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REVIEW

The Effects of Modified Curcumin Preparations on Glial Morphology in Aging and Neuroinflammation

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Abstract

Neuroinflammation is characterized by reactive microglia and astrocytes (collectively called gliosis) in the central nervous system and is considered as one of the main pathological hallmarks in different neurodegenerative diseases such as Alzheimer's disease, age-related dementia, and multiple sclerosis. Upon activation, glia undergoes structural and morphological changes such as the microglial cells swell in size and astrocytes become bushy, which play both beneficial and detrimental roles. Hence, they are unable to perform the normal physiological role in brain immunity. Curcumin, a cytokine suppressive anti-inflammatory drug, has a high proven pre-clinical potency and efficacy to reverse chronic neuroinflammation by attenuating the activation and morphological changes that occur in the microglia and astrocytes. This review will highlight the recent findings on the tree structure changes of microglia and astrocytes in neuroinflammation and the effects of curcumin against the activation and morphology of glial cells.

Keywords Neuroinflammation · Neurodegeneration · Gliosis · Glial cells · Curcumin · Morphology

Aging, Neuroinflammation, and Neurodegeneration in the CNS

Aging is a complex biological process that involves chronic oxidative and inflammatory stress which disrupts the communication and balance between the brain and the immune system [1, 2]. Aging of the brain, in particular, leads to neuroinflammation and increases the risk of age-related cognitively degenerative diseases such as dementia, including Alzheimer's disease (AD) [1]. Microarray studies revealed an increase in overall pro-inflammatory and pro-oxidant transcriptional profile with a reduction in growth and anti-oxidant gene profile in older rodent brains compared to adults [3, 4]. Moreover, several studies also reported increased levels of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, in the brains of aged rodents and humans [5–9], while a reduction in key regulatory molecules and anti-inflammatory cytokines such as IL-10 and IL-4 was noted [9, 10]. Overall, these studies support glial priming or re-activation and, in turn, increased neuroinflammation, excessive cytokine production, and cognitive deficits in the aged brain [8, 11].

Neuroinflammation, an inflammatory response within the central nervous system (CNS), is initiated in response to a variety of endogenous and exogenous factors including foreign pathogens, neuronal injury, and toxins. Inflammatory episodes are characterized by mainly microglial and astrocytic reactivation (gliosis), the release of pro-inflammatory molecules [cytokines, chemokines, prostaglandins, nitric oxide (NO), and reactive oxygen species (ROS)], increased blood–brain barrier permeability, and recruitment of peripheral immune cells into the CNS [12]. Neuroinflammation leads to neuronal and axonal injury in the CNS which is a common underlying pathoetiology of neurodegenerative conditions such as AD, Parkinson's disease, and multiple sclerosis [13, 14].

Microglia are the resident immune cells of the CNS. Their function extends beyond the role of immune sentinels and effectors to synaptic pruning and the modulation of higher cognitive functions (learning and memory), macrophage-like

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activities, and the maintenance of CNS homeostasis [12, 15–17]. In normal physiological conditions, physiological ramified microglia, present a round small cell body (large nuclei with thin cytoplasm) and are highly branched, with long thin processes, which continuously scan the entire brain for invading pathogens termed "surveilling" microglia [16, 18, 19]. According to a few investigations, ramified microglial cells have small somas, and long and thin processes, which are the typical characteristics of physiological microglial cells necessary for active surveillance of the brain [20]. Surveillant microglia are highly ramified and bushy, whereas they adopt amoeboid shape when undergoing morphological transformations and de-ramification in response to neuroinflammation with a range of intermediate activation states in between (e.g., 'intermediately activated', 'bipolar', 'rod-like', 'hypertrophied', 'bushy') [21, 19]. Ramified microglial cells have a key role in surveying the neuronal environment to maintain homeostasis, but under pathological conditions the changes in microglial cell size can influence the entire morphology [22, 23]. Microglia can acquire a primed or pro-inflammatory mRNA, protein, and morphological profile with aging and neurodegenerative disease. Damaged associated molecular patterns (DAMPs) in the microglial environment initiate a rapid morphological transformation in microglia which allows them to migrate to the site of injury/damage, alter their transcriptional profile and produce pro-inflammatory cytokines and chemokines. Reactivated microglia rapidly undergo cytoskeletal rearrangements and change their surface molecular expression thus increase their phagocytic efficiency [24]. Depending on the context, when key regulatory systems are impaired, microglia activation may become maladaptive leading to prolonged neuroinflammation and neurodegeneration. Ionized calcium-binding adaptor molecule 1 (Iba-1) is an actin-binding protein restricted to microglia/macrophages, and its expression is upregulated in reactivated microglia following brain injury and diseases [25, 26]. Thus, their expression increases when microglia morphology changes from quiescent ramified to activated amoeboid microglia [25]. Furthermore, ramified and reactivated microglia display different Iba-1 immunoreactivity with aging, where Iba-1 immunoreactivity increased at all stages of microglia reactivity compared to ramified phenotype [27]. Primed microglia phenotype displays a similar ramification pattern to the physiological microglia, but has a larger oval-shaped cell body [28, 29]. The reactive and amoeboid microglia display large amoeboid-shaped cell bodies often loaded with debris [30]. Moreover, while the reactive phenotype might display less extensive, short, thick processes, the amoeboid microglia seem to have no processes or may display a few within the length of the cell body [28, 30]. It is also important to note that microglia morphology does not necessarily reflect function, dysfunction, or RNA expression phenotype. Rather, it demonstrates how the cells respond to altered homeostasis [31]. Hence, the ramified (physiological) microglia of the healthy CNS can either be hypertrophic (reactive phenotype) due to acute injury or can undergo deterioration (dystrophic) due to age-related processes (predominantly in the neurodegeneration perspective) [31]. The morphological structure of microglia cells is highly variable and rather than categorized into polarized stages, should be considered as a continuum. The morphology can be quantified by measuring the number of processes (branches), sub-branches, and nodes that form a tree structure and a central soma that envelops the cell nucleus. Microglial architecture is more diffuse and complex with multiple primary and secondary branches not confined to a generalizable [32, 33].

