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REVIEW

Effects of Curcumin on Microglial Cells

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Abstract

Microglia are innate immune system cells which reside in the central nervous system (CNS). Resting microglia regulate the homeostasis of the CNS via phagocytic activity to clear pathogens and cell debris. Sometimes, however, to protect neurons and fight invading pathogens, resting microglia transform to an activated-form, producing inflammatory mediators, such as cytokines, chemokines, iNOS/NO and cyclooxygenase-2 (COX-2). Excessive inflammation, however, leads to damaged neurons and neurodegenerative diseases (NDs), such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Curcumin is a phytochemical isolated from *Curcuma longa*. It is widely used in Asia and has many therapeutic properties, including antioxidant, anti-viral, anti-bacterial, anti-mutagenic, anti-amyloidogenic and anti-inflammatory, especially with respect to neuroinflammation and neurological disorders (NDs). Curcumin is a pleiotropic molecule that inhibits microglia transformation, inflammatory mediators and subsequent NDs. In this mini-review, we discuss the effects of curcumin on microglia and explore the underlying mechanisms.

Keywords Curcumin · Microglia, neuroinflammation · Neuroprotection · Neurodegenerative diseases

Introduction

Turmeric (*Curcuma longa*) is a rhizomatous herbaceous flowering plant in the Ginger family (Zingiberaceae) (Hesari et al. 2018). Turmeric is widely produced in India, China, and other Asian countries and has been effectively used for centuries in traditional medicine as a remedy to cure and treat various diseases, disorders, and injuries. In addition to its use in medicine, it has been employed in the food, beverage, and cosmetic industries as a coloring agent.

Various compounds have been isolated from turmeric: the curcuminoid group (2–9%), including the three compounds curcumin/diferuloylmethane (77%), desmethoxycurcumin (18%), and bisdemethoxycurcumin (5%). Curcumin is the most bioactive compound, and while first extracted in 1815 (Gupta et al. 2013), its chemical structure was not known until 1910 (Agrawal and Mishra 2010; Hesari et al. 2018; Hosseini et al. 2018; Miłob dzka et al. 1910). Curcumin (1,7-bis-(hydroxy-3-methoxyphenyl)-1,6-heptadiena-3,5-dione) is a phenolic compound and a phytochemical yellowish pigment. It is hydrophobic and soluble in dimethyl-sulfoxide, organic solvents, or oils (Hesari et al. 2018). The presence of an active methylene group and a β-diketone moiety leads to instability and degradation by aldo-keto reductase in the liver (Liang et al. 2008). A large limitation in the clinical use of curcumin is its low bioavailability, chemical instability, rapid

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metabolism, and short half-life. Therefore, researchers have been investigating the use of various formulations in vivo, including nanoparticles, to overcome some of these challenges and improve efficacy.

Curcumin is a safe and highly pleiotropic molecule with numerous targets that have been widely studied in vivo and in vitro. Its broad range of activities include anti-tumor (Hamzehzadeh et al. 2018; Mirzaei et al. 2016), anti-inflammatory (Ghandadi and Sahebkar 2017; Karimian et al. 2017b; Panahi et al. 2015; Sahebkar et al. 2016), anti-angiogenic (Shakeri et al. 2018), neuroprotective (Ghosh et al. 2015; Hu et al. 2015), anti-ischemic (Bavarsad et al. 2018; Mokhtari-Zaer et al. 2018; Sahebkar 2010), anti-tumor (Hamzehzadeh et al. 2018; Iranshahi et al. 2009; Momtazi and Sahebkar 2016; Teymouri et al. 2017), lipid-modifying (Cicero et al. 2017; Ganjali et al. 2017; Panahi et al. 2014; Panahi et al. 2016b), antidiabetic (Panahi et al. 2018; Parsamanesh et al. 2018), hepatoprotective (Panahi et al. 2017b; Zabihi et al. 2017), analgesic (Shakeri and Sahebkar 2016), antioxidant (Panahi et al. 2016a, 2017a; Sahebkar et al. 2015), vasculoprotective (Bianconi et al. 2018; Karimian et al. 2017a), anti-thrombotic (Keihanian et al. 2018), cardioprotective (Saeidinia et al. 2018), pulmonoprotective (Lelli et al. 2017), and immunomodulatory (Abdollahi et al. 2018) effects. There is particularly strong evidence of curcumins protective effects in the context of neuroinflammation (Ameruoso et al. 2017; Hesari et al. 2018; Hosseini et al. 2018; Morales et al. 2014; Mukherjee et al. 2018; Parada et al. 2015; Sawikr et al. 2017; Venigalla et al. 2016; Wang et al. 2015; Yue et al. 2014). Curcumin can affect the MAPK, NF-κB, WNT/β-catenin, PI3K/Akt, active protein 1 (AP-1), and STAT3 signaling pathways, plus influence a diverse range of microRNAs (Hesari et al. 2018; Momtazi et al. 2016a, b).

Microglia are similar to tissue macrophages but reside in the CNS. Besides their well-known role in the immune system, they have a fundamental role in regulating neuronal homeostasis by degrading and clearing apoptotic debris (Karlstetter et al. 2011; Napoli and Neumann 2009; Sorrenti et al. 2018). In order to protect the CNS from neuronal damage or exposure to pathogenic invaders with subsequent neuroinflammatory responses, microglia transform from a ramified form to an activated form. Activated-microglia mediate neuroinflammatory responses by releasing chemokines, cytokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS) (Hidalgo-Lanussa et al. 2018; Lanussa et al. 2016). However, excessive production of inflammatory mediators can cause serious neuronal damage and death. Recent studies have shown that microglial cells are associated with neurological disorders (NDs), such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and stroke, specifically ischemic stroke (Liu et al. 2017; Sawikr et al. 2017; Yue et al. 2014). Although neuroinflammation is associated with many NDs, clinical drug trials have proven disappointing (Imbimbo et al. 2010).

