Neuromol Med (2016) 18:453–464
DOI 10.1007/s12017-016-8430-x

REVIEW PAPER

Role of dietary phenols in mitigating microglia-mediated neuroinflammation

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Received: 21 March 2016 / Accepted: 21 July 2016 / Published online: 27 July 2016

Abstract Chronic neuroinflammation is a pathological feature of a number of central nervous system (CNS) diseases and is mediated by sustained activation of microglial cells, the innate immune cells of the CNS. Studies have mainly focused on identifying the molecular and epigenetic mechanisms of microglial activation. This is crucial in designing therapeutic strategies for neuropathologies in which prolonged microglial activation is known to exacerbate disease condition. In recent years, increasing evidence show that naturally occurring compounds present in regular diet could function as "nutraceuticals," arresting microglial activation, and thus conferring neuroprotection. This review summarizes our understanding of the role of dietary phenolic nutraceuticals in mitigating microglia-mediated neuroinflammation. Studies show that these natural phenols inhibit key signaling pathways in activated microglia such as the NFκB, MAPK and JAK-STAT that trigger microglia-mediated inflammation in various neuropathological conditions such as injury, infection, stroke, autism and neurodegenerative diseases, i.e., Alzheimer's disease and Parkinson's disease. The anti-inflammatory and antioxidant effect exerted by these natural phenols have shown considerable success in improving disease condition in animal models of neuropathologies, and thus seem to be suitable candidates for developing therapeutic strategies.

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Keywords Microglia · CNS · Luteolin · Quercetin · Resveratrol · Curcumin · Neuroinflammation

Introduction

Microglia, the resident macrophages of the CNS, form the frontline defense system to respond to CNS pathologies including infections (Persidsky and Gendelman 2003; Koedel and Pfister 1999), brain injury (Ramlackhansingh et al. 2011), stroke (Kaushal and Schlichter 2008), aging-associated neurodegenerative diseases (Perry et al. 2010b) and cancer (Graeber et al. 2002). Microglial cells have numerous functions in health and disease, ranging from synaptic pruning and maintenance in the developing and healthy adult CNS to instigation of inflammation, phagocytosis, repair and regeneration in CNS pathologies (U.-K. Hanisch and Kettenmann 2007; Kettenmann et al. 2013; Thameem Dheen et al. 2007).

The primary response of microglia to a detrimental stimulus in the CNS is initiation of neuroinflammation, which has been implicated in pathology of neurodegenerative diseases, stroke, infection and brain injury. Microglia which are activated upon encountering any pathological stimulus, undergo rapid proliferation (Lalancette-Hébert et al. 2007; Gómez-Nicola et al. 2013) and migrate to the site of insult (Stence et al. 2001). Activated microglia secrete an array of pro-inflammatory cytokines (U. K. Hanisch 2002) and reactive oxygen and nitrogen species (ROS, NOS) (Dohi et al. 2010; Wilkinson and Landreth 2006; Huo et al. 2011), engulf and digest dying cells, infectious agents, toxic protein aggregates and cellular debris by phagocytosis (Cullheim and Thams 2007; Majumdar et al. 2007), and also secrete anti-inflammatory cytokines and trophic factors for repair and restoration of

