downregulated cleaved caspase-3, MPO$^+$ cells, TNF-α, IL-1β, IL-6, and MDA levels in TBI mice models.[160,161] Recently, Dong et al., demonstrated that administration of curcumin resulted in alleviation of thyroid and liver injuries in gas explosion (GE) induced TBI Sprague-Dawley rats. This study showed that curcumin treatment effectively increased body weight, liver weight, triiodothyronine (T3), tetraiodothyronine (T4), thyroid stimulating hormone (TSH), SOD, thyroglobulin, FOXE1, thyroid stimulating hormone receptor (TSHR), and thyroid stimulating hormone beta (TSHβ) levels, and reduced thyroid weight, immune cells infiltration, thyroid follicular cavity size, MDA thyrotropin-releasing hormone receptor (TRHR), transthyretin (TTR), GSH-Px, ROS, NF-κB, paired box 8 (PAX8), thyroid transcription factor 1 (TTF1), NIS, and thyroid peroxidase (TPO) levels in these GE-induced TBI rat models.[162] In another study, a curcumin derivative CNB-001 administration was reported to promote BDNF, synapsin I, CREB, SOD and learning ability and reduce foot faults and oxidized protein levels in FPI-induced TBI Sprague-Dawley rats.[163] Moreover, THC was found to significantly inhibit brain water accumulation and edema, neuronal damage and apoptosis by upregulating Nrf2 nuclear translocation, Bcl-2, SOD, GSH-Px, LC3II, beclin, and phospho Akt, and downregulating cleaved caspase-3, Bax, p62 and MDA levels in TBI rat models.[164,165] Further, curcumin niosomal NPs have been shown to suppress NSS score, brain water content, cerebral edema, Iba-1$^+$ cells, GFAP$^+$ cells, TLR4$^+$ cells, NF-κB^+ cells in TBI Wistar rats.[166]

Althouth clinical trials have shown that curcumin administration reduces inflammation in patients with spinal cord injury and TBI, well-planned large-scale trials are necessary to prove it's therapeutic potential. [188–190] Collectively, these studies suggest that curcumin and its derivatives attenuate cerebral edema and TBI by inhibiting associated inflammatory pathways.

4. Conclusions

Several etiological factors including inflammation, oxidative stress, and neuronal cell degeneration contribute to the onset and progression of NDs. Neuroinflammation followed by neuronal damage due to surge

in inflammatory molecules is believed to be the major cause of NDs. Symptoms and damage related to these diseases can be treated using various approaches. FDA and European medicine agency (EMA) have been approved several drugs to treat NDs till date. However, these medications are either focused to provide temporary symptom relief or on improving patient QoL instead of disease cure and are also found to be associated with severe adverse side effects and habituation. Compelling evidences suggest that curcumin, its derivatives and formulations prevent the onset and progression of various NDs. In particular, *in vitro, in vivo*, and clinical studies focusing at the effects of curcumin on NDs revealed that curcumin modulates important signalling pathways and molecules that regulate neuroinflammation. For example, curcumin and its derivatives have been found to regulate Akt/mTOR pathway, NF-κB pathway, β-catenin pathway, NLRP3 inflammasome pathway, BDNF/TrkB pathway, Nrf2, IL-6/STAT3 inflammatory pathways and DNA repair pathways. For decades, the low bioavailability of oral curcumin was restricted its use in NDs. However, recent development in conjugation, nanocurcumin and liposomal formulation have successfully addressed these issues and pharmacokinetics and pharmacodynamic studies have shown that these formulations facilitate the better absorption and cellular availability and can be used as effective and safer agents to treat NDs in animal models and clinical settings. Additionally, curcumin and their formulations have been found to downregulate inflammatory cytokines including IL-6, IL-1, TNF-α, IL-13, IL-17, IL-23 and upregulate anti-inflammatory molecules such as TGF and IL-10. Recent studies have also shown that curcumin and its formulations reduced cognitive impairment, memory impairment, oxidative stress, and neurodegeneration, and improved spatial learning memory, and motor activities. However, clinical trials are scarce on NDs and the current trials with low sample size have concluded the effect of curcumin. Nevertheless, it is necessary to design clinical trials for curcumin and its formulations with higher sample size to characterize the appropriate dosage, bioavailability, and safety in patients who are at risk and diagnosed with NDs.

CRediT authorship contribution statement

Prachi Garodia: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Mangala Hegde:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Ajaikumar B. Kunnumakkara:** Conceptualization, Methodology, Funding acquisition, Writing – original draft, Writing – review & editing. **Bharat B. Aggarwal:** Supervision, Conceptualization, Project administration, Writing – review & editing.

Acknowledgment

Mangala Hegde acknowledges Science and Engineering Research Board (SERB)-National Post-Doctoral Fellowship (NPDF) (PDF/2021/004053). All the figures are created using Biorender.com.

Conflicts of interests

The authors declare that they have no conflict of interest.

Funding

This project was supported by BT/556/NE/U-Excel/2016 grant awarded to ABK by Department of Biotechnology (DBT), Government of India.

Ethical statement

Not applicable.

Data availability

Data sharing is not applicable to this manuscript as no new data were created or analysed in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.100968.

References

1. Yavarpour-Bali H, Ghasemi-Kasman M, Pirzadeh M. Curcumin-loaded nanoparticles: a novel therapeutic strategy in treatment of central nervous system disorders. *Int J Nanomedicine*. 2019;14:4449–4460. doi:10.2147/IJN.S208332.
2. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. *Cold Spring Harb Perspect Biol*. 2017;9(7). doi:10.1101/cshperspect.a028035.
3. Rakotoarisoa M, Angelova A. Amphiphilic nanocarrier systems for curcumin delivery in neurodegenerative disorders. *Medicines*. 2018;5(4) (Basel). doi:10.3390/medicines5040126.
4. Sharifi-Rad M, Lankatillake C, Dias DA, et al. Impact of natural compounds on neurodegenerative disorders: from preclinical to pharmacotherapeutics. *J Clin Med*. 2020;9(4). doi:10.3390/jcm9041061.
5. Kulkarni SK, Dhir A. An overview of curcumin in neurological disorders. *Indian J Pharm Sci*. 2010;72(2):149–154. doi:10.4103/0250-474X.65012.
6. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. *Front Aging Neurosci*. 2022;14:937486. doi:10.3389/fnagi.2022.937486.
7. Ding C, Wu Y, Chen X, et al. Global, regional, and national burden and attributable risk factors of neurological disorders: the global burden of disease study 1990-2019. *Front Public Health*. 2022;10:952161. doi:10.3389/fpubh.2022.952161.
8. Singla RK, De R, Efferth T, et al. The international natural product sciences taskforce (INPST) and the power of twitter networking exemplified through #INPST hashtag analysis. *Phytomedicine*. 2023;108:154520. doi:10.1016/j.phymed.2022.154520.
9. Hegde M, Girisa S, Naliyadhara N, et al. Natural compounds targeting nuclear receptors for effective cancer therapy. *Cancer Metastasis Rev*. 2022. doi:10.1007/s10555-022-10068-w.
10. Pratheeshkumar P, Sreekala C, Zhang Z, et al. Cancer prevention with promising natural products: mechanisms of action and molecular targets. *Anticancer Agents Med Chem*. 2012;12(10):1159–1184. doi:10.2174/187152012803833035.
11. Cote B, Elbarbry F, Bui F, et al. Mechanistic basis for the role of phytochemicals in inflammation-associated chronic diseases. *Molecules*. 2022;27(3). doi:10.3390/molecules27030781.
12. Tewari D, Patni P, Bishayee A, Sah AN, Bishayee A. Natural products targeting the PI3K-Akt-mTOR signaling pathway in cancer: a novel therapeutic strategy. *Semin Cancer Biol*. 2022;80:1–17. doi:10.1016/j.semcancer.2019.12.008.
13. Cavalcanti R., Koshima C., Forster-Carneiro T., et al. Uses and applications of extracts from natural sources. 2022, 1–65. 10.1039/9781839165894-00001
14. Amalraj A, Sukumaran NP, Kunnumakkara AB, Gopi S. The chemistry and biological activities of curcuminoids: impacts on neurological disorders. *Curcumin For Neurological and Psychiatric Disorders* Elsevier; 2019:105–127.
15. Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol*. 2017;174(11):1325–1348. doi:10.1111/bph.13621.
16. Yallapu MM, Nagesh PK, Jaggi M, Chauhan SC. Therapeutic applications of curcumin nanoformulations. *AAPS J*. 2015;17(6):1341–1356. doi:10.1208/s12248-015-9811-z.
17. Mohseni M, Sahebkar A, Askari G, Johnston TP, Alikiaii B, Bagherniya M. The clinical use of curcumin on neurological disorders: an updated systematic review of clinical trials. *Phytother Res*. 2021;35(12):6862–6882. doi:10.1002/ptr.7273.
18. Girisa S, Kumar A, Rana V, et al. From simple mouth cavities to complex oral mucosal disorders-curcuminoids as a promising therapeutic approach. *ACS Pharmacol Transl Sci*. 2021;4(2):647–665. doi:10.1021/acsptsci.1c00017.
19. Kumar A, Harsha C, Parama D, et al. Current clinical developments in curcumin-based therapeutics for cancer and chronic diseases. *Phytother Res*. 2021;35(12):6768–6801. doi:10.1002/ptr.7264.
20. Shabnam B, Harsha C, Thakur KK, Khatoon E, Kunnumakkara AB. Curcumin: a potential molecule for the prevention and treatment of inflammatory diseases. *The Chemistry and Bioactive Components of Turmeric*. 2020:150–171. doi:10.1039/9781788015936-00150.
21. Jacob J, Amalraj A, Raj KKJ, Divya C, Kunnumakkara AB, Gopi S. A novel bioavailable hydrogenated curcuminoids formulation (CuroWhite) improves symptoms and diagnostic indicators in rheumatoid arthritis patients - A randomized, double blind and placebo controlled study. *J Tradit Complement Med*. 2019;9(4):346–352. doi:10.1016/j.jtcme.2018.06.001.
22. Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H. Antihepatotoxic principles of Curcuma longa rhizomes. *Planta Med*. 1983;49(3):185–187. doi:10.1055/s-2007-969845.
23. Venkatesan N. Curcumin attenuation of acute adriamycin myocardial toxicity in rats. *Br J Pharmacol*. 1998;124(3):425–427. doi:10.1038/sj.bjp.0701877.
24. Venkatesan N, Punithavathi D, Arumugam V. Curcumin prevents adriamycin nephrotoxicity in rats. *Br J Pharmacol*. 2000;129(2):231–234. doi:10.1038/sj.bjp.0703067.

25. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807–818. doi:10.1021/mp700113r.
26. Srinivasan M. Effect of curcumin on blood sugar as seen in a diabetic subject. *Indian J Med Sci*. 1972;26(4):269–270.
27. Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. *Plant Foods Hum Nutr*. 2002;57(1):41–52. doi:10.1023/a:1013106527829.
28. Zielinska A, Alves H, Marques V, et al. Properties, extraction methods, and delivery systems for curcumin as a natural source of beneficial health effects. *Medicina*. 2020;56(7) (Kaunas). doi:10.3390/medicina56070336.
29. Kim SJ, Son TG, Park HR, et al. Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J Biol Chem*. 2008;283(21):14497–14505. doi:10.1074/jbc.M708373200.
30. Shin HJ, Lee JY, Son E, et al. Curcumin attenuates the kainic acid-induced hippocampal cell death in the mice. *Neurosci Lett*. 2007;416(1):49–54. doi:10.1016/j.neulet.2007.01.060.
31. Ma QL, Yang F, Rosario ER, et al. Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *J. Neurosci.*. 2009;29:9078–9089.
32. Khayatan D, Razavi SM, Arab ZN, et al. Protective effects of curcumin against traumatic brain injury. *Biomed Pharmacother*. 2022;154:113621. doi:10.1016/j.biopha.2022.113621.
33. Cornelius C, Crupi R, Calabrese V, et al. Traumatic brain injury: oxidative stress and neuroprotection. *Antioxid Redox Signal*. 2013;19(8):836–853. doi:10.1089/ars.2012.4981.
34. Vasconcelos AR, Dos Santos NB, Scavone C, Munhoz CD. Nrf2/ARE pathway modulation by dietary energy regulation in neurological disorders. *Front Pharmacol*. 2019;10:33. doi:10.3389/fphar.2019.00033.
35. Wong M. Mammalian target of rapamycin (mTOR) pathways in neurological diseases. *Biomed J*. 2013;36(2):40–50. doi:10.4103/2319-4170.110365.
36. Sun SC. The non-canonical NF-kappaB pathway in immunity and inflammation. *Nat Rev Immunol*. 2017;17(9):545–558. doi:10.1038/nri.2017.52.
37. Liu M, Zhang X, Wang Y. Curcumin alleviates abeta(42)-induced neuronal metabolic dysfunction via the Thrb/SIRT3 axis and improves cognition in APP(TG) mice. *Neurochem Res*. 2021;46(12):3166–3178. doi:10.1007/s11064-021-03414-x.
38. Zhou HY, Sun YY, Chang P, Huang HC. Curcumin inhibits cell damage and apoptosis caused by thapsigargin-induced endoplasmic reticulum stress involving the recovery of mitochondrial function mediated by mitofusin-2. *Neurotox Res*. 2022;40(2):449–460. doi:10.1007/s12640-022-00481-y.
39. Nguyen HD, Jo WH, Hoang NHM, Kim MS. Curcumin-attenuated TREM-1/DAP12/NLRP3/caspase-1/IL1B, TLR4/NF-kappaB pathways, and tau hyperphosphorylation induced by 1,2-diacetyl benzene: an *in vitro* and in silico study. *Neurotox Res*. 2022;40(5):1272–1291. doi:10.1007/s12640-022-00535-1.
40. He W, Yuan K, Ji B, Han Y, Li J. Protective effects of curcumin against neuroin fl ammation induced by Abeta25-35 in primary rat microglia: modulation of high-mobility group box 1, toll-like receptor 4 and receptor for advanced glycation end products expression. *Ann Transl Med*. 2020;8(4):88. doi:10.21037/atm.2019.12.147.
41. De Lorenzi E, Franceschini D, Contardi C, et al. Modulation of amyloid beta-induced microglia activation and neuronal cell death by curcumin and analogues. *Int J Mol Sci*. 2022;23(8). doi:10.3390/ijms23084381.
42. Han Y, Chen R, Lin Q, et al. Curcumin improves memory deficits by inhibiting HMGB1-RAGE/TLR4-NF-kappaB signalling pathway in APPswe/PS1dE9 transgenic mice hippocampus. *J Cell Mol Med*. 2021;25(18):8947–8956. doi:10.1111/jcmm.16855.
43. Tian M, Zhou F, Teng Z, et al. Curcumin ameliorates lipid metabolic disorder and cognitive dysfunction via the ABCA1 transmembrane transport system in APP/PS1 double transgenic mice. *J Integr Neurosci*. 2021;20(4):895–903. doi:10.31083/j.jin2004091.
44. Li J, Wang S, Zhang S, et al. Curcumin slows the progression of Alzheimer's disease by modulating mitochondrial stress responses via JMJD3-H3K27me3-BDNF axis. *Am J Transl Res*. 2021;13(12):13380–13393.
45. Cakmak G, Kaplan DS, Yildirim C, Ulusal H, Tarakcioglu M, Ozturk ZA. Improvement of cognitive deficit of curcumin on scopolamine-induced Alzheimer's disease models. *Caspian J Intern Med*. 2022;13(1):16–22. doi:10.22088/cjim.13.1.16.
46. Kou J, Wang M, Shi J, et al. Curcumin reduces cognitive deficits by inhibiting neuroinflammation through the endoplasmic reticulum stress pathway in apolipoprotein E4 transgenic mice. *ACS Omega*. 2021;6(10):6654–6662. doi:10.1021/acsomega.0c04810.
47. Ahmadi N, Hosseini MJ, Rostamizadeh K, Anoush M. Investigation of therapeutic effect of curcumin alpha and beta glucoside anomers against Alzheimer's disease by the nose to brain drug delivery. *Brain Res*. 2021;1766:147517. doi:10.1016/j.brainres.2021.147517.
48. Maiti P, Manna J, Thammathong J, et al. Tetrahydrocurcumin Has Similar Anti-Amyloid Properties as Curcumin: In Vitro Comparative Structure-Activity Studies. *Antioxidants (Basel)*. 2021;10(10):1592. doi:10.3390/antiox10101592.
49. Cores A, Carmona-Zafra N, Martin-Camara O, et al. Curcumin-piperlongumine hybrids with a multitarget profile elicit neuroprotection *in vitro* models of oxidative stress and hyperphosphorylation. *Antioxidants (Basel)*. 2021;11(1). doi:10.3390/antiox11010028.
50. Jithavech P, Suwattananuruk P, Hasriadi Muangnoi C, et al. Physicochemical investigation of a novel curcumin diethyl gamma-aminobutyrate, a carbamate ester prodrug of curcumin with enhanced anti-neuroinflammatory activity. *PLoS One*. 2022;17(3):e0265689. doi:10.1371/journal.pone.0265689.
51. Manna J, Dunbar GL, Maiti P. Curcugreen treatment prevented splenomegaly and other peripheral organ abnormalities in 3xTg and 5xFAD mouse models of Alzheimer's disease. *Antioxidants (Basel)*. 2021;10(6). doi:10.3390/antiox10060899.