In the last decade, accumulating evidence suggests curcumin is a potential therapeutic agent for myriad diseases and disorders, including viral infections, cancer, rheumatoid arthritis, atherosclerosis prevention, ischemic stroke, Gulf War illness, cardiovascular diseases, intracerebral hemorrhage, and NDs induced by microglia (Agrawal and Mishra 2010; Avan et al. 2016; Choi et al. 2011; Hesari et al. 2018; Kaur et al. 2015; Kodali et al. 2018; Lee et al. 2012; Valverde et al. 2016; Zhang et al. 2017). Neuroinflammation is the initial critical step of neurodegenerative diseases (Alexiou et al. 2018). The progressive damage is induced by activation of microglia with consequent production of excessive pro-inflammatory cytokines and neurotoxic factors, such as ROS, iNOS, IL-1β, tumor necrosis factor-α (TNF-α), PGE2, and IL-6, leading to neuronal damage and cognitive deficits (Kaur et al. 2015). Due to its lipid solubility, curcumin crosses the blood-brain barrier (BBB) and inhibits microglia activation by suppressing the expression of inducible nitric oxide synthase (iNOS). This reduction in NO production and the associated signaling pathways by curcumin, as well as blocking cytokines and oxidative stress, leads to anti-neuroinflammatory effects on microglia (Akaishi and Abe 2018; Eun et al. 2017; Parada et al. 2015; Sharma et al. 2017). Moreover, curcumin has neuroprotective effects on both neuronal cells and microglia via inhibition of apoptosis, PI3k/Akt and iNOS, lipoxygenase (LOX), COX-2 and HSP60/HSF-1 expression, and inducing activation of heme-oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor 2 (Nrf-2), and the antioxidant response element (ARE) mechanism (Abdollahi et al. 2018; Cianciulli et al. 2016; Ding et al. 2016). Thus, utilizing curcumin as an anti-neuroinflammatory agent with inhibitory effects on microglia transformation could be a promising approach for the treatment of neurodegenerative disorders. Here, we review the effects and underlying mechanisms of curcumin on microglia in vitro, in vivo, and in clinical trials.

Microglia as the Resident Immune Cells in the CNS

Microglia are the major innate immune cells resident in the CNS. In a healthy normal brain, microglia display unique molecular homeostasis, including transcription activity and surface protein expression patterns which differ from tissue macrophages (Hanisch 2013). Recent studies have defined the molecular homeostatic and disease-associated signatures of microglia and how these cells are regulated, including how they contribute to healthy and morbid brain conditions (Bennett et al. 2016). Microglia scavenge dead neuronal cells and other CNS debris. Importantly, they also protect neuronal cells from invading pathogens (Bennett et al. 2016).

Microglia arise from early colonization of the CNS by the mesoderm layer originating from yolk sac-primitive macrophages (Alliot et al. 1999; Ginhoux et al. 2010). Although adult microglia are independent of hematopoietic stem cells for their maintenance, the mechanism of their differentiation is not yet fully understood. Unlike other hematopoietic lineages, microglia cells live about 4.2 years and have an annual turnover of approximately 28% (Réu et al. 2017). Microglia have a notable self-renewal capacity, exemplified by a recent study showing that following elimination of 99% of microglia cells in the CNS, newborn microglia can replenish and repopulate from residual microglia cell proliferation rather than from new progenitors (Huang et al. 2018; Rossi and Lewis 2018). In certain circumstances, peripherally derived macrophages can replace the eliminated microglia and perhaps these translocated macrophages play a role in the progression or development of neurological diseases. In mice, a lack of transforming growth factor-β1 (TGF-β1) signaling in peripherally recruited cells (to replace the deficient microglia cells) has been shown to produce a progressive and fatal demyelinating disease (Lund et al. 2018), such as multiple sclerosis.

Microglia exist in two different forms: resting (or ramified) and activated. Depending upon the normal or pathological brain condition, microglia can transform from ramified to activated. Moreover, they can exhibit both functional and phenotypic activities in both healthy and morbid brain (Colonna and Butovsky 2017; Hanisch 2013; Kettenmann et al. 2011; Ransohoff and Cardona 2010). Formerly, activated microglia were classified as M1-like (exhibiting pro-inflammatory and neurotoxicity signaling) and M2-like (inflammatory-participant cells) based on the surface molecule and cytokine expression profiles (Mantovani et al. 2005; Martinez and Gordon 2014). However, new technologies, such as epigenetic studies, RNA sequencing, and quantitative proteomics have revealed a more complex picture (Kettenmann et al. 2011; Ransohoff 2016) (Fig. 1). These technologies have revealed that microglia fundamentally differ from peripheral myeloid cells (Bennett et al. 2016). Microglia express common macrophages markers, although the amount of marker expression is different and can be used to identify microglia from macrophages. Furthermore, targeting these marks could be used in the treatment of neurological diseases. For example, microglia have a lower expression of receptor-type tyrosine-protein phosphatase C (PTPRC or known as CD45) when compared with monocytes and differing expression of scavenger receptor cysteine-rich type 1 protein M130 (CD163) (Bennett et al. 2016; Sousa et al. 2017; Vainchtein et al. 2014). *Colony-stimulating factor 1* (CSF1 or macrophage colony-stimulating factor) and its receptor (CSF1R) play an important role in microglia development. In addition, activation of CSF1 promotes differentiation of the tissue-specific signaling pathway of myeloid cells and microglia in the CNS (Ginhoux et al. 2010). Following infection or injury, microglia can be polarized to the pro-inflammatory M1 phenotype, where they start producing TNF-α and IL-1β. This state is associated with neuronal damage and has been implicated in the pathology of neurodegenerative disorders. In diseases such as PD, AD, and ALS, there is a shift in the ratio of M1:M2 microglia phenotypes towards a pro-inflammatory state. This further demonstrates the potential for targeting microglia in NDs, specifically, therapeutics which enhance polarization towards the M2 state would promote tissue repair.