the nerve tissue (Thored et al. 2009; Butovsky et al. 2006). Based on their functional response, phenotypes of activated microglia have recently been classified as M1 or "classically activated" and M2 or "alternatively activated" (Crain et al. 2013). M1-activated microglia are generally considered to be "neurotoxic" as they secrete pro-inflammatory mediators (Tumor Necrosis Factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6)), prostaglandins (COX-2), ROS and NO. In contrast, M2-activated microglia are seen to be "neuroprotective" as they secrete anti-inflammatory mediators (interleukin-10 (IL-10), transforming growth factor- beta (TGFβ)), enzymes to inhibit ROS production (Arginase), proteins to maintain extracellular matrix (Ym-1) and perform phagocytic clearance of toxic protein aggregates and cellular debris (Saijo and Glass 2011; Walker and Lue 2015; Cherry et al. 2014). The orchestration and balance of these opposing yet complementing microglial functions are crucial for an effective immune response and mitigation of the pathological insult in the CNS. However, an imbalance in these functions of activated microglia leading to exacerbated immune response is one of the major contributing factors to the progression of neuropathologies. In the event of brain injury, microglia are polarized into the reparative M2 phenotype which is gradually replaced by the toxic M1 phenotype during later stages of the disease, contributing to prolonged inflammatory reaction, and subsequently impairing neuronal repair and regeneration (Wang et al. 2013; Kumar et al. 2015). Similarly, in animal models of aging-associated neurodegenerative diseases such as Alzheimer's disease (AD), microglia assume the M2 phenotype at the initial stages of the disease to engulf the toxic amyloid plaques. However, these M2 cells transform into M1 neurotoxic cells eventually leading to worsening of the disease condition (Cherry et al. 2014). In contrast, brain tumors such as glioma induce microglia to assume a tumor supportive phenotype, which predominantly is M2-like, so as to create a favorable environment for the survival and growth of glioma (Li and Graeber 2012). These studies underline the functional diversity of activated microglia in different stages of disease progression, and therefore, it is necessary to target and mitigate detrimental responses of activated microglia and stimulate their beneficial responses as a strategy to halt disease progression.

Targeting microglial cells as a therapeutic strategy has been the one of major areas of current research in the treatment of neuropathologies. Several studies have shown that herbal and synthetic compounds such as retinoic acid, dexamethasone, dimethylsphingosine, costunolide, interferon-beta (IFN-β) and melatonin can effectively induce a neuroprotective phenotype in activated microglia (Dheen et al. 2005; Xu and Drew 2006; Huo et al. 2011; Nayak et al. 2010; Rayan et al. 2010; Chan et al. 2003; Chung and Han 2003; Thameem Dheen et al. 2007; Choi et al. 2011; Rangarajan et al. 2013).

Of the numerous dietary compounds that have been elucidated to aid in CNS disease therapies, naturally occurring phenols are a class of compounds that have proven anti-inflammatory and antioxidant properties. These are abundant compounds found in a wide variety of plant sources, with some of them being able to permeate the blood brain barrier (BBB) which is one of the most important consideration for the use of a drug for CNS disease therapy (Bisht et al. 2010; Sawmiller et al. 2014; Ishisaka et al. 2011; Perry et al. 2010a). This review discusses in detail the mechanisms of action, and the therapeutic roles of four well-studied natural phenols: Luteolin and Quercetin (flavonoids), and Resveratrol and Curcumin (non-flavonoids) in microglia in the context of various CNS pathologies (Fig. 1).

Luteolin

Luteolin (chemical name: 3′,4′,5,7-tetrahydroxyflavone) (Fig. 2) is a flavone, a type of flavonoid polyphenol present in dietary sources such as celery, green pepper, broccoli, carrots, olive oil and several other food sources (Lopez-Lazaro 2009). Luteolin has been shown to possess anti-cancer properties by promoting apoptosis, and by suppressing invasion, angiogenesis and metastasis of tumor cells (Cheng et al. 2005; Bagli et al. 2004). In addition, it can exert antioxidant effects by scavenging free oxide and nitrite ions (Lopez-Lazaro 2009; Taliou et al. 2013). Luteolin is also capable of crossing the BBB and has been tested extensively for the treatment of various CNS pathologies (Sawmiller et al. 2014).

Therapeutic effects of luteolin in CNS diseases

Recent studies have elucidated the potential of luteolin in mitigating microglia-mediated neuroinflammation in CNS disease therapy, particularly in aging-associated memory and cognitive impairments and Autism Spectrum Disorder (ASD) (Jang et al. 2010; Tsilioni et al. 2015). In the brain of AD mouse models, luteolin was found to reduce the accumulation of phosphorylated tau protein, a characteristic feature of AD pathology, and diminish the production of microglia derived pro-inflammatory cytokines (Sawmiller et al. 2014). Further, luteolin has been reported to induce anti-inflammatory effects in aging mouse brain (Burton et al. 2015).