52. Zussy C, John R, Urgin T, et al. Intranasal administration of nanovectorized docosahexaenoic Acid (DHA) improves cognitive function in two complementary mouse models of Alzheimer's disease. *Antioxidants*. 2022;11(5) (Basel). doi:10.3390/antiox11050838.
53. Ruan Y, Xiong Y, Fang W, 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 Nanobiotechnol*. 2022;20(1):322. doi:10.1186/s12951-022-01524-4.
54. Abdulmalek S, Nasef M, Awad D, Balbaa M. Protective effect of natural antioxidant, curcumin nanoparticles, and zinc oxide nanoparticles against type 2 diabetes-promoted hippocampal neurotoxicity in rats. *Pharmaceutics*. 2021;13(11). doi:10.3390/pharmaceutics13111937.
55. Noor NA, Hosny EN, Khadrawy YA, et al. Effect of curcumin nanoparticles on streptozotocin-induced male Wistar rat model of Alzheimer's disease. *Metab Brain Dis*. 2022;37(2):343–357. doi:10.1007/s11011-021-00897-z.
56. Gutierrez MEZ, Savall ASP, da Luz Abreu E, et al. Co-nanoencapsulated meloxicam and curcumin improves cognitive impairment induced by amyloid-beta through modulation of cyclooxygenase-2 in mice. *Neural Regen Res*. 2021;16(4):783–789. doi:10.4103/1673-5374.295339.
57. Gao C, Chu X, Gong W, et al. Neuron tau-targeting biomimetic nanoparticles for curcumin delivery to delay progression of Alzheimer's disease. *J Nanobiotechnol*. 2020;18(1):71. doi:10.1186/s12951-020-00626-1.
58. Xu C, Xiao Z, Wu H, et al. BDMC protects AD *in vitro* via AMPK and SIRT1. *Transl Neurosci*. 2020;11(1):319–327. doi:10.1515/tnsci-2020-0140.
59. Xu Y, Hu R, He D, et al. Bisdemethoxycurcumin inhibits oxidative stress and antagonizes Alzheimer's disease by up-regulating SIRT1. *Brain Behav*. 2020;10(7):e01655. doi:10.1002/brb3.1655.
60. Lin YW, Fang CH, Yang CY, Liang YJ, Lin FH. Investigating a Curcumin-Loaded PLGA-PEG-PLGA Thermo-Sensitive Hydrogel for the Prevention of Alzheimer's Disease. *Antioxidants*. 2022;11(4) (Basel). doi:10.3390/antiox11040727.
61. Zhang H, Jiang W, Zhao Y, et al. Lipoprotein-inspired nanoscavenger for the three-pronged modulation of microglia-derived neuroinflammation in Alzheimer's disease therapy. *Nano Lett*. 2022;22(6):2450–2460. doi:10.1021/acs.nanolett.2c00191.
62. Maiti P, Bowers Z, Bourcier-Schultz A, Morse J, Dunbar GL. Preservation of dendritic spine morphology and postsynaptic signaling markers after treatment with solid lipid curcumin particles in the 5xFAD mouse model of Alzheimer's amyloidosis. *Alzheimers Res Ther*. 2021;13(1):37. doi:10.1186/s13195-021-00769-9.
63. Xiao Y, Dai Y, Li L, et al. Tetrahydrocurcumin ameliorates Alzheimer's pathological phenotypes by inhibition of microglial cell cycle arrest and apoptosis via Ras/ERK signaling. *Biomed Pharmacother*. 2021;139:111651. doi:10.1016/j.biopha.2021.111651.
64. Bhatia NK, Srivastava A, Katyal N, et al. Curcumin binds to the pre-fibrillar aggregates of Cu/Zn superoxide dismutase (SOD1) and alters its amyloidogenic pathway resulting in reduced cytotoxicity. *Biochim Biophys Acta*. 2015;1854(5):426–436. doi:10.1016/j.bbapap.2015.01.014.
65. Lu J, Duan W, Guo Y, et al. Mitochondrial dysfunction in human TDP-43 transfected NSC34 cell lines and the protective effect of dimethoxy curcumin. *Brain Res Bull*. 2012;89(5–6):185–190. doi:10.1016/j.brainresbull.2012.09.005.
66. Dong H, Xu L, Wu L, et al. Curcumin abolishes mutant TDP-43 induced excitability in a motoneuron-like cellular model of ALS. *Neuroscience*. 2014;272:141–153. doi:10.1016/j.neuroscience.2014.04.032.
67. Duan W, Guo Y, Xiao J, et al. Neuroprotection by monocarbonyl dimethoxycurcumin C: ameliorating the toxicity of mutant TDP-43 via HO-1. *Mol Neurobiol*. 2014;49(1):368–379. doi:10.1007/s12035-013-8525-4.
68. Kobatake Y, Nakata K, Sakai H, et al. The long-term clinical course of canine degenerative myelopathy and therapeutic potential of curcumin. *Vet Sci*. 2021;8(9). doi:10.3390/vetsci8090192.
69. Drion CM, Kooijman L, Aronica E, et al. Curcumin reduces development of seizure-like events in the hippocampal-entorhinal cortex slice culture model for epileptogenesis. *Epilepsia*. 2019;60(4):605–614. doi:10.1111/epi.14667.
70. Bharal N, Sahaya K, Jain S, Mediratta PK, Sharma KK. Curcumin has anticonvulsant activity on increasing current electroshock seizures in mice. *Phytother Res*. 2008;22(12):1660–1664. doi:10.1002/ptr.2551.
71. Jyoti A, Sethi P, Sharma D. Curcumin protects against electrobehavioral progression of seizures in the iron-induced experimental model of epileptogenesis. *Epilepsy Behav*. 2009;14(2):300–308. doi:10.1016/j.yebeh.2008.11.011.
72. Du P, Li X, Lin HJ, et al. Curcumin inhibits amygdaloid kindled seizures in rats. *Chin Med J*. 2009;122(12):1435–1438 (Engl).
73. Gupta YK, Briyal S, Sharma M. Protective effect of curcumin against kainic acid induced seizures and oxidative stress in rats. *Indian J Physiol Pharmacol*. 2009;53(1):39–46.
74. Mehla J, Reeta KH, Gupta P, Gupta YK. Protective effect of curcumin against seizures and cognitive impairment in a pentylenetetrazole-kindled epileptic rat model. *Life Sci*. 2010;87(19–22):596–603. doi:10.1016/j.lfs.2010.09.006.
75. Reeta KH, Mehla J, Pahuja M, Gupta YK. Pharmacokinetic and pharmacodynamic interactions of valproate, phenytoin, phenobarbitone and carbamazepine with curcumin in experimental models of epilepsy in rats. *Pharmacol Biochem Behav*. 2011;99(3):399–407. doi:10.1016/j.pbb.2011.05.011.
76. Du P, Tang HY, Li X, et al. Anticonvulsive and antioxidant effects of curcumin on pilocarpine-induced seizures in rats. *Chin Med J*. 2012;125(11):1975–1979 (Engl).
77. Ezz HS, Khadrawy YA, Noor NA. The neuroprotective effect of curcumin and Nigella sativa oil against oxidative stress in the pilocarpine model of