Curcumin has been shown to have a profound regulatory effect on microglial responses. Liu et al. (2017) investigated the neuroprotective effect of curcumin (150 mg/kg curcumin ip) in a mouse model of ischemic stroke and demonstrated that curcumin promoted M2 polarization leading to suppress inflammation, reduce neuronal damage, and improve function tests. This research demonstrates that by inhibiting microglia-mediated pro-inflammatory responses, curcumin has the potential to reduce the progression of neurodegeneration in diseases such as PD and AD.

The Role of Microglia in Neuroinflammation and NDs

In many ND diseases, microglia lose or alter their molecular homeostatic function, resulting in impaired synaptic transmission and plasticity, and the development of neuroinflammation (Riazi et al. 2015). Consequently, chronic activated-microglia have been identified in ND diseases such as AD, PD, HD, MS, and ALS (Hesari et al. 2018; Kaur et al. 2015; Maiti et al. 2018; Sawikr et al. 2017; Tripanichkul and Jaroensuppaperch 2012; Venigalla et al. 2016). Researchers are now investigating how unique microglia signatures and forms alter across the development of specific neurodegenerative diseases. To understand microglial plasticity, it is first important to understand the mechanism of homeostatic microglial regulation and its phenotype. Ramified microglia have branches and consistently scan the environment in search of pathogens and cellular debris, in order to maintain CNS homeostasis (Colonna and Butovsky 2017; Kettenmann et al. 2011). Microglia, like other innate immune cells, express pattern recognition receptors (PRRs) that can bind to the damage-associated molecular patterns (DAMPs) and pattern-associated molecular patterns (PAMPs), prime examples being lipopolysaccharide (LPS) and lipoteichoic acid (LTA) (Jack et al. 2005). Toll-like receptors (TLRs) are important PRRs and are the main receptors in immune cells, especially microglia (Jack et al. 2005; Kettenmann et al. 2011). TLRs can bind to molecules from pathogens and protect local cells; they can also bind to LPS and LTA, triggering the transformation of microglia from the resting to the activated form.

Signal transduction and binding of TLRs to PAMPs and DAMPs are mediated through various adaptor proteins,

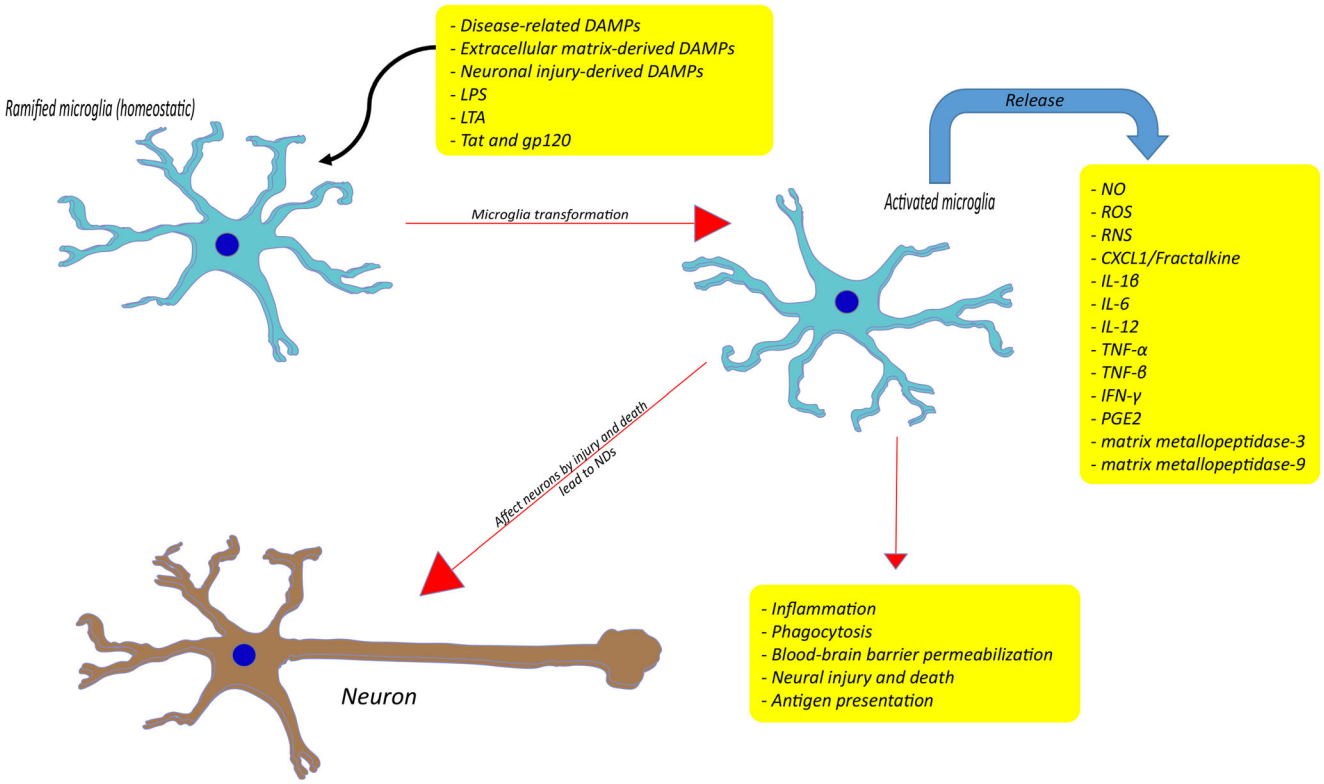

Fig. 1 Microglia activation. Some molecules such as disease-related DAMPs, extracellular matrix-derived DAMPs, neuronal injury-derived DAMPs, LPS, LTA, Tat, and gp120 can trigger microglia activation. Upon activation, microglia release some molecules including, NO, ROS, RNS, CXCL1/Fractalkine, IL-1β, IL-6, IL-12, TNF-α, TNF-β, IFN-γ, PGE2, MMP-3, and MMP-9. These molecules subsequently affect the CNS and neurons and trigger NDs