Dietary supplement of luteolin for 4 weeks inhibited the lipopolysaccharide (LPS), a bacterial endotoxin-induced microglial activation and the expression of pro-inflammatory cytokines significantly in microglial cells in aging mice (Burton et al. 2015). Since aging-associated

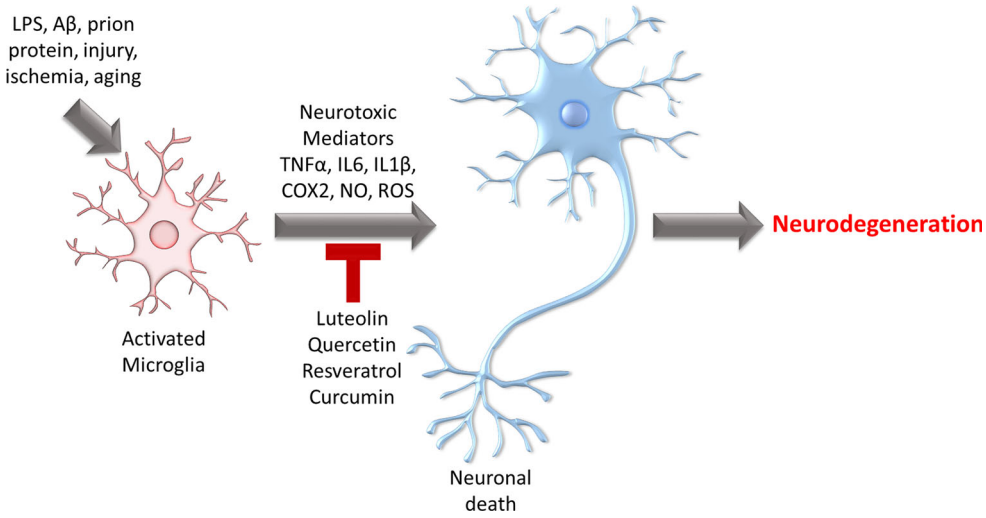

Fig. 1 Microglia are activated in response to stimuli such as lipopolysaccharide (LPS), Amyloid-beta (Aβ) peptides, injury and aging which leads to release of pro-inflammatory mediators such as TNFα, IL6, IL1β and reactive oxygen species (ROS). Chronic activation of microglia results in neurotoxic microenvironment that leads to neurodegeneration associated with a number of CNS pathologies like AD, PD, injury and ischemia

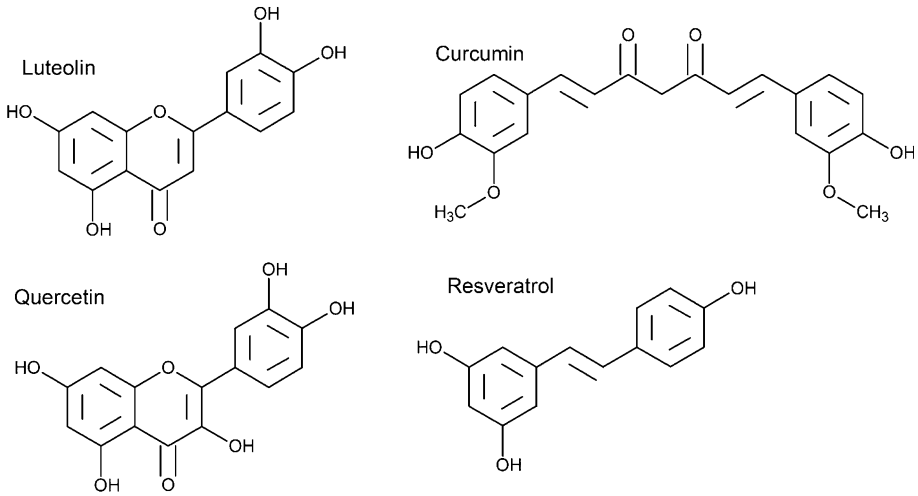

Fig. 2 Chemical structures of flavonoid and non-flavonoid dietary phenolic compounds, Luteolin, Quercetin, Curcumin and Resveratrol