Astrocytes contribute to being the most abundant cells in the CNS. Under normal physiological conditions, astrocytes modulate synaptic activity and provide major support for neuronal survival [34]. They regulate the function of microglia, oligodendrocytes, cells of the adaptive immune system and control infiltration of peripheral proinflammatory leukocytes into the CNS during neuroinflammation [35, 36]. Astrocytes are a hallmark of many neuropathologies, activated in response to neurotrauma, stroke, and many neurodegenerative diseases [37]. Reactive astrogliosis involves several processes that vary with the nature of the insult [38]. During neuroinflammation and nerve injury, astrocytes undergo a series of phenotypic and functional changes, also called reactive astrogliosis [39], and release cytokines such as IL-6, nitric oxide (NO), and other potentially cytotoxic molecules [40, 41]. During this process, naïve astrocytes undergo several changes including morphological changes (hypertrophy), proliferation, and functional changes, and differentiate into different subsets, including reactive astrocytes and scar-forming astrocytes. Reactive astrocytes can be divided into toxic A1 astrocytes, which have a toxic role and induce death of neurons, and neuroprotective A2 astrocytes, which enhance neuronal survival and tissue repair [42].

Curcumin, the active compound extracted from the dried rhizomes of *Curcuma longa* (turmeric), a member of the Zingiberaceae family, is one of the most studied natural compounds within the context of complementary medicine. Turmeric has been used traditionally as a medicinal herb in South East Asia and India for thousands of years for various illnesses including biliary disorders, anorexia, cough, hepatitis, rheumatic arthritis, and a variety of other chronic inflammatory diseases, as well as for its anti-tumorigenic potential [43–45]. Curcumin is a known anti-inflammatory agent against various inflammatory conditions. It could cross the blood–brain barrier in its native form and is active against sustained neuroinflammation without any serious adverse effects [46]. It has been reported that curcumin potentially reduced iNOS induction, thus protecting microglial cells against oxidative stress [47. Furthermore, curcumin is

