The Functional Roles of Curcumin on Astrocytes in Neurodegenerative Diseases

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Keywords

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Abstract

Progressive abnormality and loss of axons and neurons in the central nervous system (CNS) cause neurodegenerative diseases (NDs). Protein misfolding and its collection are the most important pathological features of NDs. Astrocytes are the most plentiful cells in the mammalian CNS (about 20–40% of the human brain) and have several central functions in the maintenance of the health and correct function of the CNS. Astrocytes have an essential role in the preservation of brain homeostasis, and it is not surprising that these multifunctional cells have been implicated in the onset and progression of several NDs. Thus, they become an exciting target for the study of NDs. Over almost 15 years, it was revealed that curcumin has several therapeutic effects in a wide variety of diseases' treatment. Curcumin is a valuable ingredient present in turmeric spice and has several essential roles, including those which are anticarcinogenic, hepatoprotective,

thrombosuppressive, cardioprotective, anti-arthritis, anti-inflammatory, antioxidant, chemopreventive, chemotherapeutic, and anti-infectious. Furthermore, curcumin can suppress inflammation; promote angiogenesis; and treat diabetes, pulmonary problems, and neurological dysfunction. Here, we review the effects of curcumin on astrocytes in NDs, with a focus on Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis.

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Introduction

Neurodegenerative diseases (NDs) are traditionally defined as progressive neurological disorders that affect the central nervous system (CNS). Several factors, such as neuroinflammation, accumulation of misfolded amyloid proteins, and oxidative damage, have critical roles in the initiation and progression of NDs. Several factors including oxidative stress, pH, protein concentration, and metal ions have crucial roles in amyloid protein formation. Many studies indicate that some NDs are caused by ge-

Table 1. The common neurodegenerative diseases and their genetics, symptoms, and pathology

Disease	Genes involved	Proteins involved	Pathology	Symptoms	References
Alzheimer's disease	APP, presenilin 1, 2	A β , tau	A β plaque Tau tangle Extracellular plaque neurofibrillary tangle	Memory loss Personality change Worried, depressed	[4, 7, 18]
Parkinson's disease	α -Synuclein Parkin UCHL-1 LRRK2	α -Synuclein	Lewy body, neurofibrillary tangle	Impairment of sensorimotor Coordination, cognition Abnormal muscle movement, memory loss, bradykinesia, tremor, dementia, depression, and rigidity	[8, 9, 12]
Huntington's disease	HTT	HTT	Inclusion bodies in cytoplasm and nucleus Decreased striatal volume, neuronal loss White matter loss, microgliosis	Uncontrolled movements Balance impairment Clumsiness, memory loss, cortical thinning, chorea, bradykinesia, psychiatric symptoms, and cognitive deficits	[14, 53]
Multiple sclerosis disease	HLA, IL2RA, IL7RA	Myelin	Demyelinating lesion	Physical and cognitive Disability	[11, 12, 19]
ALS	SOD1	EAAT2	Increases NF- κ B signaling expression	Bulbar symptoms, dysarthria, and dysphagia	[13, 60, 61]

APP, amyloid precursor protein; A β , β -amyloid; LRRK2, leucine-rich repeat kinase 2; UCHL-1, ubiquitin carboxyl-terminal hydrolase isozyme L1; IL2RA, interleukin-2, receptor alpha chain; IL7RA, interleukin-7, receptor subunit alpha; HLA, human leukocyte antigen; HTT, Huntingtin.

netic mutations [1]. For example, several genes are recognized as contributing to several NDs. Many of the mutations in these genes cause abnormal processing of proteins, causing their misfolding and altered physicochemical properties, leading to the accumulation of toxic aggregates in the human CNS. Accumulation of misfolded proteins, like amyloid protein, causes deficiency in neuronal communication and leads to some NDs [2]. Many mitochondrial dysfunctions in NDs are a product of nuclear or mitochondrial mutations, induced by environmental factors. Structurally and functionally damaged mitochondria with disrupted electron transport chain cause insufficient ATP production and produce more proapoptotic factors and reactive oxygen species (ROS), thereby finally leading to neuronal damage [1, 3].

Astrocytes play a crucial role in the normal function of the CNS, and disturbances in astrocytic function are involved in the pathogenesis of NDs. Furthermore, astrocytes contribute to the inflammatory/immune responses in the CNS [4]. Release of proinflammatory factors leads to cellular damage and also stimulates the production of A β in astrocytes. Microglia act as a macrophage in the CNS and have a well-established function in the programmed deletion of neural cells during development. Microglia, through the deletion of toxic cellular debris, have an essential role in the normal preservation of neu-

ronal functioning. The crucial function of microglia in the adult CNS disease is linked to neuroinflammation and emitting distress signals, leading to increased activation, proliferation, and migration of additional microglia to the site of CNS damage [5].