dysfunction of microglia is one of the major causes for the development of neurodegenerative diseases such as AD (Streit 2006), the intake of luteolin-rich diet could have protective effects on the CNS and assist in a healthy aging process by targeting the neurotoxic behavior of senescent microglia. This finding was substantiated by another study where it was observed that aged mice show reduced spatial working memory along with a concomitant increase in inflammatory markers in the hippocampal region, suggesting an increased microglial activity. On the other hand, mice that are fed with luteolin show an enhanced spatial working memory and inflammatory markers at comparable levels to young adults, thus hinting at possible anti-aging and neuroprotective role of luteolin (Jang et al. 2010). Given the emerging role of microglia in synaptic pruning and sculpting during development, memory consolidation and aging, it would be of interest to study the possible role of polyphenols in modulating these aspects of microglial behavior. Such formulations may be of interest as "nutraceuticals" assist in healthy aging of the adult human brain.

The most recent study demonstrated the beneficial effect of luteolin in the human brain. It was shown that supplementing the diet of children suffering from ASD with luteolin led to a remarkable reduction in the serum levels of pro-inflammatory cytokines such as TNF-α and IL-6 as well as an improvement in the behavioral deficits in these children (Tsilioni et al. 2015). This indicates the ability of luteolin in improving the cognitive and behavioral impairments associated with ASD by altering the microglia-mediated neuroinflammation since, the causal link between the development of ASD and the inflammatory response of microglia is now well established (Suzuki et al. 2013; Takano 2015).

Molecular targets of luteolin in Microglia

Mechanistically, luteolin mainly targets the pro-inflammatory pathways in activated microglia such as Nuclear Factor