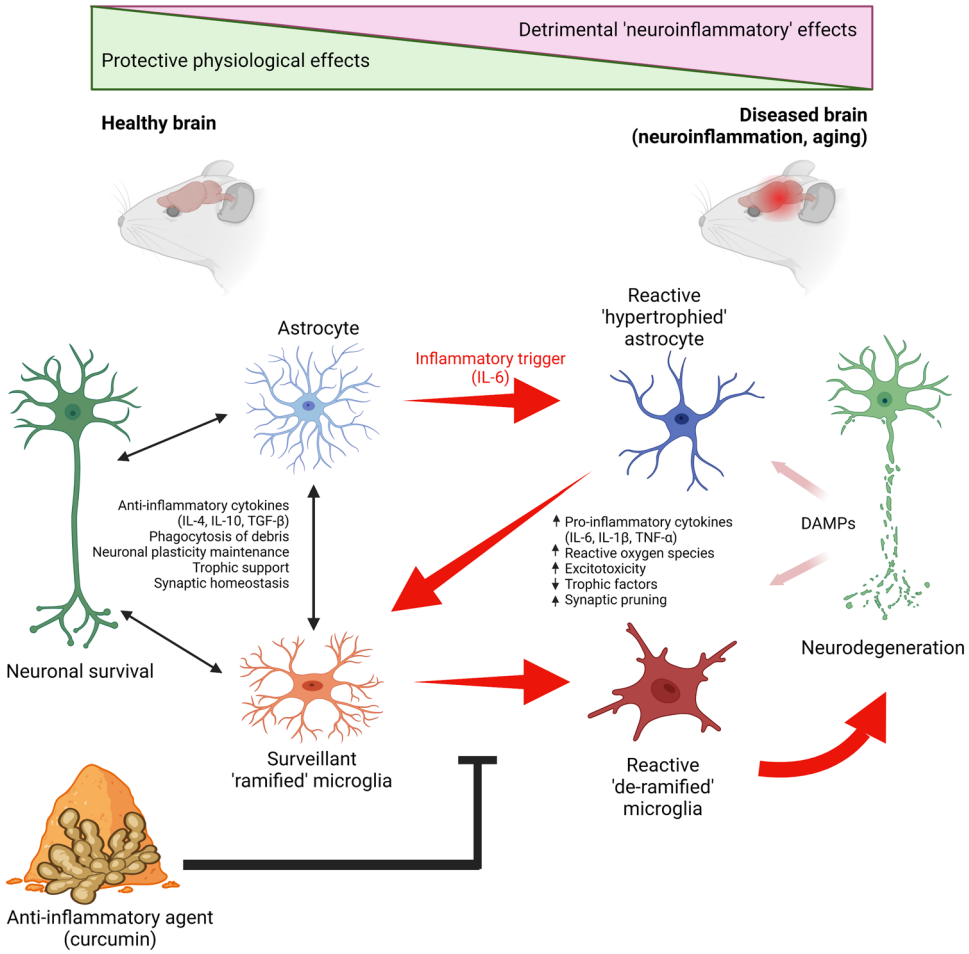

Fig. 1 Schematic overview of morphologic and functional changes in glia (microglia and astrocytes) upon re-activation in aging and neuroinflammation, in the rodent brain. *Under protective physiological (left) conditions*, resident microglia and astrocytes participate in maintaining homeostasis and healthy neuronal activity. Microglia display surveillant motile, fine processes, small cell soma, and distal arborization (light red), while astrocytes (light blue) display complex bushy morphology with fine processes, under normal physiological conditions. *Under detrimental/pathological (right) conditions*, microglia changes to a de-ramified, re-active state with retracted thick processes, enlarged cell soma, and decreased arborization (dark red). While astrocytes become hypertrophied with elongated, and thicker processes (dark blue). Moreover, continuous upregulation of proinflammatory markers such as interleukin-6 (IL-6) in astrocytes further exacerbates the transition of microglia to reactive de-ramified states leading to neurodegeneration. Damaged or dying neurons release danger-associated molecular patterns (DAMPs), which further contribute to pro-inflammatory glial activation. The vicious cycle of continuous glial activation can be reversed by the anti-inflammatory agent, curcumin. Created with BioRender.com

attributed to the inhibition of astrocyte hypertrophy in the spinal dorsal horn and phosphorylation of the ERK signaling pathway in a rat model of neuropathic pain [48]. The changes in microglia and astrocytes branched structure and the effects of curcumin to downregulate these alterations are summarized in Fig. 1.

De-ramification of Microglia During Aging and Neuroinflammation

The physiological microglia continuously scans the brain in ramified morphology with small somas and long dynamic processes [19]. However, the ramified morphology and process activity vary across brain regions [20]. The microglial morphology is highly impacted in their reactive state whereas, there is very limited information concerning the morphological characteristics of microglia in the non-diseased brain. The majority of morphological characterization of microglia has occurred in situations of extensive CNS insult (e.g. traumatic brain injury, AD) [12]. During

inflammatory conditions, the microglial cells have been observed to go into an re-activated state, where they become amoeboid-like in their morphology, becoming de-ramified microglia, which are characterized by a swollen cell body and thick processes [49].

Several studies have indicated the morphological variations of microglia across the different regions of the healthy brain [23]. Some of the studies have identified the typical morphology of microglia in rodent brains based on regions. One study has reported that the microglia in each region differs in area and perimeter [20]. The study described clear regional differences in microglial morphology, describing the occurrence of compact microglia with small round soma and short processes found exclusively in sites lacking a blood–brain barrier; longitudinally branched microglia having long primary processes; radially branched microglia with complex processes and spine structure found in the fibre tracts and white matter [20]. A study which examined the morphology of microglia across the mammalian cerebellum has reported variation of microglial morphology according to the extracellular environment of the cells. They further suggested that the microglial structure is based on the synaptic activity within a given region, while highly branched microglia extended in all directions within the cerebellar nuclei, the flattened microglia had processes that extended parallel to the axon projections in the white matter of the cerebellum [50]. Yamada and Jinno, for the first time have classified microglia based on quantitative measurements [51]. They also grouped microglia based on their discrete morphological measurements, revealing that neural tissue contains microglia that progress from highly ramified to compact and thickened processes [51]. Torres-Platas et al. for the first time studied the detailed quantitative neuroanatomical examination of microglia in the human prefrontal cortex [28]. They also identified four classes of microglia: classically ramified microglia; primed microglia (wider cell body with standard ramified processes); reactive microglia (wider cell body, few ramified processes), and amoeboid microglia [28].