Evidence shows that a well-controlled inflammatory reaction is essential for neuroregeneration and proper function of the CNS. However, chronic immune activation is one of the causes of several NDs. Although the causes of these immune responses can vary, scientists generally agree that they result in triggering cellular apoptotic pathways, which protect other nearby neurons from toxic substances [1, 6]. The most common NDs are Alzheimer's disease (AD) [7], Parkinson's (PD) and Huntington's diseases (HD) [8–10], multiple sclerosis (MS) [11, 12] and amyotrophic lateral sclerosis (ALS) [13]. The first three of the diseases have been defined with different clinical features of the disease process. However, these diseases appear to be similar at the cellular level (Table 1).

Astrocytes

Astrocytes are a large number of cells in the mammalian CNS and have critical roles in neuronal survival. Thus, loss of normal astrocyte functions eventually leads

Fig. 1. Schematic view for biomedical properties of curcumin.

to neurodegeneration. Astrocytes play essential roles in neurovascular coupling, regulating synapse formation, neuronal maintenance, and neuroplasticity, and participate in axon myelination [15]. Furthermore, the correlation between neurons, astrocytes, and blood vessels makes the role of astrocytes a fundamental element in neuronal activity and cerebral blood flow. Astrocytes, via the malate-aspartate shuttle, have an essential role in transporting different nutrients and metabolic precursors to neurons and also through their potassium channels that are located at synapses, which are crucial for extracellular potassium homeostasis [15].

Astrocytes based on their anatomical locations can be divided into 5 major groups [16]:

1. fibrous astrocytes in white matter, with a star-like appearance;
2. protoplasmic astrocytes in the gray matter, which have a less complex shape;
3. perivascular astrocytes;
4. radial glia; and
5. perivascular astrocytes.

Astrocytes secrete active molecules and numerous factors in the brain, which are critical for synthesizing neurotransmitters and maintaining proper neuronal metabolism. Astrocytes also have an important role in cell-to-cell communications, modulating synapse development, maintaining the extracellular environment, facilitating neuronal activity, and other regulatory functions. Astrocytes have several essential roles in regular CNS functions, including glutamate preservation, water homeostasis, and modulation of extracellular potassium. Further-

more, astrocytes are functionally associated with neighboring astrocytes and oligodendrocytes by gap junctions. One important function of astrocytes is monitoring and maintaining the blood-brain barrier (BBB), which provides an anatomical mechanism for selective passage of nutrients, water, ions, and cells between blood and brain. Furthermore, astrocytes help in the production of neurosteroids in the nervous system, including allopregnanolone, estrogen, and dehydroepiandrosterone. Neurosteroids can modify neuronal excitability, stimulate myelination, and reduce proinflammatory responses from astrocytes [12, 16].

Several studies showed that astrocytes have a dual role in inflammatory conditions. On the one hand, astrocytes have an important role in protecting the CNS during inflammatory conditions by decreasing reactive monocyte cell migration into the CNS and regulating T-cell activation through costimulatory factor secretions that enter the CNS [12, 17]. Furthermore, several studies have shown that the astrocytic expression of Fas ligands causes activation of T-cell apoptosis. On the other hand, subpopulations of astrocytes have phagocytic activity and may act on antigen-presenting cells (APCs) to increase T-cell-mediated CNS injury. Astrocytes also express cofactors for MHC II function, including CD80, CD40, and CD86, the cell surface proteins that are potentially associated with TCR binding and T-cell activation [5]. Activated astrocytes increase ICAM-1 and VCAM-1 that promote cell-cell interactions with surrounding leukocytes. Several molecules, including glial fibrillary acidic protein (GFAP), vimentin, glutamine synthetase, and S100 β (cal-

cium-binding protein), are astrocytic markers that are increased in some NDs. A better understanding of the various functions of astrocytes has facilitated the drug discovery for MS, AD, and other NDs [12, 18].

Curcumin

Curcumin is the main component of a yellow pigment, commonly called diferuloylmethane, and is an active ingredient in the rhizome of the herb *Curcuma longa* that represents various biomedical applications (Fig. 1). Curcumin has also been traditionally used for its medicinal benefits and wound healing for centuries. However, it was first applied as a drug to treat biliary disease in 1937. Curcumin is a lipophilic polyphenol that is relatively stable in the acidic pH but decomposes in neutral-basic conditions. Curcumin contains approximately 77% diferuloylmethane, 17% dimethoxycurcumin, and 6% bisdemethoxycurcumin. Nowadays, curcumin ($C_{21}H_{20}O_6$) has important roles in the attenuation of progression of some NDs because of its anti-amyloid and anti-inflammatory agents. In addition, curcumin also has several benefits, such as being safe, inexpensive, and readily available polyphenol that can cross the BBB, thus attracting researchers to use it for treating NDs [2, 19, 20].