epilepsy: a comparison with valproate. *Neurochem Res*. 2011;36(11):2195–2204. doi:10.1007/s11064-011-0544-9.
78. Agarwal NB, Jain S, Agarwal NK, Mediratta PK, Sharma KK. Modulation of pentylenetetrazole-induced kindling and oxidative stress by curcumin in mice. *Phytomedicine*. 2011;18(8–9):756–759. doi:10.1016/j.phymed.2010.11.007.
79. Ahmad M. Protective effects of curcumin against lithium-pilocarpine induced status epilepticus, cognitive dysfunction and oxidative stress in young rats. *Saudi J Biol Sci*. 2013;20(2):155–162. doi:10.1016/j.sjbs.2013.01.002.
80. Choudhary KM, Mishra A, Poroikov VV, Goel RK. Ameliorative effect of Curcumin on seizure severity, depression like behavior, learning and memory deficit in post-pentylenetetrazole-kindled mice. *Eur J Pharmacol*. 2013;704(1–3):33–40. doi:10.1016/j.ejphar.2013.02.012.
81. Kiasalari Z, Roghani M, Khalili M, Rahmati B, Baluchnejadmojarad T. Antiepileptogenic effect of curcumin on kainate-induced model of temporal lobe epilepsy. *Pharm Biol*. 2013;51(12):1572–1578. doi:10.3109/13880209.2013.803128.
82. Kaur H, Bal A, Sandhir R. Curcumin supplementation improves mitochondrial and behavioral deficits in experimental model of chronic epilepsy. *Pharmacol Biochem Behav*. 2014;125:55–64. doi:10.1016/j.pbb.2014.08.001.
83. Kaur H, Patro I, Tikoo K, Sandhir R. Curcumin attenuates inflammatory response and cognitive deficits in experimental model of chronic epilepsy. *Neurochem Int*. 2015;89:40–50. doi:10.1016/j.neuint.2015.07.009.
84. Zhu W, Su J, Liu J, Jiang C. The involvement of neuronal nitric oxide synthase in the anti-epileptic action of curcumin on pentylenetetrazol-kindled rats. *Biomed Mater Eng*. 2015;26(Suppl 1):S841–S850. doi:10.3233/BME-151376.
85. Jiang Z, Guo M, Shi C, et al. Protection against cognitive impairment and modification of epileptogenesis with curcumin in a post-status epilepticus model of temporal lobe epilepsy. *Neuroscience*. 2015;310:362–371. doi:10.1016/j.neuroscience.2015.09.058.
86. Saha L, Chakrabarti A, Kumari S, Bhatia A, Banerjee D. Antiapoptotic and neuroprotective role of Curcumin in Pentylenetetrazole (PTZ) induced kindling model in rat. *Indian J Exp Biol*. 2016;54(2):133–141.
87. Wang J, Liu Y, Li XH, et al. Curcumin protects neuronal cells against status-epilepticus-induced hippocampal damage through induction of autophagy and inhibition of necroptosis. *Can J Physiol Pharmacol*. 2017;95(5):501–509. doi:10.1139/cjpp-2016-0154.
88. Arbabi Jahan A, Rad A, Ghanbarabadi M, Amin B, Mohammad-Zadeh M. The role of serotonin and its receptors on the anticonvulsant effect of curcumin in pentylenetetrazol-induced seizures. *Life Sci*. 2018;211:252–260. doi:10.1016/j.lfs.2018.09.007.
89. Kumar V, Prakash C, Singh R, Sharma D. Curcumin's antiepileptic effect, and alterations in Na(v)1.1 and Na(v)1.6 expression in iron-induced epilepsy. *Epilepsy Res*. 2019;150:7–16. doi:10.1016/j.eplepsyres.2018.12.007.
90. Drion CM, Kooijman L, Chan D, et al. No persistent effects of intracerebral curcumin administration on seizure progression and neuropathology in the kindling rat model for temporal lobe epilepsy. *Epilepsy Res*. 2022;181:106873. doi:10.1016/j.eplepsyres.2022.106873.
91. Nascimento CP, Ferreira LO, da Silva ALM, et al. A Combination of curcuma longa and diazepam attenuates seizures and subsequent hippocampal neurodegeneration. *Front Cell Neurosci*. 2022;16:884813. doi:10.3389/fncel.2022.884813.
92. Hui-Yin Y, Ahmad N, Azmi N, Makmor-Bakry M. Curcumin: the molecular mechanisms of action in inflammation and cell death during kainate-induced epileptogenesis. *Indian J Pharm Educ Res*. 2018;52(1):32–41. doi:10.5530/ijper.52.1.4.
93. Atabaki R, Roohbakhsh A, Moghimi A, Mehri S. Protective effects of maternal administration of curcumin and hesperidin in the rat offspring following repeated febrile seizure: role of inflammation and TLR4. *Int Immunopharmacol*. 2020;86:106720. doi:10.1016/j.intimp.2020.106720.
94. Khadrawy YA, Sawie HG, Hosny EN. Neuroprotective effect of curcumin nanoparticles against rat model of status epilepticus induced by pilocarpine. *J Complement Integr Med*. 2018;15(3). doi:10.1515/jcim-2017-0117.
95. Agarwal NB, Jain S, Nagpal D, Agarwal NK, Mediratta PK, Sharma KK. Liposomal formulation of curcumin attenuates seizures in different experimental models of epilepsy in mice. *Fundam Clin Pharmacol*. 2013;27(2):169–172. doi:10.1111/j.1472-8206.2011.01002.x.
96. Bertoncello KT, Aguiar GPS, Oliveira JV, Siebel AM. Micronization potentiates curcumin's anti-seizure effect and brings an important advance in epilepsy treatment. *Sci Rep*. 2018;8(1):2645. doi:10.1038/s41598-018-20897-x.
97. Hickey MA, Zhu C, Medvedeva V, et al. Improvement of neuropathology and transcriptional deficits in CAG 140 knock-in mice supports a beneficial effect of dietary curcumin in Huntington's disease. *Mol Neurodegener*. 2012;7:12. doi:10.1186/1750-1326-7-12.
98. Chongtham A, Agrawal N. Curcumin modulates cell death and is protective in Huntington's disease model. *Sci Rep*. 2016;6:18736. doi:10.1038/srep18736.
99. Khyati Malik I, Agrawal N, Kumar V. Melatonin and curcumin reestablish disturbed circadian gene expressions and restore locomotion ability and eclosion behavior in Drosophila model of Huntington's disease. *Chronobiol Int*. 2021;38(1):61–78. doi:10.1080/07420528.2020.1842752.
100. Aditi K, Singh A, Shakarad MN, Agrawal N. Management of altered metabolic activity in Drosophila model of Huntington's disease by curcumin. *Exp Biol Med*. 2022;247(2):152–164 (Maywood). doi:10.1177/15353702211046927.
101. Elifani F, Amico E, Pepe G, et al. Curcumin dietary supplementation ameliorates disease phenotype in an animal model of Huntington's disease. *Hum Mol Genet*. 2019;28(23):4012–4021. doi:10.1093/hmg/ddz247.
102. 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(1):106–118. doi:10.1007/s12017-013-8261-y.
103. Gharaibeh A, Maiti P, Culver R, et al. Solid lipid curcumin particles protect medium spiny neuronal morphology, and reduce learning and memory deficits in the YAC128 mouse model of huntington's disease. *Int J Mol Sci*. 2020;21(24). doi:10.3390/ijms21249542.
104. Ouyang J, Li R, Shi H, Zhong J. Curcumin protects human umbilical vein endothelial cells against H(2)O(2)-induced cell injury. *Pain Res Manag*. 2019;2019:3173149. doi:10.1155/2019/3173149.
105. Bulboaca AE, Bolboaca SD, Stanescu IC, Sfrangeu CA, Bulboaca AC. Preemptive analgesic and antioxidative effect of curcumin for experimental migraine. *Biomed Res Int*. 2017:4754701 2017. doi:10.1155/2017/4754701.
106. Bulboaca AE, Bolboaca SD, Stanescu IC, et al. The effect of intravenous administration of liposomal curcumin in addition to sumatriptan treatment in an experimental migraine model in rats. *Int J Nanomed*. 2018;13:3093–3103. doi:10.2147/IJN.S162087.
107. Bulboaca AE, Bolboaca SD, Bulboaca AC, et al. Liposomal curcumin enhances the effect of naproxen in a rat model of migraine. *Med Sci Monit*. 2019;25:5087–5097. doi:10.12659/MSM.915607.
108. Natarajan C, Bright JJ. Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes. *J Immunol*. 2002;168(12):6506–6513. doi:10.4049/jimmunol.168.12.6506.
109. Liu JQ, Yan YQ, Liu JT, Wang YR, Wang X. Curcumin prevents experimental autoimmune encephalomyelitis by inhibiting proliferation and effector CD4+ T cell activation. *Eur Rev Med Pharmacol Sci*. 2019;23(20):9108–9116. doi:10.26355/eurrev_201910_19314.
110. Sun M, Liu N, Sun J, et al. Curcumin regulates anti-inflammatory responses by AXL/JAK2/STAT3 signaling pathway in experimental autoimmune encephalomyelitis. *Neurosci Lett*. 2022;787:136821. doi:10.1016/j.neulet.2022.136821.
111. I EL-D, Manai M, Neili NE, et al. Dual mechanism of action of curcumin in experimental models of multiple sclerosis. *Int J Mol Sci*. 2022;23(15). doi:10.3390/ijms23158658.
112. Xie L, Li XK, Funeshima-Fuji N, et al. Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. *Int Immunopharmacol*. 2009;9(5):575–581. doi:10.1016/j.intimp.2009.01.025.
113. Kanakasabai S, Casalini E, Walline CC, Mo C, Chearwae W, Bright JJ. Differential regulation of CD4(+) T helper cell responses by curcumin in experimental autoimmune encephalomyelitis. *J Nutr Biochem*. 2012;23(11):1498–1507. doi:10.1016/j.jnutbio.2011.10.002.
114. Esmaeilzadeh E, Soleimani M, Zare-Abdollahi D, Jameie B, Khorram Khorshid HR. Curcumin ameliorates experimental autoimmune encephalomyelitis in a C57BL/6 mouse model. *Drug Dev Res*. 2019;80(5):629–636. doi:10.1002/ddr.21540.
115. Boyao Y, Mengjiao S, Caicai B, Xiaoling L, Zhenxing L, Manxia W. Dynamic expression of autophagy-related factors in autoimmune encephalomyelitis and exploration of curcumin therapy. *J Neuroimmunol*. 2019;337:577067. doi:10.1016/j.jneuroim.2019.577067.
116. Barzegarzadeh B, Hatami H, Dehghan G, Khajehnasiri N, Khoobi M, Sadeghian R. Conjugated linoleic acid-curcumin attenuates cognitive deficits and oxidative stress parameters in the ethidium bromide-induced model of demyelination. *Neurotox Res*. 2021;39(3):815–825. doi:10.1007/s12640-020-00310-0.
117. Mavaddatiyan L, Khezri S, Abtahi Froushani SM. Molecular effects of curcumin on the experimental autoimmune encephalomyelitis. *Vet Res Forum*. 2021;12(1):47–52. doi:10.30466/vrf.2019.98789.2356.
118. 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(10):1449–1464. doi:10.1002/term.3110.
119. 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(3):310–320. doi:10.22037/ijpr.2020.112952.14033.
120. Lu L, Qi S, Chen Y, et al. 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. doi:10.1016/j.biomaterials.2020.119987.
121. Mohajeri M, Sadeghizadeh M, Najafi F, Javan M. Polymerized nano-curcumin attenuates neurological symptoms in EAE model of multiple sclerosis through down regulation of inflammatory and oxidative processes and enhancing neuroprotection and myelin repair. *Neuropharmacology*. 2015;99:156–167. doi:10.1016/j.neuropharm.2015.07.013.
122. Song HC, Chen Y, Chen Y, et al. GSK-3beta inhibition by curcumin mitigates amyloidogenesis via TFEB activation and anti-oxidative activity in human neuroblastoma cells. *Free Radic Res*. 2020;54(11–12):918–930. doi:10.1080/10715762.2020.1791843.
123. Buccarello L, Dragotto J, Iorio F, Hassanzadeh K, Corbo M, Feligioni M. The pivotal role of SUMO-1-JNK-Tau axis in an *in vitro* model of oxidative stress counteracted by the protective effect of curcumin. *Biochem Pharmacol*. 2020;178:114066. doi:10.1016/j.bcp.2020.114066.
124. Vajragupta O, Boonchoong P, Watanabe H, Tohda M, Kummasud N, Sumanont Y. Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. *Free Radic Biol Med*. 2003;35(12):1632–1644. doi:10.1016/j.freeradbiomed.2003.09.011.
125. Kemadjou Dibacto RE, Akamba Ambamba BD, Ella FA, et al. The neuroprotective effect of Xylopia parviflora against aluminum chloride-induced neurotoxicity in rats. *Heliyon*. 2022;8(7):e09896. doi:10.1016/j.heliyon.2022.e09896.
126. Elbini I, Doghri R, Ellefi A, Degrach I, Srairi-Abid N, Gati A. Curcumin attenuated neurotoxicity in sporadic animal model of Alzheimer's disease. *Molecules*. 2021;26(10). doi:10.3390/molecules26103011.