Increased numbers of activated microglia in aging brains are the most likely indication of neuroinflammation, which may underlie age-related alterations in the brain's response to insult and recovery from insult. This is most likely due to the phenotypic alterations of microglia in the aging brain that have reduced arborisation patterns and branch density which results in decreased area of surveillance contributing to the impairment of homeostatic functions [52, 53]. The evidence suggests that the microglia even in the non-pathological aged brain are in a hyperactivated state compared to those in the young healthy brain, in both rodents [54] and humans [55]. A study on microglial morphology in the human cerebral cortex of two nondemented subjects, using high-resolution LN-3 immunohistochemistry, also observed an approximately ten-fold increase in dystrophic microglia in the 68-year-old brain compared with the brain of a 38-year-old subject [56]. Overall, these studies are proposing that microglial senescence and resultant functional changes may provision the development of neurodegenerative diseases like AD and thus exacerbate the risk of cognitive changes associated with normal aging [52, 56, 57]. Microglia may develop an altered profile that resembles an increased inflammatory state, with aging. As reviewed by Nordan et al. [2], this 'primed' profile is defined by (1) excessive baseline expression of inflammatory mediators and markers, (2) a lower activation threshold to 'switch' to a pro-inflammatory state, and (3) an excessive prolonged inflammatory response following immune activation. Primed microglia of the aged brain is characterized by increased mRNA and protein expression of various pro-inflammatory markers and morphological alterations. The senescent or age-related dystrophic microglial cells convert from a highly ramified morphology to a de-ramified (decreased arborized processes) morphology. The de-ramification includes; loss of finely branched cytoplasmic processes; cytoplasmic beading/spheroid formation; in some instances, partial or complete cytoplasmic fragmentation [58]. A study on microglial morphology in the non-demented aged human cerebral cortex reported shorter and less branched dendritic arbors than microglia of young adults [12]. Several studies have detected similar alterations using Iba-1 immunostaining. Iba-1 microglia from the hippocampus of aged gerbils showed increased cell body size, thickened proximal processes, and decreased ramification of distal branches compared to young adults [59]. Moreover, Iba-1 immunoreactive microglia displayed hypertrophied cell bodies, thickened and de-ramified processes in the dentate gyrus of aged dogs [60]. Nonetheless, expression of the antigen-presenting molecule major histocompatibility complex (MHC) II was increased specifically on microglia of the aged brain [6]. It was also confirmed that the de-ramified morphology of microglia in aged rats corresponded with higher levels of MHC II expression [27], a marker of primed/reactive microglia. Further evidence emerged from positron emission tomography (PET) data that evaluated microglial activation in older humans. PET imaging, using The ligand PK [11C] (R)PK11195 which binds to translocator protein (TSPO) receptors expressed in mitochondria of activated microglia, showed heightened levels in several cortical and subcortical areas of older individuals [61]. Overall, these studies suggest microglial priming increases with aging and may shift towards a more activated morphology contributing to the augmented inflammatory status of the aged brain.

Accumulating shreds of evidence suggest that microglia can become chronically activated by either a single stimulus (e.g., traumatic brain injury (TBI), lipopolysaccharide, D-galactose, or any neuronal damage) or multiple stimuli

exposures that result in cumulative neuronal loss with time though the exact mechanism is still unknown [62]. Microglia are activated in response to immunological stimuli, neurodegenerative conditions and brain injuries result in dramatic alterations in morphology, changing from resting, ramified microglia into de-ramified state [63]. The microglial cells are activated in traumatic brain injury and changes in microglial cells morphology have been observed in several TBI rodents models. Microglia undergo considerable remodeling by retracting their processes and adopting an amoeboid morphology [64]. The spatiotemporal changes in microglia morphology over 28 days following rat midline fluid percussion injury (mFPI) as a first step in exploiting microglia morphology to reflect altered brain physiology. The morphology of microglia altered and a de-ramification was observed in the somatosensory cortex barrel field (S1BF) following mFPI [65].

In neuroinflammation, a de-ramification of microglia has been observed, in which the microglia enter an activated state characterized by swollen ramified cells with shorter dendrites [66]. One of our recent study conducted in a mouse model of chronic neuroinflammation (GFAP-IL6 mice) has revealed that microglial cells undergo morphological transformations, such as increased soma size and thickening of the processes in response to IL-6 over expression resulting in chronic neuroinflammation [67]. The study investigated and quantified some of the morphological changes between ramified and non-ramified microglia and found that the microglial cells of GFAP-IL6 mice had significantly larger soma areas, small convex areas, and convex perimeter than those of wild type [67]. Similarly, another study conducted by our group in the same mouse model has revealed a de-ramification of microglia characterized by a significant increase in soma area and soma perimeter in both the hippocampus and cerebellum of the GFAP-IL6 mice compared with those of the wild type mice [68].

Evidence suggests the role of microglial function and morphology changes in the CRND8 mice, a mouse model of AD which carries a mutated form of the human amyloid precursor protein gene. The microglia in the proximity of Aβ plaques were less ramified compared to microglia distant from Aβ plaques, as well as compared to microglia from wild-type mice [69]. A most recent study conducted on human subjects has opened a new window for further investigation of microglial morphology. The morphology of microglial cells was assessed in 32 controls, 44 AD cases, and 16 AD cases from patients immunized against Aβ42 (iAD) using 2D and 3D approaches. The results showed that ramified microglia were fewer in AD compared to the controls but increased in iAD compared to AD and controls whereas, 3D reconstructions highlighted larger cell bodies in AD compared to the controls and increased total process length in iAD compared to AD. Altogether, the reactive/amoeboid microglia were the most represented population in the aged human brain. In contrast, Aβ removal by immunotherapy leads to increased ramified microglia [70].