Curcumin is an NF- κ B inhibitor by interrupting ZO-1 expression and localization, MLC phosphorylation, and ROS generation inhibition, which constrains disruption of the BBB by Th17 cells. Furthermore, curcumin, through its NF- κ B inhibitory effect, causes intestine dendritic cell differentiation into tolerogenic phenotypes, as well as naive T cells to differentiate into FoxP3⁺ regulatory T cells (intestine protective, Treg). Thus, curcumin can prevent colitis, due to its anti-inflammatory function. Curcumin has a critical role in transcription factor regulation. Furthermore, curcumin can regulate cytokines, adhesion molecules, protein kinases, redox status, and inflammation-associated enzymes [19–21].

Animal studies have shown that curcumin is poorly absorbed, has limited bioavailability, and is immediately metabolized in the liver and excreted in the feces. Nowadays, researchers focus on improving its bioavailability in humans by conjugating it to a stable carrier or by the use of curcumin metabolism inhibitors [6, 20]. Furthermore, recent advances showed that other approaches include the use of curcumin nanoparticles, liposomes, micelles, and phospholipid complexes that can increase the bioavailability of curcumin. This method contributes to an increase in the circulation of curcumin, cellular permea-

bility, and resistance to metabolic processes [22, 23]. The pharmacological activities of curcumin are antimicrobial, anti-inflammatory, antioxidant, and anticarcinogenic. It also exhibits potent immunoregulatory activities that can modulate the T cells, B cells, neutrophils, natural killer cells, and macrophage activation and function. Curcumin has been shown to be protective for several cells, including astrocytes, neurons, microglia, and different part of the CNS such as hippocampal, mesencephalic, cortical, and spinal cord [2, 6, 19, 20].

An MS animal study showed that curcumin regulates T-cell responses to IL-12 by blocking IL-12 production, and IL-12 signaling, through inhibiting JAK-STAT signaling activation. Thus, it has been suggested that curcumin could be used for treating MS and other Th1-cell-mediated inflammatory diseases. Furthermore, curcumin at high doses can directly induce T-cell apoptosis and inhibit T-cell proliferation through blocking of the IL-2 signaling pathway, high-affinity IL-2R, and interfering with IL-2R signaling. These data indicate that curcumin has immunosuppressive effects on many pathways. Thus, curcumin, through its proinflammatory cytokines, decreases TNF- α/β , IL-1, IL-6, and IL-8, and COX-2 provides a therapeutic effect by reducing inflammatory conditions [12, 22, 24].

Curcumin can cross BBB and, by inhibiting proinflammatory cytokines, can regulate homeostasis of the CNS. The BBB has a crucial role in controlling the homeostasis of the brain microenvironment. Thus, because autoreactive T-cell penetration plays a key role in MS lesion development, the role of curcumin to protect the BBB could reduce the severity of MS. Curcumin also decreases the severity of chronic inflammatory diseases, such as rheumatoid arthritis, asthma, AD, and cancer. In phase II clinical trial, curcumin was used orally in a mouse model of colorectal cancer. It has been demonstrated that curcumin can prevent carcinogenesis through different mechanisms such as reduction of cyclooxygenases 1 and 2, 5-lipoxygenase, prostaglandin E₂ (PGE₂), and 5-hydroxyeicosatetraenoic acid production inhibition [25]. Fortunately, curcumin via inhibition of NF- κ B signaling pathways can improve the effects of some chemotherapy drugs. For example, in the mouse model of human breast cancer, curcumin, in conjunction with paclitaxel, can slow breast cancer progression and metastasis to the lung. Unfortunately, curcumin has several disadvantages in cancer treatment, including inhibition of some chemotherapy drug activities. For example, curcumin decreased camptothecin-induced death in cultured breast cancer cells and inhibited breast tumor regression in mice. Fur-

thermore, curcumin can also interfere with colon cancer treatment through the change in irinotecan absorption and efficacy [21, 26].

According to Alavez et al. [27], curcumin, through its involvement in the regulation of protein homeostasis, can increase life span in several species, except for mice. As will be discussed later, curcumin binds and inhibits amyloid- β , tau, α -synuclein, Huntingtin, and prion protein aggregations. Maiti and Dunbar [10] reported that curcumin, through an unknown mechanism, could restore dysfunction of molecular chaperones (heat-shock proteins), which are necessary for correct folding of proteins and the degradation of misfolded proteins. Due to the importance of astrocytes' role in the pathophysiology of ND and the protective effect of curcumin on the ND, the aim of this study is to review the neuroprotective effects of curcumin on astrocytes in 5 common NDs such as AD, PD, MS, HD, and ALS [12, 17].