including MyD88 (Deguine and Barton 2014). MyD88 is the major component of the innate immune system and is a downstream member of signaling pathways in the TLR and interleukin-1 receptor (IL-1R) families. It can promote transcription factor activation of NF-κB and MAPK, thereby leading to the expression of inflammatory mediators (Deguine and Barton 2014). In the normal healthy brain, microglia are in the resting ramified form. However, when pathogens, like Gram-negative bacteria, invade the brain, LPS, or LTA promote microglia transformation to the activated form. To fight pathogens, the activated-form of microglia secretes pro-inflammatory cytokines, chemokines, and neurotoxic factors (Yu et al. 2018; Zhou et al. 2017), which produce neuroinflammation leading to neuronal damage and death (Bennett et al. 2016; Hesari et al. 2018; Zhou et al. 2017). Inflammation and oxidative stress processes are the major protagonists in neurodegeneration and are highly co-dependent (Cabezas et al. 2018; Cabezas et al. 2012). Oxidative stress is critical in the pathology of NDs and has many destructive effects related to the generation of ROS and RNS, which can lead to neuronal DNA damage and death. This excessive oxidative stress also promotes the release of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, contributing to the development of NDs such as AD, MS, PD, ALS, and HD (Bennett et al. 2016; Hesari et al. 2018; Zhou et al. 2017).

Molecular Targets of Curcumin in Reducing Microglial Activation and Associated Neuroinflammation

Curcumin is able to cross the BBB and directly affect microglia activation (Tsai et al. 2011). Accumulating evidence has demonstrated promising pharmacological properties of curcumin, such as anti-inflammatory, immune-modulatory, and neuroprotective effects. The main anti-neurodegenerative effect of curcumin is via inhibition of apoptosis, TNF-α, iNOS, RNS, COX-2, and LOX.

Oxidative and pro-inflammatory molecules activate Keap-NRF2 (Kelch-like ECH-associated protein (Yu et al. 2018). Thereupon, the separated NRF2 translocates to the nucleus and binds to antioxidant stress condition (ARE) that can protect cells by activating antioxidant genes (Tocharus et al. 2012). NRF2 activates many antioxidant genes, the primary one being HO-1. Recent studies have shown the therapeutic potential in NDs of targeting NRF-2 and HO-1 (Eun et al. 2017). Curcumin activates NRF-2 and HO-1 in microglia, consequently reducing oxidative stress and neuroinflammation. Thus, curcumin can be considered as a potential neuroprotective agent working through the NRF-2 pathway (Bhattacharjee et al. 2016). In certain circumstances, LPS can cross the BBB and mediate the release of TNF-α in microglia and neuronal cells, inducing

inflammatory responses and pro-apoptotic activity via the NF-κB and MAPK pathways. Additionally, curcumin inhibits TNF-α and other pro-inflammatory cytokines contributing to its neuroprotective effects.

The STAT3 signaling pathway has been widely studied for its role in immunity and growth regulation, early embryonic development and inflammation (Hillmer et al. 2016; Subramaniam et al. 2013). STAT3 activation is mediated by the JAK family of tyrosine-kinases, especially JAK1 (Tripanichkul and Jaroensuppaperch 2012). Activation of STAT3 by v-src leads to activation of the NF-κB signaling pathway which, subsequently, produces inflammatory cytokines, such as IL-6 (Hillmer et al. 2016). Additionally, persistent STAT3 activation is associated with various diseases, such as immunodeficiency, autoimmunity, and cancer (Hillmer et al. 2016). Curcumin modulates NF-κB activation via STAT3 inhibition. The PI3K/Akt pathway plays a considerable role in activating the microglia. Suppression of the PI3K/Akt pathway with curcumin caused a significant downregulation of pro-inflammatory mediators and microglia activation.

Peroxisome proliferation-activated receptor-γ (PPARγ) is a transcription factor and nuclear receptor protein that regulates inflammatory responses in microglia, astrocytes (Iglesias et al. 2017), and in the CNS (Jacob et al. 2007). Activated-PPARγ binds to the peroxisome proliferator response element (PPRE) and subsequently suppresses the production of pro-inflammatory cytokines and inflammatory pathways (Jacob et al. 2007). Curcumin activates PPARγ which reduces NF-κB cytokine production in a mouse model of AD, in rat hippocampal primary cell lines (Liu et al. 2016b), and primary astrocytes (Wang et al. 2010). Curcumin also suppresses neuroinflammatory signaling via reduced AP-1 activation, reducing neuronal apoptosis (Ref). Heat shock protein 60 (HSP60) is a ligand for TLR-4 and promotes microglia activation; the level of heat shock factor-1 (HSF-1) is upregulated under LPS stimulation which increases the expression of HSP60 (Ding et al. 2016). Finally, curcumin suppresses NF-κB, MAPK/JNK, STAT3, iNOS, PI3K/Akt, and NADPH oxidase (NOX), HSP60, HSF-1, as well as beta-amyloid (Aβ), COX-2, and NO production. In addition, curcumin induces anti-inflammatory mediators, such as HO-1/NRF-2, PPARα-γ, and IL-4 (Ding et al. 2016; Hosseini et al. 2018; Jacob et al. 2007; Karlstetter et al. 2011).

Effects of Curcumin on Microglial Function In Vitro

Under normal conditions, microglia protect and regulate the homeostasis of neuronal cells. At times, in an effort to protect, activated-microglia produce excessive factors, such as pro-inflammatory cytokines, chemokines, ROS, and RNS. These pro-inflammatory components lead to the development of NDs (Yu et al. 2018). Curcumin exerts a therapeutic effect on microglia and NDs which have been reported in both in vitro and in vivo research.