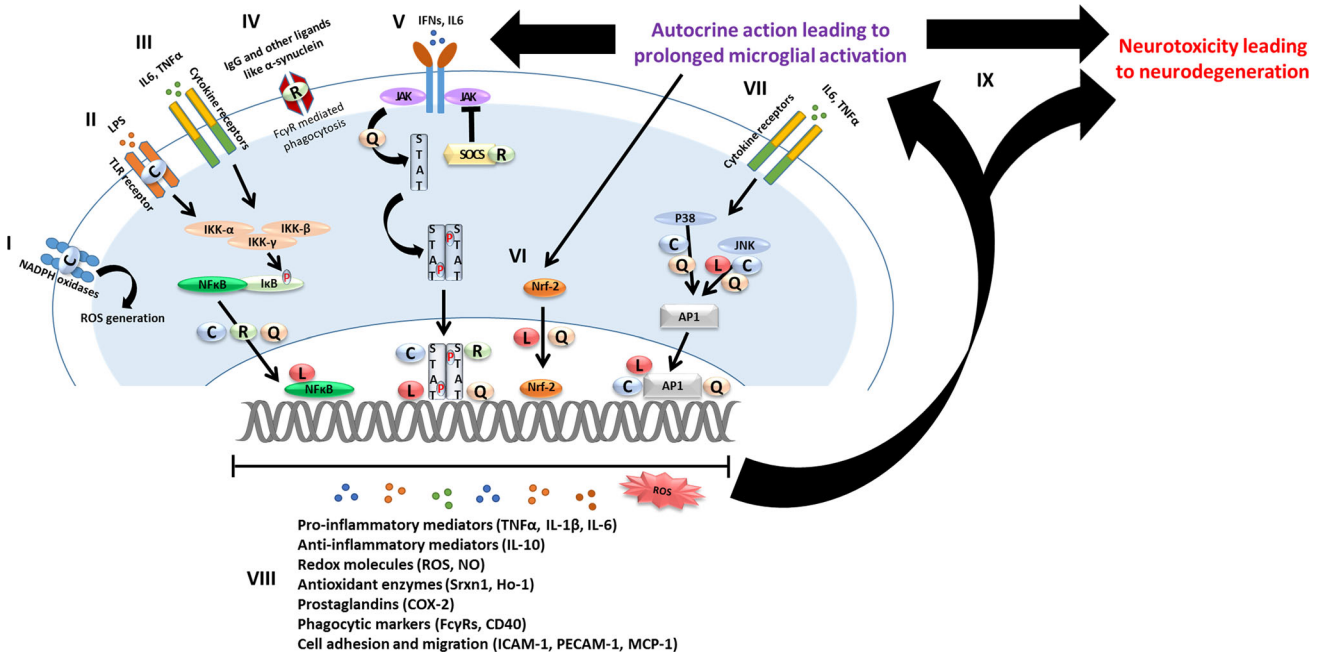

Fig. 3 Schematic represents the key signaling cascades that are involved in microglial activation. The four polyphenols Luteolin, Resveratrol, Quercetin and Curcumin are depicted as (L), (R), (Q) and (C), respectively. (I) NADPH oxidases are membrane-associated enzymes that induce ROS generation and this process is inhibited by (C). (II) The NFκB signaling pathway is activated by the action of LPS on the TLR receptors. (C), (R) and (Q) prevent phosphorylation of IκB which is a critical event in the nuclear translocation of NFκB and subsequent transcription of pro-inflammatory factors such as IL6 and TNFα. (III) IL6 and TNFα in turn activate the NFκB pathway further. (IV) Other crucial response of microglial activation is FcγR-mediated phagocytosis that is initiated by IgG and other ligands, which can be inhibited by (R). (V) Interferons and IL6 induce activation of the JAK-STAT signaling pathway, wherein (Q) inhibits the phosphorylation of STAT. Furthermore, STAT mediated transcription of inflammatory genes is dampened by (L), (R), (Q) and (C). (VI) Nrf-2 transcription factor is known to transactivate the antioxidant genes (Srxn1, Ho-1) containing antioxidant response elements (ARE) in their promoters. This pathway is activated by the action of (L) and (Q), providing an antioxidant defense mechanism to microglial cells. (VII) The MAP Kinases (MAPK) are ubiquitous signaling molecules that are activated by a number of extracellular cues, leading to downstream activation of the AP1 and NFκB transcription system. This signaling cascade is inhibited by the action of (C), (Q) and (L) which prevent phosphorylation of the MAP Kinases p38 and JNK. (VIII) Microglial activation results in production of a number of soluble factors including pro- and anti-inflammatory molecules and redox molecules that lead to (IX) an autocrine activation of microglia. This eventually results in chronic neuroinflammation and neurodegeneration that is a pathological feature of a number of CNS pathologies

kappa B (NFκB), Jun N-terminal Kinase (JNK), Activator-Protein 1 (AP1) and Signal Transducers and Activation of Transcription (STATs) mediated-signaling pathways. Luteolin blocks NFκB activation (Fig. 3 (II)) thereby inhibiting the transactivation and production of pro-inflammatory mediators such as IL-1β, TNF-α, COX-2, inducible nitrogen oxide synthase (iNOS) as well as NO production in LPS-stimulated microglia in vitro (L.-H. Zhu et al. 2011). Luteolin also inhibits JNK phosphorylation and subsequent binding of AP1 to the promoter of pro-inflammatory cytokine IL-6, thereby inhibiting the IL-6 induction in activated microglia (Fig. 3 (VII)) (Jang et al. 2008). Further, luteolin attenuates oxidative stress and promotes protein phosphatase activity causing the inactivation of upstream members of the Mitogen Activated Protein Kinase (MAPK) and NFκB pathways in activated microglia (Kao et al. 2011). It also induces an anti-inflammatory phenotype in activated microglia by repressing STAT1-mediated expression of CD40 (a receptor involved in microglia activation) (Fig. 3 (V)), and pro-inflammatory factors TNF-α and IL-6 (Rezai-Zadeh et al. 2008). A transcriptomic analysis showed that the effect of luteolin on microglia is not just limited to its inflammatory response as expression levels of genes involved in apoptosis, anti-oxidant metabolism, phagocytosis, ramification and chemotaxis are also critically regulated (Dirscherl et al. 2010). In this study, the antioxidant genes such as Sulfiredoxin-1 (Srxn1) and Heme oxygenase-1 (Ho-1), containing antioxidant response elements (ARE) in their promoters were upregulated. This indicates that luteolin treatment could trigger Nuclear factor (erythroid-derived 2)-like 2 (Nrf-2), a transcription factor, which in turn leads to transactivation of these antioxidant genes in microglia (Reichard et al. 2007; Soriano et al. 2008; Dirscherl et al. 2010) (Fig. 3 (VI)).