Astrocytes Hypertrophy During Aging and Neuroinflammation

Astrocytes directly communicate with microglia. In aged rats, astrocytes shift from resting state to hypertrophic activated state, affecting microglial regulation [71, 72]. In the aged brains of both humans and rodents, the astrocyte inflammatory markers glial fibrillary acidic protein (GFAP) and vimentin were increased [72]. A study on the effect of normal aging and LPS-induced inflammation on astroglia-neuron interaction demonstrated that astrocytes were smaller with thicker and shorter branches, as well as less numerous, in the CA1 stratum radiatum of aged rats when compared to adult and lipopolysaccharide (LPS)-treated rats [5]. This study indicated active participation of astrocytes and microglia in the hippocampus of aged and LPS-infused rats in the clearance of cellular debris associated with programmed cell death [5].

Astrocytes exhibit a complex bushy or spongiform morphology, and their very fine processes are in close contact with synapses and other components of brain parenchyma [73]. Shreds of evidence have suggested that the morphometric changes occur in astrocytes during CNS insults but the fine neuroanatomy of astrocytes; however, remains to be investigated in these neurological conditions. Astrocytes are thought to undergo cellular hypertrophy and increase the thickness of their main cellular processes during neuroinflammation [37, 67].

There are two main types of astrocytes in rodents, largely based on their fine anatomical structures: protoplasmic and fibrous astrocytes [74]. Protoplasmic astrocytes are bushier with extended processes located in the gray matter. They form the outermost wall of the blood–brain barrier by extending their processes to blood vessels and enwrap them to form the glial limiting membrane. They play a key role in the modulation of synaptic functions and regulation of local blood flow in response to synaptic activities [75–77]. On the other hand, fibrous astrocytes possess straight and long processes and are widely distributed in white matter. This type of astrocyte associated with the blood vessels via their processes just like the protoplasmic astrocytes but their function is not clear [78]. The 3D reconstruction of astrocytes revealed that the reactive astrocytes increased the thickness of their main cellular processes but did not extend to occupy a greater volume of tissue than nonreactive astrocytes [37, 79]. Our recent two studies have described new evidence about the astrocytes hypertrophy during neuroinflammation [67, 68].

These studies [67, 68] analyzed the GFAP-IL6 mice, a chronic neuroinflammatory mouse model, using multiple experimental approaches including immunohistochemistry, 3D reconstruction software Neurolucida360 (MBF Bioscience), Sholl, and morphometric analysis. Specifically, the authors demonstrated that a significant increase in cellular hypertrophy was seen in reactive astrocytes in the inflamed mice which lead to a significant increase in the thickness and length of their main cellular processes in hippocampus and cerebellum areas. Furthermore, a significant increase in the overall convex area (cell area) of the reactive astrocytes occurred compared to nonreactive ones [67, 68]. Astrocyte reactivity in response to injury is termed astrogliosis [80], which involves changes in morphology, increased expression of the intermediate filament proteins, GFAP, and vimentin, heightened proliferation and secretion of inflammatory mediators and growth factors [81, 82]. These reactive astrocytes adopt hypertrophic morphology after injury, involving the extension of processes and swelling of cell bodies. A study conducted in a mouse mild-moderate controlled cortical impact (CCI) model reported hypertrophic astrocytes in the lesional and peri-lesional area 3 days after TBI [83]. Similarly, astrocytes undergo numerous morphological alterations over time including rapid swelling and dendrites extensions [84, 85] after focal ischemic stroke, resulting from the blockage of cerebral blood vessels, which leads to cell death and brain damage [86]. A study conducted on the morphology of reactive astrocytes after ischemic and hemorrhagic stroke in rats revealed the morphological changes in the astrocytes based on GFAP staining in the regions of the sensorimotor cortex and dorsolateral striatum. There was an increase in the number and length of primary processes (ramification) of reactive astrocytes occurred increased compared with the astrocytes in a sham control group [87].

Astrocytes have different morphology in humans compared to rodents. Recent work has revealed the morphological structure and diversity of cortical astrocytes in humans. Human astrocytes were found to be proportionally larger than rodents and their processes were more elaborate [88]. A study conducted on human brain samples investigated the morphological changes that occur in two different types of astrocytes in depression conditions. The study investigated the morphometric structure of protoplasmic and fibrous astrocytes in Golgi-stained postmortem anterior cingulate cortex (ACC) samples from depressed suicides and matched non-psychiatric controls [89]. Based on literature evidence, patients suffering from depression have significantly higher levels of circulating pro-inflammatory cytokines and local inflammation [90]. Therefore, the fibrous astrocytes in the depressed brains reflect local inflammation in the white matter which leads to the hypertrophy of astrocytes [89].