In a 2011 report by Karlstetter et al., curcumin treatment altered the expression of 49 different transcriptional elements in LPS-activated microglia BV-2 cells. Curcumin demonstrated anti-inflammatory effects by causing diverse alterations in the transcriptome, such as inhibiting NOS2, IL-6, and COX-2, which are related to the NF-κB, AP-1, and STAT3 target pathways. In addition, curcumin reduced TLR-2 expression in resting microglia and after microglia activation and induced IL-4 and PPARα expression. This study supported the pleiotropic, anti-neuroinflammatory, neuroprotective, and antioxidant effects of curcumin (Karlstetter et al. 2011). A 2014 study demonstrated that curcumin has antioxidant and neuroprotective (specifically axon protective) effects via inhibition of MyD88/p38 MAPK (Tegenge et al. 2014). While Shi et al. (2015) used primary BALB/c microglia cultures to demonstrate that curcumin suppresses ERK1/2 and p38 MAPK, attenuating inflammatory responses (Shi et al. 2015).

In 2016, Bhattacharjee et al. reported that curcumin inhibited miRNA-34a promotor-luciferase activity. MiRNA-34a targets the triggering receptor expressed in myeloid/microglial cells-2 (TREM2), which is crucial for Aβ42-peptide clearance, and this targeting leads to NDs (Bhattacharjee et al. 2016). Cianciulli et al. used BV-2 LPS-stimulated microglia to demonstrate that curcumin attenuates LPS-induced inflammatory responses and downregulates the PI3K/Akt pathway in microglia (Cianciulli et al. 2016). Another study with LPS-activated BV-2 microglia demonstrated that curcumin has neuroprotective and anti-inflammatory properties via inhibition of HSF-1, HSP60, TLR-4, MyD88, and NF-κB (Ding et al. 2016). Curcumin was shown to ameliorate the phagocytic and anti-inflammatory effects of N9 microglia cells. In addition, curcumin had direct regulatory effects on phagocytosis of Aβ42-peptide, as well as attenuating effects on PGE2-stimulated N9 cells (He et al. 2016). Liu et al. used a neuroprotective potential algorithm to suggest that curcumin's neuroprotective and anti-neuroinflammation effects could produce a therapeutic benefit in AD (Liu et al. 2016a).

Previously, it has been shown that microglia play an important role in the pathogenesis of HIV-associated neurodegenerative disorders. Virus products, such as gp-120 and Tat, can activate microglia producing subsequent neuronal damage. Additionally, curcumin reduced inflammation caused by gp-120 on BV-2 microglia cells via inhibiting the phosphorylation of p-PI3K, p-Akt, and p-IKK and downregulating NF-κB (Chen et al. 2018a). A recent study on LTA-induced BV-2 microglia reported that curcumin inhibits iNOS, NO, PGE2, and TNF-α. Additionally, curcumin inhibited the MAPK phosphorylation and NF-κB translocation, as well as activating the HO-1 protecting neuronal cells against oxidative stress (Yu et al. 2018). A summary on the in vitro effects of curcumin are displayed in Table 1.

Table 1 In vitro effects of Curcumin

Authors	Species and cell type	Agent	Dose/route	In vitro effects	Refs.
Yu et al. (2018)	BV-2 microglia cells	Curcumin	5–20 μM	Curcumin had anti-neuroinflammatory via inhibiting NF-κB and p38 MAPK activation and inducing the expression of Nrf2 and HO-1.	(Yu et al. 2018)
He et al. (2014)	N9 cell line	Curcumin	5, 10, 20 μM	Curcumin ameliorated the phagocytic ability by preventing the pro-inflammatory activity in an NF-κB and STAT3-dependent manner.	(He et al. 2014)
He et al. (2016)	N9 cell line	Curcumin	5, 10, 20 μM	Curcumin reduced phagocytic abilities of PGE2-stimulated N9 cells. And also restored the attenuating effect of PGE2 on fαβ-induced microglia phagocytosis through signaling mechanism associated by EP2 and PKA.	(He et al. 2016)
Chen et al. (2018a)	Gp-120 induced BV-2 Microglia cells	Curcumin	10 μL	Curcumin inhibited NF-κB by preventing the translocation of NF-κB p65 and also inhibited the phosphorylation of p-PI3K, p-AKT, and p-IKK which downregulate the NF-κB and subsequently reducing inflammation.	(Chen et al. 2018a)
Karlstetter et al. (2011)	LPS-activated BV-2 microglia cells	Curcumin	20 μM	This study showed that curcumin has a potent modulatory of microglia transcriptome and attenuated the microglia migration and triggers a phenotype with anti-inflammatory and neuroprotective properties.	(Karlstetter et al. 2011)
Lee et al. (2012)	Murine cell line (RAW 264.7) and BV-2 microglia cells	Synthesized and modified Curcumin, called BDMC33	100 μL/well	BDMC33 efficiently suppresses the production of IL-1β, TNF-α and NO via INF-γ/LPS-induced microglia. Anti-inflammatory effects of BDMC33 were associated through intervention in JNK-ERK-AP-1 and/or NF-κB signaling pathways in microglia.	(Lee et al. 2012)
Akaishi and Abe (2017)	Wistar rats glial culture	CNB-001 (a pyrazole derived from Curcumin)	1–10 μM	For the first time, this study has shown inhibitory effects of CNB-001 on iNOS expression and NO expression in microglia.	(Akaishi and Abe 2018)
Shi et al. (2015)	Glial culture from neonatal BALB/c mice	Curcumin	10 μM	Curcumin did not influence on microglia cell viability and have a safe pharmacology activity.	(Shi et al. 2015)
Tegenge et al. (2014)	primary microglia cultures of Sprague-Dawley rats or C57BL/6 J mice	Curcumin	10 mM prepared in ethanol and DMSO, respectively	This study identified curcumin as a neuroprotective agent especially for axon and inhibited axon degeneration mediated by microglia MyD88/p38 MAPK signaling and NO production.	(Tegenge et al. 2014)
Yang et al. (2008)	Pregnant Fischer F344 rats and mesencephalic neuron-glia cultures	Curcumin and the spin trap agent DMPO (80 mM)	1–10 μM	Curcumin protected dopaminergic neuron in post/pre-treatment through the inhibition of overactivation induced by LPS.	(Yang et al. 2008)
Tocharus et al. (2012)	*HAPI* rat microglia *cell line*	Chemically modified curcumin (curcuminoid analogs)	10 to 40 μM	Nine curcuminoid analogs downregulated the expression of iNOS-mRNA and inhibited NO production in activated microglia induced by LPS.	(Tocharus et al. 2012)
Liu et al. (2016a)	One of its step is BV-2 microglia cells	Turmeric: curcumin	Dissolved in DMSO	This study supported the neuroprotective effect of curcumin on BV-2 microglia cells.	(Liu et al. 2016a)