Alzheimer's Disease

AD is the most common progressive ND worldwide. AD is associated with the presence of β -amyloid ($A\beta$) in the brain cells and is characterized by memory loss, especially for cognitive decline, and short-term memory that eventually leads to dementia. The γ -secretase through sequential proteolysis processing can produce $A\beta$ from amyloid precursor protein (APP). There are 2 important forms of $A\beta$ with different lengths. $A\beta_{40}$ is the most abundant form that contains about 90% of the total $A\beta$ in the brain. The other form, $A\beta_{42}$, is relatively more aggregation-prone and has an important role in AD pathogenesis. The AD is associated with a special pathology in the brain, such as neurofibrillary tangles and senile plaques or $A\beta$. Cumulated $A\beta$ in senile plaques constructs a β -sheet secondary structure and is assembled in fibrils [6, 27].

A notable quantity of neuronal degeneration has been recorded during AD progress (e.g., hippocampus, basal forebrain, and associative cerebral cortex). At the molecular level, this neuronal degeneration appears to be linked with a decrease of choline acetyltransferase action. Currently, none of the available drugs are to prevent this neuronal degeneration. Nowadays, the potential anti-amyloid therapeutic strategies to treat AD are directed on the amyloid cascade theory, such as the $A\beta$ vaccine or treatment with metal-complexing agents [28, 29].

Calcium levels are irregular in AD models. The $A\beta$, by improving calcium signaling, can disrupt gliotransmis-

sion in astrocytes. This calcium/gliotransmission modification is a key role that astrocytes play in AD pathology. Because of astrocytes significance in brain homeostasis, they have become an important target for AD investigations and their malfunctions can be observed in AD patients [4]. Astrocytes act as neuroinflammation regulators and have an important role in neuronal functions. Thus, $A\beta$ can cause extensive proliferation of astrocytes that leads to cognitive decline in AD. Astrocytes have a crucial role in the pathophysiology of AD and are involved in the uptake, degradation, and clearance of neurotoxic $A\beta$ from the brain. Furthermore, astrocytes, by protease secretions, are directly involved in $A\beta$ catabolism and, indirectly, through the release of apolipoprotein E (ApoE), act as important microglial phagocytosis regulators. The ApoE has an important role in deposited $A\beta$ degradation, given that astrocytes can reduce $A\beta$ plaques. This process is likely to be impaired in AD [27, 30]. Furthermore, the aggregated amyloid phagocytosis by brain macrophages has a significant role in AD prevention and AD patients have shown to have defective $A\beta$ -plaque phagocytosis. Astrocytes might be involved in controlling neurodegenerative processes through the release of several mediators and cytokines, and also through the expression of different proteases that can remove pathological $A\beta$ [4, 6].

Astrocyte cells express several metalloendopeptidase enzymes such as NEP, IDE, ECE1, and ECE2, which are involved in monomeric $A\beta$ degradation, although NEP metalloendopeptidase can also hydrolyze the oligomerized form of $A\beta$. Additionally, astrocytes express and secrete diverse MMPs, including MMP-2 and MMP-9, that have some important roles in both monomeric and fibrillar extracellular forms of $A\beta$ degradation. Some studies have shown that curcumin has a therapeutic effect on AD by several molecular mechanisms, including decreasing oxidative damage and constraining the creation of the $A\beta$ fibrils in vitro. The anti-inflammation effects of curcumin as a food additive were evaluated in the APPSw mice (Alzheimer-like model) at several doses. The results have indicated that low-dose curcumin (160 ppm) reduced GFAP, which is an astrocytic marker associated with inflammatory processes. Furthermore, the effect of curcumin on spatial memory (an AD symptom) in AD rat models has shown that curcumin significantly decreases GFAP mRNA in hippocampal astrocytes, which improves the spatial memory in the AD rat model [28, 29]. Ambegaokar et al. [31] reported that the inhibition property of curcumin is dose- and time-dependent. For example, curcumin concentrations of 15–30 μ M are more

effective for short trials (<24 h), while its concentrations of 5–15 μM are better suited for longer periods (4–6 days). These data suggest that curcumin may be more effective in preventing AD in low doses if used for long periods [31].