Curcumin: An Anti-neuroinflammatory Compound and Modified Curcumin Preparation

Curcumin, a polyphenolic compound, an active component of turmeric, is a potent cytokine-suppressive anti-inflammatory drug (CSAID) and exerts a broad range of anti-inflammatory effects [91–93]. In the nervous system, curcumin and its modified formulations have been studied in the context of neurodegenerative diseases, e.g. neuroinflammation, AD and Parkinson's disease, chronic pain, and epilepsy [94]. These studies revealed that curcumin may influence several intracellular signaling pathways, yielding neuroprotective and anti-inflammatory microglia-attenuating effects [47]. Curcumin exerts anti-inflammatory effects through several signaling pathways that are associated with inflammation including Toll-like receptor-4 (TLR-4) pathway [95]. TLR4 plays an important role in the recognition of endogenous agonists, such as heat shock protein, products of proteolytic cascades, intracellular components of ruptured cells, and the genes that are activated by inflammation [96, 97]. Activation of TLRs initiates signal transduction cascade leads to the activation of nuclear factor-kappa B (NF-κB) transcription factor, a transcriptional factor required for the expression of many inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [98], and the mitogen-activated protein kinases (MAPKs). It has been reported that curcumin administration attenuates the TLR4/NF-κB inflammatory signaling pathway [99]. Curcumin was also shown to down-regulate the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, IL-1, -2, -6, -8, and -12 [100]. It has been reported that curcumin achieves its anti-inflammatory activity in the brain by inhibiting of janus kinase (JAK)-STAT signaling pathway [101]. It modulates the activity of several transcription factors (e.g., STAT, nuclear factor-κB, AP-1) and their pro-inflammatory molecular signaling pathways. It inhibits the expression of many pro-inflammatory cytokines which further interferes with the first signaling steps downstream of the IL-6 receptor in microglial activation [102] and astrocyte hypertrophy [103].

During neuroinflammation, the morphology of microglia and astrocytes is dramatically affected, leading to altering their normal physiological functions. Curcumin has known and prominent therapeutic potential to reverse these morphological changes that occur in these cells and can bring them to the normal structure [67, 68]. Curcumin, a CSAID, is frequently used as a drug of choice against inflammatory conditions due to its low toxicity and high preclinical efficacy and has the potential ability to reverse

the structural topology of the glial cells [104]. It is a pleiotropic molecule that inhibits microglia transformation to an activated state and subsequent neurodegenerative diseases [105].

Despite its low toxicity profile and wide range of therapeutic applications, curcumin exhibits extremely low bioavailability, mainly due to its poor aqueous solubility, poor stability in solution, and rapid intestinal first-pass and hepatic metabolism [106]. Curcumin is insoluble at room temperature in water at both acidic and neutral pH. While it is soluble in an oil-soluble compound, practically alkali, it is very susceptible to auto-degradation. Therefore, various formulations have been developed in order to get enhanced bioavailability and consequent bio-efficacy [107, 108]. These modified curcumin preparation include liposomes, micelles, emulsions, microemulsions, nano-emulsions, phospholipid complexes, solid lipid nanoparticles, nanostructured lipid carriers, biopolymer nanoparticles, and microgels which enhance the efficacy, absorption, bioavailability, and permeation in the small intestine of curcumin formulation, summarized in Table 1 [109].

Impact of Curcumin on Re-ramified Microglia

It is reported through several pre-clinical trials that neuroinflammation is characterized by the activation of microglia and astrocytes [122], which lead to structural and functional neurological impairments that typify various neurodegenerative diseases [123]. Some of the studies have reported the effects of curcumin in reducing the de-ramification of microglial cells in the brain and bringing microglia back to normal size. A recent study conducted in 5xFAD mice, a mouse model for AD has highlighted the role of curcumin to reduce the de-ramification of microglial cells in the 5xFAD mice. They reported that ip. injection of curcumin for 5 days has significantly reduced the aggregation and de-ramification of microglial cells [124]. Our recent two studies have highlighted the specific effects of curcumin on microglial tree structure in neuroinflammation [67, 68]. One of our studies has reported that the phytosomal curcumin preparation (Meriva®) significantly reduced the soma area and soma perimeter in both hippocampus and cerebellum and reduced the de-ramification of microglia after 4 weeks of treatment via chow (874 ppm) [68]. Similarly, another study conducted on the solid lipid nanoparticle curcumin formulation (Longvida®) has reported the effects of curcumin on the activated and de-ramified microglial cells. Briefly, the study investigated the effect of Longvida® curcumin (LC) in a mouse model of chronic neuroinflammation. The LC diet mixed in chow was fed to 2 months old mice orally in a 500 ppm dose for the period of 6 months. The study confirmed that curcumin has significantly downregulated the de-ramification of microglial cells by reducing the soma size and soma perimeter of activated microglia [67] (Fig. 2).

The Role of Curcumin in Astrocyte Hypertrophy

Curcumin has a demonstrated role against astrocyte hypertrophy in different CNS conditions. A study conducted on 5xFAD mice, a mouse model of familiar AD, has observed and reported a decrease in activation and hypertrophy of astrocytes after being treated with solid lipid curcumin particles [124]. Emerging studies conducted in rats have reported the effects of curcumin against the hypertrophy of astrocytes in the CNS. One such study has reported that a lipid curcumin formulation