127. Chen J, Tang XQ, Zhi JL, et al. Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2-mitochondria-ROS-iNOS pathway. *Apoptosis*. 2006;11(6):943–953. doi:10.1007/s10495-006-6715-5.
128. Pandey N, Strider J, Nolan WC, Yan SX, Galvin JE. Curcumin inhibits aggregation of alpha-synuclein. *Acta Neuropathol*. 2008;115(4):479–489. doi:10.1007/s00401-007-0332-4.
129. Wang J, Du XX, Jiang H, Xie JX. Curcumin attenuates 6-hydroxydopamine-induced cytotoxicity by anti-oxidation and nuclear factor-kappa B modulation in MES23.5 cells. *Biochem Pharmacol*. 2009;78(2):178–183. doi:10.1016/j.bcp.2009.03.031.
130. Ortiz-Ortiz MA, Moran JM, Ruiz-Mesa LM, et al. Curcumin exposure induces expression of the Parkinson's disease-associated leucine-rich repeat kinase 2 (LRRK2) in rat mesencephalic cells. *Neurosci Lett*. 2010;468(2):120–124. doi:10.1016/j.neulet.2009.10.081.
131. Yu S, Zheng W, Xin N, et al. Curcumin prevents dopaminergic neuronal death through inhibition of the c-Jun N-terminal kinase pathway. *Rejuvenation Res*. 2010;13(1):55–64. doi:10.1089/rej.2009.0908.
132. Wang MS, Boddapati S, Emadi S, Sierks MR. Curcumin reduces alpha-synuclein induced cytotoxicity in Parkinson's disease cell model. *BMC Neurosci*. 2010;11:57. doi:10.1186/1471-2202-11-57.
133. Jaisin Y, Thampithak A, Meesarapee B, et al. Curcumin I protects the dopaminergic cell line SH-SY5Y from 6-hydroxydopamine-induced neurotoxicity through attenuation of p53-mediated apoptosis. *Neurosci Lett*. 2011;489(3):192–196. doi:10.1016/j.neulet.2010.12.014.
134. Liu Z, Yu Y, Li X, Ross CA, Smith WW. Curcumin protects against A53T alpha-synuclein-induced toxicity in a PC12 inducible cell model for Parkinsonism. *Pharmacol Res*. 2011;63(5):439–444. doi:10.1016/j.phrs.2011.01.004.
135. Wang YL, Ju B, Zhang YZ, et al. Protective effect of curcumin against oxidative stress-induced injury in Rats with Parkinson's disease through the Wnt/beta-catenin signaling pathway. *Cell Physiol Biochem*. 2017;43(6):2226–2241. doi:10.1159/000484302.
136. Wang YL, Liu XS, Wang SS, et al. Curcumin-activated mesenchymal stem cells derived from human umbilical cord and their effects on MPTP-mouse model of Parkinson's disease: a new biological therapy for Parkinson's disease. *Stem Cells Int*. 2020;2020:4636397. doi:10.1155/2020/4636397.
137. He HJ, Xiong X, Zhou S, et al. Neuroprotective effects of curcumin via autophagy induction in 6-hydroxydopamine Parkinson's models. *Neurochem Int*. 2022;155:105297. doi:10.1016/j.neuint.2022.105297.
138. Zbarsky V, Datla KP, Parkar S, Rai DK, Aruoma OI, Dexter DT. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. *Free Radic Res*. 2005;39(10):1119–1125. doi:10.1080/10715760500233113.
139. Rajeswari A. Curcumin protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Eur Rev Med Pharmacol Sci*. 2006;10(4):157–161.
140. Mansouri Z, Sabetkasaei M, Moradi F, Masoudnia F, Ataie A. Curcumin has neuroprotection effect on homocysteine rat model of Parkinson. *J Mol Neurosci*. 2012;47(2):234–242. doi:10.1007/s12031-012-9727-3.
141. Du XX, Xu HM, Jiang H, Song N, Wang J, Xie JX. Curcumin protects nigral dopaminergic neurons by iron-chelation in the 6-hydroxydopamine rat model of Parkinson's disease. *Neurosci Bull*. 2012;28(3):253–258. doi:10.1007/s12264-012-1238-2.
142. Tripanichkul W, Jaroensuppaperch EO. Curcumin protects nigrostriatal dopaminergic neurons and reduces glial activation in 6-hydroxydopamine hemiparkinsonian mice model. *Int J Neurosci*. 2012;122(5):263–270. doi:10.3109/00207454.2011.648760.
143. Tripanichkul W, Jaroensuppaperch EO. Ameliorating effects of curcumin on 6-OHDA-induced dopaminergic denervation, glial response, and SOD1 reduction in the striatum of hemiparkinsonian mice. *Eur Rev Med Pharmacol Sci*. 2013;17(10):1360–1368.
144. Song S, Nie Q, Li Z, Du G. Curcumin improves neurofunctions of 6-OHDA-induced parkinsonian rats. *Pathol Res Pract*. 2016;212(4):247–251. doi:10.1016/j.prp.2015.11.012.
145. Motawi TK, Sadik NAH, Hamed MA, Ali SA, Khalil WKB, Ahmed YR. Potential therapeutic effects of antagonizing adenosine A(2A) receptor, curcumin and niacin in rotenone-induced Parkinson's disease mice model. *Mol Cell Biochem*. 2020;465(1–2):89–102. doi:10.1007/s11010-019-03670-0.
146. El Nebrisi E, Javed H, Ojha SK, Oz M, Shehab S. Neuroprotective effect of curcumin on the nigrostriatal pathway in a 6-hydroxydopmine-induced rat model of Parkinson's disease is mediated by alpha7-nicotinic receptors. *Int J Mol Sci*. 2020;21(19). doi:10.3390/ijms21197329.
147. Khatri DK, Juvekar AR. Neuroprotective effect of curcumin as evinced by abrogation of rotenone-induced motor deficits, oxidative and mitochondrial dysfunctions in mouse model of Parkinson's disease. *Pharmacol Biochem Behav*. 2016:39–47 150-151. doi:10.1016/j.pbb.2016.09.002.
148. Rajeswari A, Sabesan M. Inhibition of monoamine oxidase-B by the polyphenolic compound, curcumin and its metabolite tetrahydrocurcumin, in a model of Parkinson's disease induced by MPTP neurodegeneration in mice. *Inflammopharmacology*. 2008;16(2):96–99. doi:10.1007/s10787-007-1614-0.
149. Pandareesh MD, Shrivash MK, Naveen Kumar HN, Misra K, Srinivas Bharath MM. Curcumin monoglucoside shows improved bioavailability and mitigates rotenone induced neurotoxicity in cell and drosophila models of Parkinson's disease. *Neurochem Res*. 2016;41(11):3113–3128. doi:10.1007/s11064-016-2034-6.
150. Ramires Junior OV, Alves BDS, Barros PAB, et al. Nanoemulsion improves the neuroprotective effects of curcumin in an experimental model of Parkinson's disease. *Neurotox Res*. 2021;39(3):787–799. doi:10.1007/s12640-021-00362-w.
151. de Guzman ACV, Razzak MA, Cho JH, Kim JY, Choi SS. Curcumin-loaded human serum albumin nanoparticles prevent Parkinson's disease-like symptoms in C. elegans. *Nanomaterials*. 2022;12(5) (Basel). doi:10.3390/nano12050758.
152. Mobahat M, Sadroddiny E, Nooshabadi VT, et al. Curcumin-loaded human endometrial stem cells derived exosomes as an effective carrier to suppress alpha-synuclein aggregates in 6OHDA-induced Parkinson's disease mouse model. *Cell Tissue Bank*. 2022. doi:10.1007/s10561-022-10008-6.
153. Peng H, Li Y, Ji W, et al. Intranasal administration of self-oriented nanocarriers based on therapeutic exosomes for synergistic treatment of Parkinson's disease. *ACS Nano*. 2022;16(1):869–884. doi:10.1021/acsnano.1c08473.
154. Deng I, Garg S, Zhou XF, Bobrovskaya L. The effects of novel formulations of edaravone and curcumin in the mouse intrastriatal lipopolysaccharide model of Parkinson's disease. *Front Biosci*. 2022;14(2):13 (Schol Ed). doi:10.31083/j.fbs1402013.
155. Zhu HT, Bian C, Yuan JC, et al. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-kappaB signaling pathway in experimental traumatic brain injury. *J Neuroinflammation*. 2014;11:59. doi:10.1186/1742-2094-11-59.
156. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. *Exp Neurol*. 2006;197(2):309–317. doi:10.1016/j.expneurol.2005.09.004.
157. Sharma S, Zhuang Y, Ying Z, Wu A, Gomez-Pinilla F. Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. *Neuroscience*. 2009;161(4):1037–1044. doi:10.1016/j.neuroscience.2009.04.042.
158. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: a possible role for aquaporin-4? *J Neurochem*. 2010;113(3):637–648. doi:10.1111/j.1471-4159.2010.06630.x.
159. Samini F, Samarghandian S, Borji A, Mohammadi G, bakaian M. Curcumin pretreatment attenuates brain lesion size and improves neurological function following traumatic brain injury in the rat. *Pharmacol Biochem Behav*. 2013;110:238–244. doi:10.1016/j.pbb.2013.07.019.
160. Dai W, Wang H, Fang J, et al. Curcumin provides neuroprotection in model of traumatic brain injury via the Nrf2-ARE signaling pathway. *Brain Res Bull*. 2018;140:65–71. doi:10.1016/j.brainresbull.2018.03.020.
161. Dong W, Yang B, Wang L, et al. Curcumin plays neuroprotective roles against traumatic brain injury partly via Nrf2 signaling. *Toxicol Appl Pharmacol*. 2018;346:28–36. doi:10.1016/j.taap.2018.03.020.
162. Dong X, Deng L, Yao S, et al. Protective effects of curcumin against thyroid hormone imbalance after gas explosion-induced traumatic brain injury via activation of the hypothalamic-pituitary-thyroid axis in male rats. *Environ Sci Pollut Res Int*. 2022;29(49):74619–74631. doi:10.1007/s11356-022-20943-2.
163. Wu A, Ying Z, Schubert D, Gomez-Pinilla F. Brain and spinal cord interaction: a dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. *Neurorehabil Neural Repair*. 2011;25(4):332–342. doi:10.1177/1545968310397706.
164. Wei G, Chen B, Lin Q, et al. Tetrahydrocurcumin provides neuroprotection in experimental traumatic brain injury and the Nrf2 signaling pathway as a potential mechanism. *Neuroimmunomodulation*. 2017;24(6):348–355. doi:10.1159/000487998.
165. Gao Y, Li J, Wu L, et al. Tetrahydrocurcumin provides neuroprotection in rats after traumatic brain injury: autophagy and the PI3K/AKT pathways as a potential mechanism. *J Surg Res*. 2016;206(1):67–76. doi:10.1016/j.jss.2016.07.014.
166. Narouiepour A, Ebrahimzadeh-Bideskan A, Rajabzadeh G, Gorji A, Negah SS. Neural stem cell therapy in conjunction with curcumin loaded in niosomal nanoparticles enhanced recovery from traumatic brain injury. *Sci Rep*. 2022;12(1):3572. doi:10.1038/s41598-022-07367-1.
167. Ringman JM, Frautschy SA, Teng E, et al. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. *Alzheimers Res Ther*. 2012;4(5):43. doi:10.1186/alzrt146.
168. Ngolab J, Donohue M, Belsha A, et al. Feasibility study for detection of retinal amyloid in clinical trials: the anti-amyloid treatment in asymptomatic Alzheimer's disease (A4) trial. *Alzheimers Dement (Amst)*. 2021;13(1):e12199. doi:10.1002/dad2.12199.
169. Small GW, Siddarth P, Li Z, et al. Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: a double-blind, placebo-controlled 18-month trial. *Am J Geriatr Psychiatry*. 2018;26(3):266–277. doi:10.1016/j.jagp.2017.10.010.
170. Chico L, Ienco EC, Bisordi C, et al. Amyotrophic lateral sclerosis and oxidative stress: a double-blind therapeutic trial after curcumin supplementation. *CNS Neurol Disord Drug Targets*. 2018;17(10):767–779. doi:10.2174/1871527317666180720162029.
171. Ahmadi M, Agah E, Nafissi S, et al. Safety and efficacy of nanocurcumin as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a pilot randomized clinical trial. *Neurotherapeutics*. 2018;15(2):430–438. doi:10.1007/s13311-018-0606-7.
172. Rezaie S, Askari G, Khorvash F, Tarrahi MJ, Amani R. Effects of curcumin supplementation on clinical features and inflammation, in migraine patients: a double-blind controlled, placebo randomized clinical trial. *Int J Prev Med*. 2021;12:161. doi:10.4103/ijpvm.IJPVM_405_20.
173. Abdolahi M, Tafakhori A, Togha M, et al. The synergistic effects of omega-3 fatty acids and nano-curcumin supplementation on tumor necrosis factor (TNF)-alpha gene expression and serum level in migraine patients. *Immunogenetics*. 2017;69(6):371–378. doi:10.1007/s00251-017-0992-8.
174. Abdolahi M, Sarraf P, Javanbakht MH, et al. A novel combination of omega-3 fatty acids and nano-curcumin modulates interleukin-6 gene expression and high sensitivity C-reactive protein serum levels in patients with migraine: a randomized clinical trial study. *CNS Neurol Disord Drug Targets*. 2018;17(6):430–438. doi:10.2174/1871527317666180625101643.
175. Abdolahi M, Jafarieh A, Sarraf P, et al. The neuromodulatory effects of omega-3 fatty acids and nano-curcumin on the COX-2/iNOS network in migraines: a clinical