Accumulating data show that $\text{A}\beta$ can increase the expression of COX-2, IL-1, and IL-6, while decreasing the peroxisome proliferator-activated receptor-gamma (PPAR γ) in amyloid-beta protein precursor transgenic mice, and curcumin can inhibit this function in amyloid-beta-treated astrocytes. Researchers demonstrated that GW9662, a PPAR γ antagonist, can abolish the anti-inflammatory effect of curcumin. Thus, curcumin might act as a PPAR γ agonist. As a result, most of the literature about curcumin indicates that this spice has especially strong properties against AD. For instance, the incidence of AD among Indian people (who regularly consume these spices) is very low when compared with the reported incidence in Western countries. Only 0.7% of 70–79 years old people in India are affected by AD; however, about 3.1% of Americans in this age range are also affected. Up to now, the potential anti-amyloid therapeutic methods for AD treatment have been focused on the amyloid cascade theory, on which the use of $\text{A}\beta$ vaccines and metal-complexing agents is based. Strimpakos et al. reported that curcumin has anti-amyloidogenic properties, thus acting against AD-induced $\text{A}\beta$ fibrils in vitro and improving cognitive functioning in vivo [28, 29].

There is an IRE in the 5'UTR of the APP mRNA; thus, iron metabolism has an important role in AD pathogenesis, and great amounts of iron and copper are present in the amyloid plaques that lead to ROS generation, DNA oxidation, and lipid peroxidation but decrease the rate of cytochrome *c* oxidase. Scientist also reported that NF- κB , as a transcription factor, is an important protein associated with neuroinflammation in the AD [6].

Parkinson's Disease

PD is the second most common progressive ND worldwide and is classified as a movement disorder. The environmental, genetic, and immune system status factors are associated with the onset of PD. The Lewy bodies in the substantia nigra are a pathological hallmark of PD, which are associated with the abnormal expression of α -synuclein and lead to the loss of dopaminergic neurons and to dopamine (DA) deficiency in the striatum of the brain. Because DA does not cross the BBB, pharmacological studies have centered on developing drugs capable of increas-

ing DA or decreasing acetylcholine action in the brain. Thus, increasing the decline of dopaminergic neurons during aging can influence the onset and progression of PD [32, 33].

Furthermore, environmental toxins, oxidative stress, and mutations in the α -synuclein gene can increase the speed of pathogenesis, which encodes a protein found in Lewy bodies of idiopathic PD lesions. α -Synuclein is a presynaptic neuronal protein, that is, plentiful in the human brain, and is linked to the neuropathology associated with PD. α -Synuclein, through aberrant soluble oligomerized conformations, mediates disruption in synaptic function and cellular homeostasis, which consequently leads to neuronal death [32, 34]. Several studies show that astrocytes may play dual roles in PD pathophysiology. On the one hand, α -synuclein acts as a potent inflammatory activator through stimulating astrocytes to produce IL-6 and ICAM-1. On the other hand, ICAM-1-positive astrocytes attract reactive microglia with LFA-1 receptor to the midbrain and cause an inflammatory reaction in PD. Several studies have shown that a pair of mutations in the PARK7 (DJ-1) on chromosome1p36 have been distinguished as having been involved in autosomal recessive PD. Data showed that DJ-1 is expressed mainly by astrocytes in human brain tissue and astrocyte cultures of the mouse brain, and also the DJ-1 expression level is sensitive to oxidative stress situations. These results confirmed that neuronal-astrocytic interactions are crucial in PD. As already noted, the Nrf2-ARE pathway has a protective role, in contrast to oxidative stress in several models of ND [32, 35].

Furthermore, the onset of ND was postponed by astrocyte-specific overexpression of Nrf2, which prolonged survival in a PD mouse model and in humans with α -synuclein (A53T) mutation [17, 36]. Astrocytes, through increasing the activity of glutathione peroxidase, protect DA cells from oxidative damage, neuronal degeneration, and cell death during the progression of PD pathology. Astrocytes, through upregulated protease-activated receptor-1 that was expressed in human astrocytes in substantia nigra, cause glutathione peroxidase activation [37, 38]. Data from animal models suggest that dietary curcumin is an important candidate in the prevention or treatment of PD. Recent evidence indicates decreased superoxide dismutase 1 (SOD1) expression in reactive astrocytes in the damaged substantia nigra, thus leading to inflammation and oxidative stress that contribute to the degeneration of dopaminergic neurons in PD. Curcumin, through the preservation of SOD1 expression in reactive striatal astrocytes in hemiparkinsonian mice,

has anti-inflammatory properties. Gui et al. [39] showed that curcumin, through the inhibition of CYP2E1 (the cytochrome P450 2E1) expression and its activity in reducing ROS and maleic dialdehyde in astrocytes, leads to protection of the mesencephalic astrocytes against LPS-induced toxicities. These results indicate that curcumin could affect the metabolism of several compounds in the CNS and provide evidence for the therapeutic approach in PD using curcumin at low concentration [39]. Studies show that the oral administration of curcumin (150 mg/kg/day for a week) in mouse models of PD reversed GFAP and inducible nitric oxide synthase protein expression and also decreased proinflammatory cytokine in the striatum, suggesting that curcumin can improve motor performance in a mouse model of PD [37, 40].