Effects of Curcumin on Microglial Function In Vivo

In vivo studies using curcumin have been performed to study the effects in animal models. Several studies have utilized in vitro and in vivo models. In 2010, He et al. showed that curcumin inhibits pre-oligodendrocyte (preOL) apoptosis and decreases iNOS, NOX, and microglia activation in preOL culture with microglia. Using neonatal (P2) Sprague-Dawley rats, they showed that curcumin (100 mg/kg, intraperitoneally, ip) ameliorates white matter injury and preOL death, as well as inhibiting iNOS expression and NOX (p67phox and gp91phox) in microglia (He et al. 2010). Indeed, employing exosome-encapsulated curcumin on the glioblastoma cell line GL26 and in C57BL/6j mice inhibited tumor growth and microglia apoptosis. Intranasal administration of exosome-encapsulated curcumin (1.5 nmol) reduced the development of lipopolysaccharide (LPS)-induced brain inflammation, experimental autoimmune encephalitis, and delayed the growth of GL26 brain tumors in C57BL/6j mice (Zhuang et al. 2011). This method produced rapid drug delivery, which is a noninvasive therapeutic strategy for inflammatory-associated CNS diseases (Zhuang et al. 2011).

Tripanichkul and Jaroensuppaperch assessed the effect of curcumin on nigrostriatal dopaminergic (DA) neurons and glial responses in 31 male ICR mice with 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease. Curcumin (200 mg/kg, ip) protected the DA neurons, as well as reducing lesions and glial/microglia activation (Tripanichkul and Jaroensuppaperch 2012). As previously noted, gp-120 from HIV-1 can induce microglia activation and neuronal death. Indeed, gp-120 induced the N9 microglia cells to produce ROS, TNF-α, and monocyte chemoattractant protein-1 (MCP-1). HIV-1 gp-120 promoted apoptosis in cortical neurons of 1-day-old Sprague-Dawley rats which were attenuated by curcumin treatment. Curcumin inhibited ROS, TNF-α, and MCP-1 production in gp-120-induced microglia and protected cortical neurons (Guo et al. 2013).

In order to improve the pharmacokinetic profile of curcumin, Hoppe et al. (2013) developed a lipid-core nanocapsule loaded with curcumin, whereby low dose nanocapsulate curcumin (2.5 mg/kg, ip) showed a similar neuroprotective result to free high dose (50 mg/kg, ip) in an animal model of AD (Hoppe et al. 2013). Furthermore, in 2017, Liu et al. demonstrated that curcumin can reduce the expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12, and lead to survival of microglia in a mouse model of ischemic stroke (Liu et al. 2017). Curcumin delays retinal degeneration via suppression of microglia activation in retinas of rd1 mice (Wang et al. 2017). In a similar way, Niskanen et al., in 2016, examined boron nitride nanotubes (BNNTs) as mechanisms for intracellular delivery of fluorescent drugs, including curcumin, to the microglia (Niskanen et al. 2016). Curcumin-loaded BNNTs readily entered the microglia and reduced the pro-inflammatory factors such as NO, TNF-α, and IL-6 (Niskanen et al. 2016). Recently, Maiti et al. (2018) suggested that solid lipid curcumin particles have better neuroprotective, anti-inflammatory, and anti-amyloidogenic effects than curcumin in a 5xFAD (B6SJL-Tg) mouse model of AD (Maiti et al. 2018).

Fractalkine (FKN) promotes neuroinflammation in diet-induced models of obesity (Xu et al. 2016). Fructose feeding induces hippocampal microglia activation with neuroinflammation via activation of TLR-4 and NF-κB, which led to reduced neurogenesis (Xu et al. 2016). Moreover, the FKN level and CX3CR1 expression increased in fructose-induced mice, leading to neuroinflammation (Xu et al. 2016). Curcumin protects the fructose-induced mice via inhibition of microglia activation and suppression of FKN/CX3CR1 upregulation in the CNS (Xu et al. 2016). In a clinical trial, Mazzolani et al. utilized Meriva, a curcumin-phospholipid (lecithin) delivery system (Norflo tablet), to avoid poor bioavailability and treat central serous chorioretinopathy (Mazzolani and Togni 2013). The main effects of curcumin on microglia in vivo are summarized in Table 2.