Table 1 Modified curcumin formulations

Modified curcumin formulations	Commercial Product available	References
Microcrystalline cellulose/lecithin	Meriva®	[68, 110]
Docosahexaenoic acid/lecithin/stearic acid	Longvida®	[67, 111]
Turmeric oil	BCM-95®; BioCurcumax®	[108, 112]
Piperine	Curcumin C3 Comples®	[113, 114]
ɣ-Cyclodextrin	Cavacurmin®	[115]
Cellulosic derivatives	CurcuWIN®	[112]
Silicon dioxide/triacetin/Panodan®	Micronized Curcumin	[110]
Carbohydrates/protein/oil/fiber	Cureit®; Acumin®	[116]
Gelucire®/Polysorbate 20	BioCurc®	[109]
Galactomannan fiber	CurQfen®	[117]
Ghatti gum/glycerin/lipids/hydroxymethyl	Theracurmin®	[118, 119]
Cellulose/sodium alginate	MicroActive Curcumin™	[120]
Surfactants/polar lipids solvents	HydroCurc™	[121]

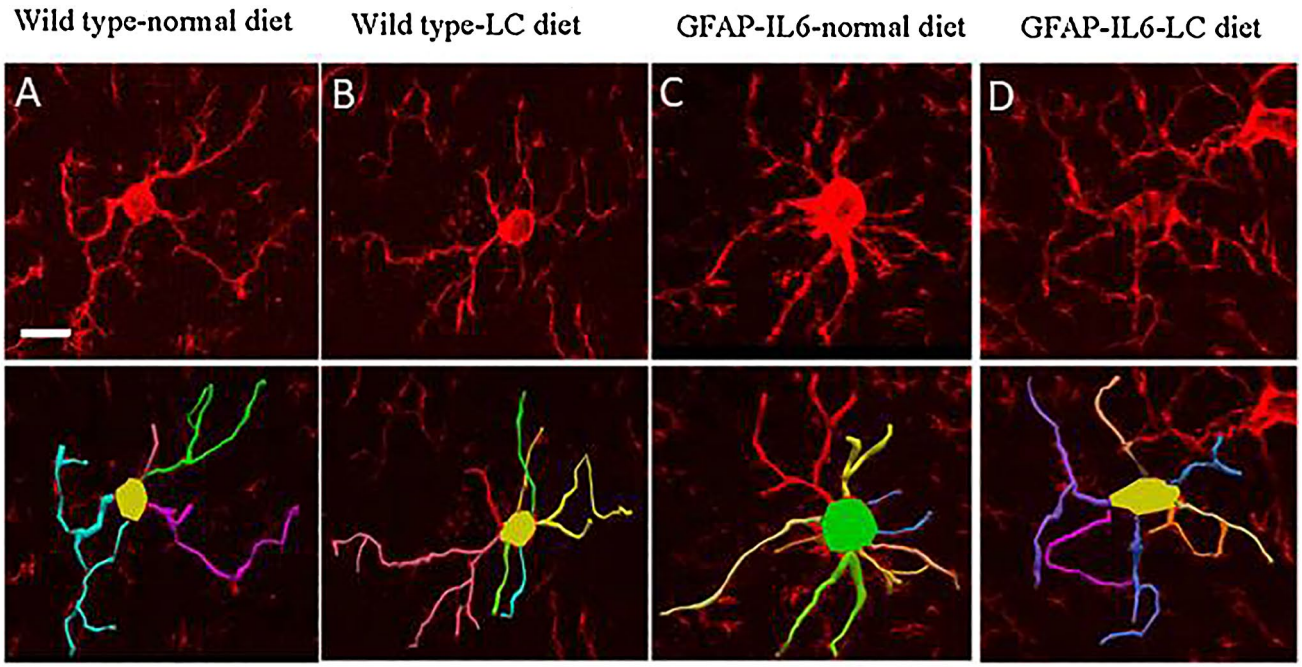

Fig. 2 Effect of Longvida® curcumin (LC) on microglial tree structure. Feeding the LC for 6 months to both WT and GFAP-IL6 mice with high neuroinflammation has significantly reduced the de-ramification of microglia (**A**–**D**). The representative images of microglia immunostained for Iba-1 showing that the Iba-1^{+} microglial cells of the GFAP-IL6 LC fed mice had a significantly reduced soma area (**D**), soma perimeter, and a higher number of nodes than that of the GFAP-IL6 mice on regular diet. Scale bar 10 µm [67]

was able to decrease astrocyte activation and the number of branches of the astrocytes in the rat hippocampus [5]. Similarly, another study conducted in a Sprague–Dawley rat model of chronic constriction injury model has provided evidence that solid lipid curcumin curcumin attenuates the activation of astrocytes. The study reported a decrease in hypertrophy of astrocytes in the injured rats after being treated with curcumin [48, 124]. We have recently conducted studies in the GFAP-IL6 mouse model of chronic neuroinflammation that have outlined more detailed structural and morphological changes that occurred in astrocytes during chronic neuroinflammation and the effect of modified curcumin preparations [67, 68]. These studies have revealed that astrocytes in the hippocampus and cerebellum regions in the GFAP-IL6 mice on normal-diet mice have a significantly larger dendritic length, the number of processes, convex area, convex perimeter, and the number of nodes compared to the wild types. Consuming curcumin diets, have significantly decreased the hypertrophy of astrocytes by decreasing the dendritic length, the number of processes, convex area, convex perimeter, and the number of nodes of astrocytes [67, 68] briefly; the study investigated the effects of LC in GFAP-IL6 mice by feeding to 2 months old mice for the period of 6 months. The study confirmed that the LC diet has potentially decreased the hypertrophy of astrocytes (Fig. 3).