In addition, curcumin, through the Bcl-2-mitochondria-ROS-inducible nitric oxide synthase pathway, can protect against MPP⁺ (1-methyl-4-phenylpyridinium)- and MPTP⁺ (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced apoptosis in PC12 cells. Furthermore, the inhibition of the JNK pathway can also help in the survival of dopaminergic neurons in the SH-SY5Y cells. Previous studies indicate that dopaminergic neuronal apoptosis may be caused by the activation of NF- κ B in reactive astrocytes of the substantia nigra in mouse models of PD and that curcumin can significantly inhibit NF- κ B translocation and activation in astrocytes. These data propose that the modulation of NF- κ B activation in astrocytes may be a useful intervention in PD treatment where dopaminergic neuronal loss plays an important role in disease pathogenesis [41, 42].

Multiple Sclerosis

MS is a chronic neurological disease that is one of the most important causes of disability in young people. Disease initiation is characterized by clinical exacerbations and an increase of demyelinating CNS lesions [1, 43]. MS is usually considered as an autoimmune disease, and several immunological, genetic, and environmental factors have critical roles in its pathogenesis [19, 43]. In the 1940s, Roy Swank was one of the first scientists to propose an association between nutrition and MS [1, 43]. Elyaman et al. reported that proinflammatory cytokines, including TNF- α , and interleukins such as IL-17, IL-22, and IL-23, have crucial roles in MS development [44]. In addition, B cells, through abnormal antibody generation, APC, and inflammatory cytokine secretions, such as IL-6, IL-12, and TNF- α , have crucial roles in MS pathophysiology [11, 22].

Environmental conditions, such as smoking, Epstein-Barr virus infection, high salt diet, and vitamin D deficiency, are risk factors for MS [43]. ROS can freely oxidize other molecules and are suspected of contributing to demyelination and axonal damage in EAE and MS, but antioxidants can suppress the oxidation of other molecules through reacting with ROS [12, 43]. MS is a chronic inflammatory autoimmune and a long-lasting ND that affects the CNS, which is caused by damage to the myelin sheath that surrounds axons, leading to nonfunctioning or slowdown of nerve impulses [11, 12, 22].

The main hallmark of MS is the formation of sclerotic plaque in the CNS. MS plaques increase levels of ROS and also decrease levels of key antioxidants. A small amount of antioxidant activity and the elevated amount of ROS in white matter may increase the peroxidation of myelin lipids in EAE [43]. Demyelination and axonal damage are two important pathological hallmarks of MS that can happen within the CNS, leading to complexity and heterogeneity in the clinical signs of disease [23].

MS can cause difficulties with coordination and balance, visual problems, chronic pain syndromes, and other body functions. Studies show an important role of reactive astrocytes in MS pathology. For instance, in biopsy specimens from the white and gray matter of CNS, there are regions of focal, reactive astrogliosis that consist of plaques of demyelination, which are surrounded by reactive astrocytes [45]. Also, GFAP, an important marker for reactive astrocytes, was first isolated from old demyelinated plaques from MS patients [46]. Wang et al. [47] collected data, showing that axonal injury happens before significant T-cell entry into the CNS, and astrocyte hypertrophy coincides with the advent of axonal damage and early inflammation in EAE, an animal model of MS. Zeinstra et al. [48], using postmortem specimens from patients with MS, showed that astrocytes in active chronic plaques are MHC class II positive and act as APCs for T-cell activation and invasion to initiate the inflammatory cascade, leading to demyelination in MS. Finally, astrocytes, as the most abundant cells in the CNS, play a prominent role in maintaining homeostatic, as well as a complex pathological function in CNS autoimmunity conditions, such as MS [24, 48].

Astrocytes have multiple crucial roles in the progression of MS injuries, including the recruitment of lymphocytes, stimulation of wound healing, and confinement of inflammation [12, 49]. Th17 cells have an important role as key immunological players in the pathophysiological development of MS. According to current data, activated microglia, astrocytes, macrophages, and DCs stimulate

recruitment and activation of infiltrating leukocytes and help the production of main proinflammatory cytokines, including TNF- α , IL-6, IL-17, IL-1 β , IL-23, and PGE-2 [24, 50]. These cytokines can lead to the expression of IL-17 on microglia, astrocytes, and macrophages, in an autocrine manner, resulting in Th17 differentiation from naïve CD4⁺ T cells [21].