The Promise of Curcumin for ND Therapy

As previously noted, curcumin has many properties which can be utilized in the treatment of NDs. Although curcumin can inhibit microglia activation via various signaling pathways, it is controversial because of a lack of robust pharmacokinetic activity. Nonetheless, curcumin has a safe profile without side effects and can be used in high doses. The use of drug delivery systems, such as nanoencapsulating, is able to compensate for curcumins poor pharmacokinetics, leading to enhanced effectiveness at low doses. LPS, LTA, and gp120 promote microglia activation which is central to the release of pro-inflammatory factors and excessive production of the mediators is implicated in the pathology of NDs. Curcumin is a pleiotropic molecule that affects many signaling pathways with effects on microglia. Curcumin is a very promising therapeutic agent that can be used in the treatment of NDs. Although recent studies demonstrate significant amelioration in treating NDs and other microglia-associated disorders and injuries. Further in vivo studies still need to be undertaken to assess various curcumin formulations and delivery mechanisms in models of neurodegenerative disease. The use of formulations, such as liposomal curcumin, polymeric nanocurcumin, and polylactic glycolic acid co-polymer (PLGA)–curcumin (Chiu et al. 2011), has resulted in the differential distribution of intravenous curcumin formulations in the rat brain and improved pharmacokinetics. However, curcumin levels detected in the brain remain low (< 0.5%), emphasizing the importance of assessing the long-term effects of curcumin on the pathology of NDs. It is also important that

Table 2 In vivo effects of curcumin

Authors	Species	Agent	Dose/Route	In vivo effects	Refs.
Tripanichkul and Jaroensuppaperch (2013)	ICR strain mouse model	Curcumin	200 mg/kg injected intraperitoneally	Curcumin induced nigrostriatal DA axons protection and Decreased the microglia and astrocyte activation.	(Tripanichkul and Jaroensuppaperch 2013)
Zhu et al. (2014)	Adult male C57BL/6 mice	Curcumin	50, 100, 200 mg/kg injected intraperitoneally	Curcumin attenuated TLR4-mediated acute activation of microglia, pro-inflammatory mediators release and neuronal via inhibition MyD88/ NF-κB signaling cascade in trauma brain injury (TBI).	(Zhu et al. 2014)
Chen et al. (2018b)	Pregnant BALB/c mice and primary cortex culture	Curcumin	40 mg/kg	This study indicated that curcumin alleviated neuroinflammation in fetal brain promoted by LPS.	(Chen et al. 2018b)
(Liu et al. 2016b)	Transgenic mice (APPswe/PS119)	Curcumin and PPARγ inhibitor	150 mg/kg curcumin and 4 mg/kg of inhibitor GW9662 dissolved in DMSO, injected intraperitoneally	Curcumin demonstrated beneficial effects on inflammatory response in AD and also improvement of curcumin on memory deficits in AD might be through activation of PPARγ pathway, which alleviated neuroinflammation response via inhibiting NF-κB signaling pathways.	(Liu et al. 2016b)
Yuan et al. (2017)	Adult male C57BL/6 mice	Curcumin	100 mg/kg injected intraperitoneally	Curcumin inhibited microglia activation and matrix metallopeptidase-9 expression.	(Yuan et al. 2017)
Kaur et al. (2015)	Wistar rats	Curcumin	100 mg/kg injected intraperitoneally	Immunohistochemical analysis showed a significant reduction in the number of glia (microglia) cells on curcumin administration to pentylenetetrazole treated animals.	(Kaur et al. 2015)
Mukherjee et al. (2016)	Adult male C57BL/6 mice (Glioblastoma GL261-implanted mice)	Curcumin derivatives	Intraperitoneal infusion of a lipid-encapsulated formulation	Delivered curcumin can directly kill Glioblastoma cells and also repolarize the tumor-associated microglial cells (TAMs) to the tumoricidal M1 state.	(Mukherjee et al. 2016)
Wang et al. (2017)	C57BL/6 and rd1 mice, BV-2 microglia cells and 661 cells	Curcumin	10 μM/L into the vitreous humor \with a syringe	Curcumin suppressed microglia activation and subsequently delayed retinal degeneration.	(Wang et al. 2017)
Yang et al. (2008)	Murine microglia BV-2 and hippocampal HT22 cells	Curcumin	0, 5, 10, 20 μM/L Injected intraperitoneally	Curcumin inhibited microglia activation	(Yang et al. 2008)
Dong et al. (2018)	Wild-type male C57BL/6 and Nrf2 gene knockout	Curcumin dissolved in DMSO	50 mg/kg body weight injected intraperitoneally	This study showed the neuroprotective role of curcumin in mouse TBI is dependent on Nrf-2 pathway and reduced microglia activation.	(Dong et al. 2018)
Sorrenti et al. (2018)	Male C57BL/6 mice	Curcumin in 1% methylcellulose	50 mg/kg orally administered for 2 consecutive days	Curcumin reduced microglia activation and had a preventive effects in inhibiting the acute neuroinflammation could be beneficial in reducing the long-term results of brain inflammation.	(Sorrenti et al. 2018)
Liu et al. (2017)	Adult male C57BL/6 mice and BV-2 microglia cells	Curcumin	150 mg/kg injected intraperitoneally	This study showed a powerful regulatory on microglia responses, promoting M2 microglia polarization and inhibiting microglia-mediated pro-inflammatory responses.	(Liu et al. 2017)

Table 2 (continued)