trial study from gene expression to clinical symptoms. *Endocr Metab Immune Disord Drug Targets*. 2019;19(6):874–884. doi:10.2174/1871530319666190212170140.
176. Djalali M, Djalali M, Abdolahi M, et al. The effect of nano-curcumin supplementation on pentraxin 3 gene expression and serum level in migraine patients. *Rep Biochem Mol Biol*. 2020;9(1):1–7. doi:10.29252/rbmb.9.1.1.
177. Djalali M, Abdolahi M, Hosseini R, Miraghajani M, Mohammadi H, Djalali M. The effects of nano-curcumin supplementation on Th1/Th17 balance in migraine patients: a randomized controlled clinical trial. *Complement Ther Clin Pract*. 2020;41:101256. doi:10.1016/j.ctcp.2020.101256.
178. Parohan M, Sarraf P, Javanbakht MH, Foroushani AR, Ranji-Burachaloo S, Djalali M. The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial. *Nutr Neurosci*. 2021;24(4):317–326. doi:10.1080/1028415X.2019.1627770.
179. Honarvar NM, Soveid N, Abdolahi M, Djalali M, Hatami M, Karzar NH. Anti-neuroinflammatory properties of n-3 fatty acids and nano- curcumin on migraine patients from cellular to clinical insight: a randomized, double-blind and placebo-controlled trial. *Endocr Metab Immune Disord Drug Targets*. 2021;21(2):365–373. doi:10.2174/1871530320666200729144430.
180. Sedighiyan M, Abdolahi M, Jafari E, et al. The effects of nano-curcumin supplementation on adipokines levels in obese and overweight patients with migraine: a double blind clinical trial study. *BMC Res Notes*. 2022;15(1):189. doi:10.1186/s13104-022-06074-4.
181. Soveyd N, Abdolahi M, Djalali M, et al. The combined effects of omega -3 fatty acids and nano-curcumin supplementation on intercellular adhesion molecule-1 (ICAM-1) gene expression and serum levels in migraine patients. *CNS Neurol Disord Drug Targets*. 2018;16(10):1120–1126. doi:10.2174/1871527317666171213154749.
182. Abdolahi M, Karimi E, Sarraf P, et al. The omega-3 and Nano-curcumin effects on vascular cell adhesion molecule (VCAM) in episodic migraine patients: a randomized clinical trial. *BMC Res Notes*. 2021;14(1):283. doi:10.1186/s13104-021-05700-x.
183. Dolati S, Ahmadi M, Aghebti-Maleki L, et al. Nanocurcumin is a potential novel therapy for multiple sclerosis by influencing inflammatory mediators. *Pharmacol Rep*. 2018;70(6):1158–1167. doi:10.1016/j.pharep.2018.05.008.
184. Dolati S, Ahmadi M, Rikhtegar R, et al. Changes in Th17 cells function after nanocurcumin use to treat multiple sclerosis. *Int Immunopharmacol*. 2018;61:74–81. doi:10.1016/j.intimp.2018.05.018.
185. Dolati S, Aghebati-Maleki L, Ahmadi M, et al. Nanocurcumin restores aberrant miRNA expression profile in multiple sclerosis, randomized, double-blind, placebo-controlled trial. *J Cell Physiol*. 2018;233(7):5222–5230. doi:10.1002/jcp.26301.
186. Dolati S, Babaloo Z, Ayromlou H, et al. Nanocurcumin improves regulatory T-cell frequency and function in patients with multiple sclerosis. *J Neuroimmunol*. 2019;327:15–21. doi:10.1016/j.jneuroim.2019.01.007.
187. Ghodsi H, Rahimi HR, Aghili SM, Saberi A, Shoeibi A. Evaluation of curcumin as add-on therapy in patients with Parkinson's disease: a pilot randomized, triple-blind, placebo-controlled trial. *Clin Neurol Neurosurg*. 2022;218:107300. doi:10.1016/j.clineuro.2022.107300.
188. Hatefi M, Ahmadi MRH, Rahmani A, Dastjerdi MM, Asadollahi K. Effects of curcumin on bone loss and biochemical markers of bone turnover in patients with spinal cord injury. *World Neurosurg*. 2018;114:e785–e791. doi:10.1016/j.wneu.2018.03.081.
189. Allison DJ, Josse AR, Gabriel DA, Klentrou P, Ditor DS. Targeting inflammation to influence cognitive function following spinal cord injury: a randomized clinical trial. *Spinal Cord*. 2017;55(1):26–32. doi:10.1038/sc.2016.96.
190. Shadnoush M, Zahedi H, Norouzy A, et al. Effects of supplementation with curcuminoids on serum adipokines in critically ill patients: a randomized double-blind placebo-controlled trial. *Phytother Res*. 2020;34(12):3180–3188. doi:10.1002/ptr.6749.
191. Hamaguchi T, Ono K, Yamada M. REVIEW: curcumin and Alzheimer's disease. *CNS Neurosci Ther*. 2010;16(5):285–297. doi:10.1111/j.1755-5949.2010.00147.x.
192. Farkhondeh T, Samarghandian S, Pourbagher-Shahri AM, Sedaghat M. The impact of curcumin and its modified formulations on Alzheimer's disease. *J Cell Physiol*. 2019;234(10):16953–16965. doi:10.1002/jcp.28411.
193. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25(24). doi:10.3390/molecules25245789.
194. Jaskulska A, Janecka AE, Gach-Janczak K. Thapsigargin-from traditional medicine to anticancer drug. *Int J Mol Sci*. 2020;22(1). doi:10.3390/ijms22010004.
195. Sagara Y, Wade JB, Inesi G. A conformational mechanism for formation of a dead--end complex by the sarcoplasmic reticulum ATPase with thapsigargin. *J Biol Chem*. 1992;267(2):1286–1292.
196. Tadini-Buoninsegni F, Smeazzetto S, Gualdani R, Moncelli MR. Drug interactions with the Ca(2+)-ATPase from sarco(Endo)plasmic reticulum (SERCA). *Front Mol Biosci*. 2018;5:36. doi:10.3389/fmolb.2018.00036.
197. Sehgal P, Szalai P, Olesen C, et al. Inhibition of the sarco/endoplasmic reticulum (ER) Ca(2+)-ATPase by thapsigargin analogs induces cell death via ER Ca(2+) depletion and the unfolded protein response. *J Biol Chem*. 2017;292(48):19656–19673. doi:10.1074/jbc.M117.796920.
198. Wang K, Zhang W. Mitochondria-associated endoplasmic reticulum membranes: at the crossroad between familiar and sporadic Alzheimer's disease. *Synapse*. 2021;75(6):e22196. doi:10.1002/syn.22196.
199. Nguyen HD, Jo WH, Hoang NHM, Yu BP, Chung HY, Kim MS. 1,2-diacetylbenzene impaired hippocampal memory by activating proinflammatory cytokines and upregulating the prolactin pathway: an *in vivo* and *in vitro* study" [Int. Immunopharmacol. 108 (2022) 108901]. *Int Immunopharmacol*. 2022;111:109156. doi:10.1016/j.intimp.2022.109156.