Moreover, Th17 cells can produce unusual amounts of IL-17 and IL-22, which can cross the BBB and, through activation of neuroinflammation, interfere with nerve signals in the CNS [11, 19]. Michel et al. [51] report that BAFF production by sensitive astrocytes, through stimulating B-cell proliferation and survival in the CNS, have important roles in MS pathogenesis. BAFF levels were shown to be increased in the CSF of MS patients compared to healthy controls [52]. In addition, the expression of BAFF is upregulated in MS lesions, similar to levels seen in lymphatic tissues. BAFF was observed to be expressed in active astrocytes, alongside inflammatory cells that expressed BAFF receptors [51, 52]. Recent studies suggest that curcumin, through reduced MMP-9 enzyme activity and decreased release of IL-6 in the astrocyte population of CNS, might beneficially cause anti-inflammatory responses in NDs, such as MS [1].

Curcumin represents some potential for treatments of various autoimmune diseases related to Th17 cells including MS [21]. Curcumin, through interfering with protein kinase C activity and Ca²⁺ entry, can eliminate both PMA and thapsigargin-induced ROS generation by the dose-dependent manner [23]. Curcumin can prevent the production of H₂O₂ and NO; the free radicals produced by macrophages and astrocytes in vitro [12]. In EAE, curcumin has important roles in lymphocyte proliferation inhibition, reductions of IL-17 production by Th17 cells, and Toll-like receptors 4 and 9 (TLR 4 and 9) downregulations [43]. Xie et al. [21] reported that in EAE mice or rats, curcumin shrinks inflammatory cells, including Th17 cells, and hinders its infiltration and differentiation in the CNS. Curcumin has the promising potential for treating MS, and researchers continue to focus on more efficacious curcumin-based drugs.

Huntington's Disease

HD is a fatal, autosomal dominant, and devastating genetic disorder, characterized by motor abnormalities, as well as mental decline and psychiatric symptoms. HD is more common in people of northern European origin and was described by George Huntington, in 1872. HD is

one of an increasing number of neurodegenerative disorders in the human caused by triple-repeat expansion (CAG/polyglutamine) mechanisms, and HD is described by a complex and variable group of symptoms including psychological, motor, and cognitive components [15]. HD, categorized as a neurodegenerative disorder, is also characterized by aggregation of amyloid-like mutated huntingtin protein [53].

In the first 6 months of life, pathological aggregation of huntingtin in the nucleus and cytoplasm has been shown. Expression of mutant Huntingtin (HTT) protein with extended poly Q sequence in the *Drosophila* model leads to the development of inclusion bodies, increased toxicity in cells, motor disability, and reduced viability. The pathological modifications mostly affect the medium spiny neurons of the striatum and also lead to a reduced amount of cortex. Furthermore, loss of γ -aminobutyric acid and enkephalin neurons of basal ganglia have been shown in HD, as well as alterations in the number of N-methyl-D-aspartate receptors [53, 54].

This ND is caused by a polyglutamine repeat expansion (51–122 glutamines) in the first exon of the huntingtin protein that forms altered high molecular weight protein aggregates with a fibrillary or ribbon-like morphology that finally leads to unusual movements, known as chorea, and is associated with cognitive and psychiatric problems, although polyglutamine repeats in the normal range (20–30 glutamines) are not pathological [33, 54]. Astrocytes support the neuronal cell survival and prevent glutamate neurotoxicity through expressing glutamate transporters that uptake extracellular glutamate. Experiments show that mutant huntingtin is expressed in astrocyte cells in the brains of patients and HD mouse models [54, 55]. Also, studies showed that mHTT could increase the ability of astrocytes to bind to transcription factor Sp1 and decrease the ability of Sp1 to associate with the promoter of glutamate transporter genes, thus leading to inhibition of Sp1 use of the GLT-1 promoter. Furthermore, mHTT aggregation in the astrocytes is harmful to both astrocytic and neuronal health [17].

These findings demonstrate an important role of mHTT in astrocytes for HD pathology and recommend that promoting astrocyte functioning could be an effective therapeutic strategy for HD. Previous studies demonstrated that misfolded proteins, including mHTT, are identified to localize in the perivascular region of the cells [17, 56]. Studies using established yeast models showed that curcumin inhibits mHTT aggregation, by acting through endosome-sorting complexes required for transport machinery and also destabilizes preformed aggre-

gates. Curcumin, by downregulation of Vps36, a component of the endosome-sorting complexes required for transport-II complex, prevents recruitment of misfolded protein to the perivascular compartment, thus inhibiting the formation of large aggregates [17, 57]. The amyloid-binding ability and anti-amyloid properties of curcumin, along with its ease of oral administration, make it an attractive therapeutic candidate for several NDs [29, 58].