Quercetin

Quercetin (chemical name: 3,3′,4′,5,7-pentahydroxyflavone) (Fig. 2) is a flavonol, a type of flavonoid phenol commonly found in food sources such as onions, tomatoes, radish and caper leaves, and several other fruits, leaves and vegetables (Vidak et al. 2015). Like luteolin, quercetin is an antioxidant, anti-inflammatory and DNA repair compound (Guardia et al. 2001; Nichols and Katiyar 2010) which has potential in treatment of cancer (Murakami et al. 2008), neurodegenerative disorders (Youdim et al. 2004) and heart disease (Lee et al. 2011).

Therapeutic effects of quercetin in CNS diseases

The therapeutic effects of quercetin have been demonstrated in animal models of chronic stress. It has been shown that orally administered quercetin was able to cross the BBB and accumulate in regions of the brain such as the hippocampus and striatum to reduce ROS generated by chronic stress in rats (Ishisaka et al. 2011). Quercetin reversed behavioral and molecular alterations associated with olfactory bulbectomy-induced depression via inhibition of microglial activation (Rinwa and Kumar 2013). The ability of quercetin in improving behavioral traits has also been demonstrated in a Huntington's disease rat model wherein quercetin treatment attenuated microglial activation by targeting their proliferation. In addition, quercetin attenuated anxiety and motor coordination deficits in these animals (Chakraborty et al. 2014).

The neuroprotective effects of quercetin have been observed in animal models of neuropathologies such as stroke, Parkinson's disease (PD) and AD. In a rat models of ischemic and hemorrhagic stroke, quercetin treatment caused a significant reduction of infarct size, neuronal death, inflammation and oxidative stress resulting in improved motor skills (Ahmad et al. 2011; Zhang et al. 2015). Inflammation following stroke is known to be mediated primarily by activated microglia (Taylor and Sansing 2013), and in vitro studies have shown that quercetin inhibits the production of inflammatory cytokines by activated microglia (Chen et al. 2005). It is possible that quercetin exerts its anti-inflammatory effect through the suppression of nitric oxide production in activated microglia (Kao et al. 2010). Furthermore, quercetin reduced MPP + (a derivative of MPTP which causes death of dopaminergic neurons)-induced oxidative stress in microglia thereby rescuing neurons from cell death in a microglia-neuron co-culture model (Bournival et al. 2012). In animal models of AD, quercetin is found to improve hippocampal neurogenesis and restore long-term potentiation (LTP), which is important for memory formation and cognitive functions (Tchantchou et al. 2009; Ho et al. 2013; Sabogal-Guáqueta et al. 2015). Although the detrimental role of chronically activated microglia in aging-associated neurodegenerative disorders such as AD and PD is well documented, the effect of quercetin on microglial inflammatory response in animal models of AD and PD is yet to be clearly demonstrated.