200. Duc Nguyen H, Hee Jo W, Hong Minh Hoang N, Kim MS. Anti-inflammatory effects of B vitamins protect against tau hyperphosphorylation and cognitive impairment induced by 1,2 diacetyl benzene: an *in vitro* and in silico study. *Int Immunopharmacol*. 2022;108:108736. doi:10.1016/j.intimp.2022.108736.
201. Nguyen HD, Jo WH, Hoang NH, Yu BP, Chung HY, Kim MS. Age-dependent alteration of microRNAs related to brain cancer in C6 glioma cells and young and old hippocampal rats after exposure to 1, 2-Diacetylbenzene. Toxicology and Environmental Health Sciences. 2023 Jun;15(2):181-97.
202. Kim MS, Sabri MI, Miller VH, Kayton RJ, Dixon DA, Spencer PS. 1,2-diacetylbenzene, the neurotoxic metabolite of a chromogenic aromatic solvent, induces proximal axonopathy. *Toxicol Appl Pharmacol*. 2001;177(2):121–131. doi:10.1006/taap.2001.9301.
203. Kim MS, Park HR, Chung HY, et al. Organic solvent metabolite, 1,2-diacetylbenzene, impairs neural progenitor cells and hippocampal neurogenesis. *Chem Biol Interact*. 2011;194(2–3):139–147. doi:10.1016/j.cbi.2011.10.001.
204. Nguyen HD, Jo WH, Hoang NH, Kim MS. Risperidone ameliorated 1, 2-Diacetylbenzene-induced cognitive impairments in mice via activating prolactin signaling pathways. International Immunopharmacology. 2023 Feb 1;115:109726.
205. Utomo RY, Sugie A, Okada S, Miura K, Nakamura H. Detoxification of amyloid beta fibrils by curcumin derivatives and their verification in a Drosophila Alzheimer's model. *Chem Commun*. 2022;58(15):2576–2579 (Camb). doi:10.1039/d1cc07000b.
206. Xie Z, Tanzi RE. Alzheimer's disease and post-operative cognitive dysfunction. *Exp Gerontol*. 2006;41(4):346–359. doi:10.1016/j.exger.2006.01.014.
207. Yoon WB, Choi HJ, Kim JE, et al. Comparison of scopolamine-induced cognitive impairment responses in three different ICR stocks. *Lab Anim Res*. 2018;34(4):317–328. doi:10.5625/lar.2018.34.4.317.
208. Tang KS. The cellular and molecular processes associated with scopolamine-induced memory deficit: a model of Alzheimer's biomarkers. *Life Sci*. 2019;233:116695. doi:10.1016/j.lfs.2019.116695.
209. Gilles C, Ertle S. Pharmacological models in Alzheimer's disease research. *Dialogues Clin Neurosci*. 2000;2(3):247–255. doi:10.31887/DCNS.2000.2.3/cgilles.
210. Mostafa DK, El Azhary NM, Nasra RA. The hydrogen sulfide releasing compounds ATB-346 and diallyl trisulfide attenuate streptozotocin-induced cognitive impairment, neuroinflammation, and oxidative stress in rats: involvement of asymmetric dimethylarginine. *Can J Physiol Pharmacol*. 2016;94(7):699–708. doi:10.1139/cjpp-2015-0316.
211. Lin YT, Seo J, Gao F, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron*. 2018;98(6):1141–1154 e1147. doi:10.1016/j.neuron.2018.05.008.
212. Esquerda-Canals G, Montoliu-Gaya L, Guell-Bosch J, Villegas S. Mouse models of Alzheimer's disease. *J Alzheimers Dis*. 2017;57(4):1171–1183. doi:10.3233/JAD-170045.
213. Theendakara V, Peters-Libeu CA, Bredesen DE, Rao RV. Transcriptional effects of ApoE4: relevance to Alzheimer's disease. *Mol Neurobiol*. 2018;55(6):5243–5254. doi:10.1007/s12035-017-0757-2.
214. Uddin MS, Kabir MT, Al Mamun A, Abdel-Daim MM, Barreto GE, Ashraf GM. APOE and Alzheimer's disease: evidence mounts that targeting APOE4 may combat Alzheimer's pathogenesis. *Mol Neurobiol*. 2019;56(4):2450–2465. doi:10.1007/s12035-018-1237-z.
215. Feldman EL, Goutman SA, Petri S, et al. Amyotrophic lateral sclerosis. *Lancet*. 2022;400(10360):1363–1380. doi:10.1016/S0140-6736(22)01272-7.
216. Benatar M, Wuu J, McHutchison C, et al. Preventing amyotrophic lateral sclerosis: insights from pre-symptomatic neurodegenerative diseases. *Brain*. 2022;145(1):27–44. doi:10.1093/brain/awab404.
217. Zou ZY, Zhou ZR, Che CH, Liu CY, He RL, Huang HP. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2017;88(7):540–549. doi:10.1136/jnnp-2016-315018.
218. Chia R, Chio A, Traynor BJ. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. *Lancet Neurol*. 2018;17(1):94–102. doi:10.1016/S1474-4422(17)30401-5.
219. Makino J, Kamiya T, Hara H, Adachi T. TPA induces the expression of EC-SOD in human monocytic THP-1 cells: involvement of PKC, MEK/ERK and NOX-derived ROS. *Free Radic Res*. 2012;46(5):637–644. doi:10.3109/10715762.2012.664841.
220. Forouzanfar F, Majeed M, Jamialahmadi T, Sahebkar A. Curcumin: a review of its effects on epilepsy. *Adv Exp Med Biol*. 2021;1291:363–373. doi:10.1007/978-3-030-56153-6_21.
221. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet*. 2019;393(10172):689–701. doi:10.1016/S0140-6736(18)32596-0.
222. Bonilla L, Esteruelas G, Ettcheto M, et al. Biodegradable nanoparticles for the treatment of epilepsy: from current advances to future challenges. *Epilepsia Open*. 2022;7(Suppl 1):S121–S132 Suppl 1. doi:10.1002/epi4.12567.
223. Ali O, Shaikh MF, Hasnain MS, Sami F, Khan A, Ansari MT. Nanotechnological Advances in the Treatment of Epilepsy. *CNS Neurol Disord Drug Targets*. 2022;21(10):994–1003. doi:10.2174/1871527321666211221162104.
224. Zuccato C, Valenza M, Cattaneo E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. *Physiol Rev*. 2010;90(3):905–981. doi:10.1152/physrev.00041.2009.
225. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;443(7113):787–795. doi:10.1038/nature05292.
226. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. *J Psychiatry Neurosci*. 2006;31(1):21–29.
227. Tabrizi SJ, Estevez-Fraga C, van Roon-Mom WMC, et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. *Lancet Neurol*. 2022;21(7):645–658. doi:10.1016/S1474-4422(22)00121-1.
228. MacDonald ME, Ambrose CM, Duyao MP, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72(6):971–983. doi:10.1016/0092-8674(93)90585-e.
229. Kremer B. Clinical neurology of Huntington's disease. Oxford Monographs on Medical Genetics 2002, 45, 28–61.

230. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin lowering strategies for disease modification in huntington's disease. *Neuron*. 2019;102(4):899. doi:10.1016/j.neuron.2019.05.001.
231. Monroy A, Lithgow GJ, Alavez S. Curcumin and neurodegenerative diseases. *Biofactors*. 2013;39(1):122–132. doi:10.1002/biof.1063.
232. Marsh JL, Thompson LM. Can flies help humans treat neurodegenerative diseases? *Bioessays*. 2004;26(5):485–496. doi:10.1002/bies.20029.
233. Marsh JL, Pallos J, Thompson LM. Fly models of Huntington's disease. *Hum Mol Genet*. 2003(12):R187–R193 Spec No 2. doi:10.1093/hmg/ddg271.
234. Bonini NM, Fortini ME. Human neurodegenerative disease modeling using Drosophila. *Annu Rev Neurosci*. 2003;26:627–656. doi:10.1146/annurev.neuro.26.041002.131425.
235. Lee WC, Yoshihara M, Littleton JT. Cytoplasmic aggregates trap polyglutamine-containing proteins and block axonal transport in a Drosophila model of Huntington's disease. *Proc Natl Acad Sci U S A*. 2004;101(9):3224–3229. doi:10.1073/pnas.0400243101.
236. Mangiarini L, Sathasivam K, Seller M, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell*. 1996;87(3):493–506. doi:10.1016/s0092-8674(00)81369-0.
237. Lione LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ, Dunnett SB. Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. *J Neurosci*. 1999;19(23):10428–10437. doi:10.1523/JNEUROSCI.19-23-10428.1999.
238. Carter RJ, Lione LA, Humby T, et al. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J Neurosci*. 1999;19(8):3248–3257. doi:10.1523/JNEUROSCI.19-08-03248.1999.
239. Global Burden of Disease StudyC. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the global burden of disease study 2013. *Lancet*. 2015;386(9995):743–800. doi:10.1016/S0140-6736(15)60692-4.
240. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163–2196. doi:10.1016/S0140-6736(12)61729-2.
241. Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019;92(19):e2250–e2260. doi:10.1212/WNL.0000000000007452.
242. Jain S, Silberstein SD. Invited commentary on preventive anti-migraine therapy (PAMT). *Curr Treat Options Neurol*. 2019;21(4):14. doi:10.1007/s11940-019-0555-4.
243. Ashina M, Buse DC, Ashina H, et al. Migraine: integrated approaches to clinical management and emerging treatments. *Lancet*. 2021;397(10283):1505–1518. doi:10.1016/S0140-6736(20)32342-4.
244. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology*. 2015;84(7):688–695. doi:10.1212/WNL.0000000000001256.
245. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. *Headache*. 2019;59(3):306–338. doi:10.1111/head.13459.
246. Xie L, Li XK, Takahara S. Curcumin has bright prospects for the treatment of multiple sclerosis. *Int Immunopharmacol*. 2011;11(3):323–330. doi:10.1016/j.intimp.2010.08.013.
247. Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain*. 2017;140(3):527–546. doi:10.1093/brain/aww258.
248. Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol*. 2019;26(1):27–40. doi:10.1111/ene.13819.
249. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: from risk factors to prevention-an update. *Semin Neurol*. 2016;36(2):103–114. doi:10.1055/s-0036-1579693.
250. Comabella M, Khoury SJ. Immunopathogenesis of multiple sclerosis. *Clin Immunol*. 2012;142(1):2–8. doi:10.1016/j.clim.2011.03.004.
251. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000;343(13):938–952. doi:10.1056/NEJM200009283431307.
252. Greer JM, McCombe PA. Role of gender in multiple sclerosis: clinical effects and potential molecular mechanisms. *J Neuroimmunol*. 2011;234(1–2):7–18. doi:10.1016/j.jneuroim.2011.03.003.
253. Goldenberg M.M. Multiple sclerosis review. P T 2012, 37 (3), 175–184.
254. Lees JR, Iwakura Y, Russell JH. Host T cells are the main producers of IL-17 within the central nervous system during initiation of experimental autoimmune encephalomyelitis induced by adoptive transfer of Th1 cell lines. *J Immunol*. 2008;180(12):8066–8072. doi:10.4049/jimmunol.180.12.8066.
255. Benameur T, Giacomucci G, Panaro MA, et al. New Promising Therapeutic Avenues of Curcumin in Brain Diseases. *Molecules*. 2021;27(1). doi:10.3390/molecules27010236.
256. Abdul-Latif R, Stupans I, Allahham A, Adhikari B, Thrimawithana T. Natural antioxidants in the management of Parkinson's disease: review of evidence from cell line and animal models. *J Integr Med*. 2021;19(4):300–310. doi:10.1016/j.joim.2021.03.007.
257. Lazaro DF, Pavlou MAS, Outeiro TF. Cellular models as tools for the study of the role of alpha-synuclein in Parkinson's disease. *Exp Neurol*. 2017;298(Pt B):162–171. doi:10.1016/j.expneurol.2017.05.007.
258. Moors T, Paciotti S, Chiasserini D, et al. Lysosomal Dysfunction and alpha-Synuclein Aggregation in Parkinson's Disease: diagnostic Links. *Mov Disord*. 2016;31(6):791–801. doi:10.1002/mds.26562.
259. Przedborski S, Vila M. MPTP: a review of its mechanisms of neurotoxicity. *Clin Neurosci Res*. 2001;1(6):407–418. doi:10.1016/S1566-2772(01)00019-6Get.
260. Sawada H, Ibi M, Kihara T, et al. Estradiol protects dopaminergic neurons in a MPP+Parkinson's disease model. *Neuropharmacology*. 2002;42(8):1056–1064. doi:10.1016/s0028-3908(02)00049-7.
261. Coulom H, Birman S. Chronic exposure to rotenone models sporadic Parkinson's disease in Drosophila melanogaster. *J Neurosci*. 2004;24(48):10993–10998. doi:10.1523/JNEUROSCI.2993-04.2004.
262. Khatri DK, Juvekar AR. Propensity of Hyoscyamus niger seeds methanolic extract to allay stereotaxically rotenone-induced Parkinson's disease symptoms in rats. *Orient Pharm Exp Med*. 2015;15(4):327–339. doi:10.1007/s13596-015-0202-x.
263. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol*. 2014;16(Suppl 4) Suppl 4iv1-63. doi:10.1093/neuonc/nou223.
264. Weathers SP, Gilbert MR. Advances in treating glioblastoma. F1000. *Prime Rep*. 2014;6:46. doi:10.12703/P6-46.
265. Klinger NV, Mittal S. Therapeutic Potential of Curcumin for the Treatment of Brain Tumors. *Oxid Med Cell Longev*. 2016;2016:9324085. doi:10.1155/2016/9324085.
266. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide *versus* radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459–466. doi:10.1016/S1470-2045(09)70025-7.
267. Johnson DR, Leeper HE, Uhm JH. Glioblastoma survival in the United States improved after Food and Drug Administration approval of bevacizumab: a population-based analysis. *Cancer*. 2013;119(19):3489–3495. doi:10.1002/cncr.28259.
268. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996. doi:10.1056/NEJMoa043330.
269. Michinaga S, Koyama Y. Pathophysiological responses and roles of astrocytes in traumatic brain injury. *Int J Mol Sci*. 2021;22(12). doi:10.3390/ijms22126418.
270. Chevin M, Chabrier S, Allard MJ, Sebire G. Necroptosis blockade potentiates the neuroprotective effect of hypothermia in neonatal hypoxic-ischemic encephalopathy. *Biomedicines*. 2022;10(11). doi:10.3390/biomedicines10112913.
271. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. *Nat Rev Neurosci*. 2012;13(4):267–278. doi:10.1038/nrn3174.
272. Thapa K, Khan H, Singh TG, Kaur A. Traumatic brain injury: mechanistic insight on pathophysiology and potential therapeutic targets. *J Mol Neurosci*. 2021;71(9):1725–1742. doi:10.1007/s12031-021-01841-7.