Amyotrophic Lateral Sclerosis

ALS is known as the most important adult motor neuron disease and is also a fatal ND. ALS is described by both upper and lower motor neuron involvement. Almost 25% of familial ALS patients are caused by missense mutations in the generally expressed SOD1 enzyme gene, which has key roles in destroying the superoxide and releasing reactive oxygen. Furthermore, other mutations in several genes including dynactin, alsin, and senataxin had been reported in familial ALS [55, 59].

ALS patients according to symptoms can be classified into two groups, either the spinal onset or the bulbar onset. In about 30% of ALS patients, bulbar symptoms such as dysarthria and dysphagia are the early exhibition, which is a key prognostic factor. For instance, patients with bulbar-onset symptoms have been shown a worse prognosis than others [55, 59]. Furthermore, other factors including oxidative stress, mitochondrial dysfunction, and neuroinflammation are implicated in ALS pathologically. Neuroinflammation, via NF- κ B proinflammatory cellular pathway activation, plays a central role in ALS pathogenesis [13, 59, 60]. Several ALS patients had been shown an increased NF- κ B signaling expression in microglia. Thus, through NF- κ B expression reducing in microglia can slow the progress of disease and lengthen the survival in ALS mouse models [60, 61].

As the scientist report, glutamate excitotoxicity is reduced through astrocytic glutamate transporters, which present a basic role in motor neurons' safety. A potential cause of ALS is an inactive astrocytic GLT-1/EAAT2 glutamate transporter, which is shown in SOD1-mutant animals and human patients. Moreover, β -lactam antibiotics (such as ceftriaxone) through the transcriptional up-regulation of the GLT-1/EAAT2 transporter can increase overall survival in ALS mice models.

Curcumin delivering to the animal models through intraperitoneal injection or oral administration leads to NF- κ B pathway activation decreasing in rat and mouse microglial cell cultures and also in the rat brain. Further-

more, curcumin can also reduce NF- κ B activation in human cell lines. Despite the hopeful preclinical documents, a clinical trial through applying a high bioavailable oral form of curcumin (Theracurmin) in several cancer patients did not change NF- κ B levels in peripheral blood monocytes. Furthermore, prolonged overall survival and reduced ALS disease progression had been shown in several mouse models of ALS because of NF- κ B expression reduction in microglia [62–64].

Oxidative stress such as increased oxidative species has an essential role in ALS pathology and its increasing in patients can cause disease severity and antioxidants reduction in their blood. The Nrf2-ARE antioxidant pathway induction through compound consumption can slow down disease progress in some mouse models of ALS [65, 66].

Furthermore, curcumin can neutralize ROS in vitro and can stimulate the Nrf2-ARE pathway similarly in the brain and skeletal muscles of mice and also in isolated rat astrocytes [67, 68]. SOD1-misfolded and -aggregated proteins in the motor neurons have an important role in disease pathogenesis, and its targeting treatment can decrease ALS progression in animal models. As previously shown, curcumin can constrain SOD1 aggregation in vitro. However, the concentrations of curcumin that used in this study were too high to be applicable in humans.

Curcumin through gene expression can also stimulate the clearance of the aggregated protein in PALS and Alzheimer's disease blood cells. Up to the present time, several studies confirm that regimens' treatment can cause motor neuron enhancement (although there are several different descriptions for these improvements). Furthermore, a small pilot trial revealed some advantage of curcumin in PALS [13, 65, 66, 69].

Conclusion

In this review, we described the importance of astrocytes in their normal functions and in pathological states of the CNS. Also, the effect of curcumin on astrocytes in common NDs was examined. Astrocytes, through neuroprotective mechanisms, are essential for repair and regeneration of neurons and their exacerbation of damage comprise their dual roles in ND pathology. Therefore, modulation of astrocyte function can be an effective way to improve many efficient therapeutic strategies in several chronic CNS disorders. Curcumin, as a natural cost-effective product with proven pharmacological safety, has strong antioxidant and anti-inflammatory effects through

modulating many cellular signaling pathways, affects numerous molecular targets in astrocytes, and is a promising candidate for the prevention and treatment of various NDs, including AD, PD, HD, and MS. However, more research is needed to optimize the therapeutic interventions in astrocytes with curcumin.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Amir Mohammadi wrote and arranged the primary manuscript. Ayeh Khorshidian helped to Amir Mohammadi. Abasalt Hosseinzadeh Colagar edited the manuscript and helped to Amir Mohammadi. Seyed Mohammad Amini designed and conducted this manuscript and edited the final version of the manuscript.

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