Molecular targets of quercetin in Microglia

It has been shown that one of the targets of quercetin in counteracting progression of CNS disorders is activated microglia. Quercetin inhibits the expression of interleukin-12 (IL-12), a pro-inflammatory cytokine, by activated microglia (Schmitt et al. 1994; Muthian and Bright 2004). Further, quercetin also deters the LPS- and IFNγ-induced oxidative stress by inhibiting iNOS expression and secretion of NO in activated microglia. Quercetin dampens the oxidative stress by blocking the activation of an array of molecules which are critical for the microglial inflammatory response such as IκB kinase (IKK), NFκB, AP-1 STAT-1, janus kinase-1 (JAK-1), c-Jun N-terminal kinase, p38 and interferon regulatory factor-1 (IRF-1) (Fig. 3 (II) (III) (V) (VII)) (Chen et al. 2005; Kao et al. 2010). Quercetin also activates Ho-1, an enzyme that induces the expression of anti-inflammatory mediators, IL-10 and antagonist of IL-1 receptor (Chen et al. 2005; Piantadosi et al. 2011). Similar to the action of luteolin, quercetin treatment also led to an increase in the Nrf-2-mediated transactivation of Ho-1 expression in LPS-activated microglia in vitro (Sun et al. 2015) (Fig. 3 (VI)). Thus, it is clear that quercetin has a strong anti-inflammatory and antioxidative effect on activated microglia.

Resveratrol

Resveratrol (chemical name: 3, 4′, 5 trihydroxystilbene) (Fig. 2) is a naturally occurring phenolic compound present in the skin of grapes and berries such as blueberry, mulberry and raspberries, and several other plant species (Frémont 2000; Labinskyy et al. 2006; Jasiński et al. 2013). Resveratrol has been shown to extend life span in lower organisms like yeast and nematodes (Labinskyy et al. 2006). However, the anti-aging effect of resveratrol in humans is yet to be convincingly proven.

So far, studies have shown that resveratrol is capable of exerting antioxidant and anti-inflammatory properties when tested on various types of disease models. By inducing expression of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase in the brain (Mokni et al. 2007; Chun-Fu et al. 2013), resveratrol can reduce levels of ROS. It can also downregulate various inflammation associated genes like TNF-α and NFκB. Thus, it is not surprising that this compound has been widely studied

for its potential therapeutic role in pathologies perpetuated by inflammation and oxidative stress such as cancer, neurodegenerative and cardiovascular diseases (Chun-Fu et al. 2013).

Therapeutic effects of Resveratrol in CNS diseases

The therapeutic effects of resveratrol have been demonstrated in a mouse AD model, wherein resveratrol was found to reduce Aβ plaque formation, a molecular event that leads to synaptic loss and memory deficits (Karuppagounder et al. 2009). Further, orally administered resveratrol was capable of reducing microglial activation associated with the amyloid plaques in a mouse model of AD (Capiralla et al. 2012). The use of stilbene, a resveratrol analogue, significantly reduced the cognitive and behavioral deficits and improved the working memory in aged mice (Joseph et al. 2008). In addition, the therapeutic potential of resveratrol became evident in mouse model of autism spectrum disorder (ASD) since valproic acid-induced social impairments were mitigated by the prenatal administration of resveratrol (Bambini-Junior et al. 2014). In a PD rat model, treatment with resveratrol inhibited the inflammatory response as observed by reduced TNF-α and COX-2 levels in the substantia nigra (F. Jin et al. 2008). Rat pups treated with resveratrol intraperitoneally and subjected to contusion injury showed a significant decrease in hippocampal neuronal loss and reduced anxiety in these mice, suggesting the neuroprotective action of this compound (Sönmez et al. 2007). The daily oral intake of resveratrol protected the cerebrovasculature from damage during recurrent ischemic stroke in rats (Clark et al. 2012). The underlying effector in these neurodegenerative diseases and neurological disorders, as substantiated by multiple lines of evidence are, activation of microglia, which leads to the speculation that resveratrol-induced neuroprotection could be mediated via suppression of microglial activation at the molecular level.

Molecular targets of Resveratrol in Microglia

Resveratrol mediates an anti-inflammatory effect by preventing phosphorylation of the inhibitor of NFκB (IκB) molecule, an event that disrupts nuclear translocation of the NFκB complex (Fig. 3 (II)) and subsequent expression of pro-inflammatory factors like IL-6 and TNF-α (Capiralla et al. 2012). Resveratrol also inhibits microglia-mediated oxidative stress by reducing NO production by activated microglia (Lorenz et al. 2003; Park et al. 2012) and instead induces the expression of anti-inflammatory cytokines such as IL-10 through the JAK-STAT signaling pathway (Cianciulli et al. 2015). It has been further shown that resveratrol exerts anti-inflammatory effects in microglia by inhibiting their activation via upregulation of Suppressor of cytokine signaling-1 (SOCS-1), a signaling pathway which negatively regulates the immune response of microglia (Fig. 3 (V)) (Dragone et al. 2014). Apart from mitigating the release of toxic mediators, resveratrol also targets microglial phagocytosis (Fig. 3 (IV)) by suppressing the expression of rotenone (a pesticide causing PD) induced expression of Fcγ receptor (an immune cell receptor important for phagocytosis) (Chang et al. 2013).