Authors	Species	Agent	Dose/Route	In vivo effects	Refs.
Canales-Aguirre et al. (2012)	Female Wistar rats	Curcumin	200 mg/kg body weight in the food	Curcumin reduced microglia activation and diminished the apoptosis against oxidative stress induced by prolonged exposure to parathion.	(Canales-Aguirre et al. 2012)
Sharma et al. (2017)	Sprague-Dawley rats	Curcumin	40 mg/kg body weight injected intraperitoneally	Curcumin protected dopaminergic neuron against inflammatory responses induced by LPS which is associated with blockade the glial (microglia and astrocyte) activation and transcription factor NF-κB and also curcumin suppressed microglia oxidase activity.	(Sharma et al. 2017)
Guo et al. (2013)	Male mice of the ICR strain	Curcumin dissolved in DMSO	200 mg/kg injected intraperitoneally	Curcumin protected nigrostriatal dopaminergic neurons and their projection, leading to a lesser extent of injury induced by glial responses.	(Guo et al. 2013)
He et al. (2010)	Neonatal Sprague-Dawley rats	Curcumin	50 mg/kg injected intraperitoneally	Curcumin ameliorated the white matter injury and loss of pre-oligodendrocytes and attenuated the microglia activation and expression iNOS and translocation of p67phox and gp91phox to the microglial cell membranes in neonatal rat brains.	(He et al. 2010)
Kodali et al. (2018)	Sprague-Dawley rats (Gulf War Illness model)	Curcumin	30 mg/kg in 0.1 mL of 33% DMSO injected intraperitoneally	Curcumin reduced astrocyte hypertrophy and activated microglia. Enhanced neurogenesis, restrained inflammation and oxidative stressed, and better mood and memory function mediated by curcumin.	(Kodali et al. 2018)
Naeimi et al. (2018)	Male Wistar rats	Curcumin loaded Nanoparticles (NPs)	12.5 mg/kg injected intraperitoneally	Level of inflammation and glial activation alleviated in lesion site in lysolecithin receiving animals and curcumin-loaded NPs suppressed upregulation of iNOS and NOX which leading to inhibition of oxidative stress pathway.	(Naeimi et al. 2018)
Maiti et al. (2018)	B6SJL-Tg mice	Curcumin and solid lipid curcumin particles	50 mg/kg body weight injected intraperitoneally	Solid lipid curcumin particles demonstrated greater effects than normal curcumin.	(Maiti et al. 2018)
Xu et al. (2016)	Male mice of the ICR strain	Curcumin	20, 40, 80 mg/kg by gavage	Curcumin protected the hippocampal dentate gyrus from neuronal damage via suppressing the activation of microglia and suppressing the upregulation of fractalkine/CX3CR1.	(Xu et al. 2016)

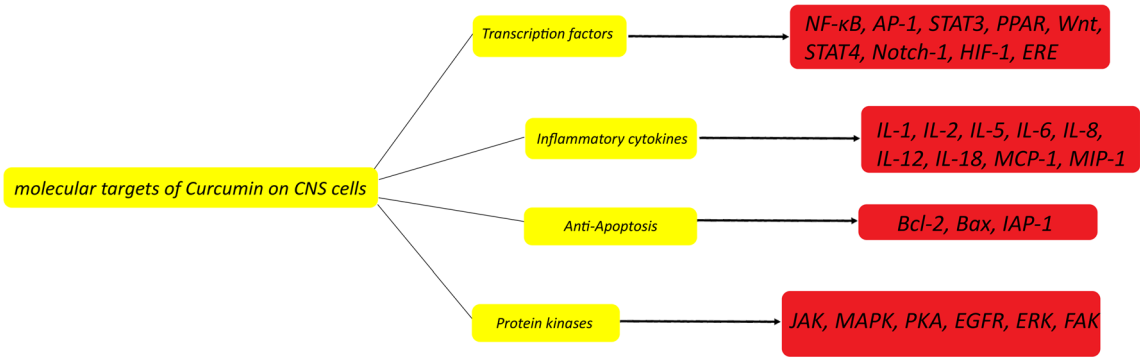

Fig. 2 Curcumin functions on CNS signaling pathways

animal studies also assess the effect of curcumin on behavioral phenotypes in animal models of NDs, as this is important for determining whether curcumin could help improve the quality of life in patients with neurodegenerative diseases. Based on the US clinicaltrials.gov website, clinical trials are being performed to assess the effectiveness of curcumin in a variety of disorders, including cancer, Alzheimer's disease, dementia, and schizophrenia. High doses of curcumin (3.6–12 g/day for 3–4 months) have been proved to be safe in phase 1 clinical studies, with mild nausea and diarrhea reported in some cases (Cheng et al. 2001; Lao et al. 2006; Sharma et al. 2004). A 6-month pilot clinical trial assessed the effect of curcumin in patients with AD and found that it was well tolerated and produced an increase in plasma A-beta deposits which the authors suggested was a consequence of disaggregation of A-beta deposits in the brain. Although promising, the short length of this trial and limited use of AD behavioral scales demonstrates the need for further pre-clinical and clinical trials to assess the effectiveness of curcumin in NDs.

Curcumin Analogs

Curcumin is a natural phytochemical isolated from turmeric and has been utilized for centuries (Hesari et al. 2018; Hosseini et al. 2018). Curcumin is known worldwide, and particularly in Asia, for its therapeutic properties especially in NDs (Hesari et al. 2018; Yu et al. 2018; Zhu et al. 2014). However, it has poor bioavailability/pharmacokinetics and is readily degraded in the body. Modified curcumin has been shown to improve the pharmacokinetics. Curcumin analogs, such as BDMC33, demethoxycurcumin, CNB-001, and bis-demethoxycurcumin, have been produced to circumvent the issues of poor bioavailability/pharmacokinetics (Akaishi and Abe 2018; Lee et al. 2012; Zhang et al. 2010; Zusso et al. 2017).

Conclusions

Microglia are the primary immune cells in the CNS. In order to regulate homeostasis and fight pathogens, microglia can produce inflammatory cytokines. Excessive production of inflammatory cytokines can lead to neuronal inflammation, causing neuronal injury and death. Moreover, neuroinflammation is the major initial step in NDs.

Curcumin has the ability to treat and potentially cure many diseases, especially NDs (Fig. 2). It is a pleiotropic molecule involved in many signaling pathways. Curcumin inhibits/reduces the inflammatory factor production via inhibiting activation of microglia. However, curcumin has poor pharmacokinetics and is readily degraded by aldo-keto reductase in the liver. Curcumin is, however, safe and can be used in a high dose to ameliorate its poor pharmacokinetics. Overall, curcumin is a promising therapeutic agent to reduce inflammatory and apoptotic mediators in microglia.

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All authors have approved final manuscript and submission.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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