Future Directions

The structural morphology of microglia and astrocytes has an important role in understanding the pathophysiology of neurodegenerative diseases. Research on microglia and astrocytes and their structural and functional changes regarding neuroinflammation, injury, and neuronal disorders is gaining a lot of prominence. Thus, it is important to investigate the glial connections to neuronal networks both during healthy and pathological aging to better understand the etiology of diseases like AD and their impact on memory. It is also still inconclusive whether inflammation is a cause or a result of the observed neurodegeneration in these diseases. Thus, studies focusing on both neuroinflammation and neurodegeneration will help to design target-specific therapeutic interventions when treating related cognitive impairments. There are no therapies purposely designed against microglia- and astrocyte-specific targets in clinical practice. Furthermore, there are limited studies that elaborate on the effects of curcumin against glial cell activation. The presented evidence and findings

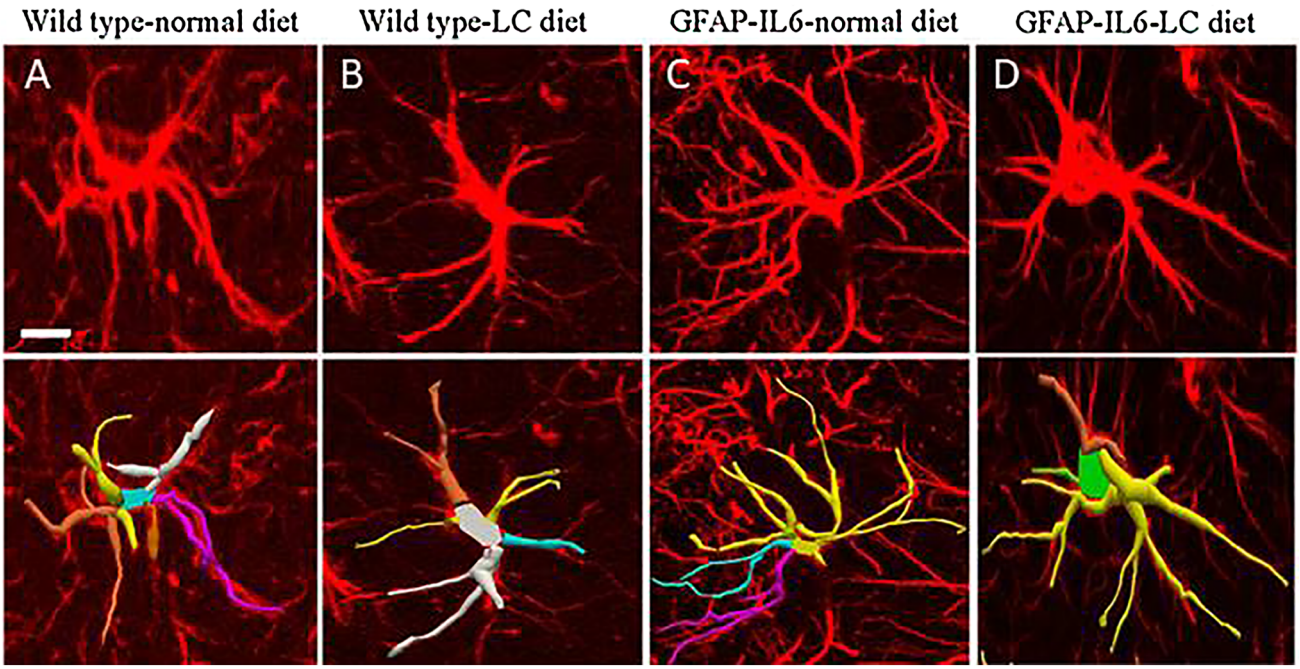

Fig. 3 Effect of Longvida curcumin (LC) on astrocyte hypertrophy showing a significant decrease in overall astrocytes size in LC-fed GFAP-IL6 mice. LC diet reversed the activation of astrocytes resulting in a decrease in the hypertrophy of astrocytes (**A**–**D**). 3D reconstruction of astrocytes in wild type and GFAP-IL6 in both showing that the LC diet treated and non-treated mice significantly reduced the astrocytes hypertrophy by decreasing the dendritic length, number of processes, convex area, convex perimeter, and number of nodes than that of GFAP-IL6 normal-fed mice. Scale bar 10 µm [67]

will hopefully boost more coordinated and better-focused efforts to improve and therapeutically exploit the role of curcumin against reactive microglial cells and astrocytes in chronic neuroinflammation and brain injuries.

Taken together, this review discussed the tree structure of microglial cells and the astrocytes hypertrophy upon activation, in response to neuroinflammation, brain injury, and other kinds of CNS assaults. The study has highlighted the effects of curcumin against the glial cell activation and its potential to reverse the morphological changes that occur upon activation. This work showed that curcumin has a key role to reverse the activation of glial cells and, decrease the de-ramification of microglia and hypertrophy of astrocytes. This study could be the possible clue to cope with the neuroinflammation characterized by activation of microglia and astrocytes and alteration in their structural morphology.

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Declarations

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