Curcumin

Curcumin (Chemical name: diferuloylmethane) (Fig. 2) is a natural phenol derived from the rhizomes of *Curcuma longa* (turmeric), which has been in use as a condiment and as a medicinal herb for centuries in many Asian countries. The antibacterial properties of curcumin were first described more than 60 years ago (Schraufstätter and Bernt 1949) and since then, numerous in vitro and in vivo studies and clinical trials have been conducted to explore the wide-ranging therapeutic effects of curcumin in several human disorders. Some of the known properties of curcumin include anti-tumor, anti-inflammatory, antioxidant and hypoglycemic (Maheshwari et al. 2006; Gupta et al. 2011).

Therapeutic effects of curcumin in CNS diseases

Curcumin has been widely tested both in vivo and in vitro for the treatment of several brain disorders such as stroke, traumatic brain injury, glioma, ASD, AD and stress. In a rat model of cerebral ischemia, treatment with curcumin resulted in an improvement in neurological scores and reduction in infarct volume (Zhao et al. 2010). At the cellular level, curcumin treatment prevented neuronal apoptosis, oxidative stress and decreased pro-inflammatory mediators in the CNS (Dohare et al. 2008; Zhao et al. 2010; Liu et al. 2013). Similarly, in the rat model of traumatic brain injury, curcumin pre-treatment resulted in restoration of synaptic plasticity, reduction of brain lesion size and oxidative stress, and a significant improvement in cognitive and motor skills (Wu et al. 2006; Samini et al. 2013). Further, curcumin treatment was found to mitigate the NFκB-mediated microglial inflammatory response (H. Zhu et al. 2014). It was reported that curcumin is capable of crossing the BBB in glioma mouse models and inhibits glioma-induced angiogenesis, thereby deterring glioma progression (Perry et al. 2010a). In an experimental rat model of ASD, oral administration of curcumin restored the behavioral deficits such as social interaction, anxiety, depression, memory and learning through the reduction of oxidative stress, mitochondrial dysfunction and pro-inflammatory cytokines in the brain tissue (Bhandari and Kuhad 2015). An early report of the therapeutic effect of

curcumin in AD mouse models showed that curcumin scavenges ROS and inhibits the secretion of pro-inflammatory cytokines by activated microglia and astrocytes (Lim et al. 2001). More recently, curcumin was found to tag and disintegrate Aβ aggregates and cause a significant restoration of dendritic structures (Garcia-Alloza et al. 2007). Clinical trials on the therapeutic effects of curcumin in AD patients are currently ongoing and may provide insights into the protective role of dietary curcumin in mitigating age-related cognitive and memory decline induced by AD. Despite evidence from clinical trials that show the therapeutic efficacy of curcumin in different disorders such as its anti-neoplastic effects in cancer, curcumin has not been approved for therapeutic use in humans (Gupta et al. 2013). With the availability of nutraceutical formulations of curcumin, it is important to evaluate the risks and benefits of the drug before its therapeutic effects can be effectively utilized (Zou et al. 2015).

Molecular targets of curcumin in Microglia

In several studies, curcumin has been shown to target key molecular mechanisms that control microglial activation, leading to microglia-mediated neurotoxicity. Comparable to the action of luteolin, quercetin and resveratrol on molecular mechanisms that regulate microglia functions, curcumin also has myriads of actions on microglia. Curcumin treatment of LPS-stimulated microglia led to a reduction in the expression of iNOS and NO production. Further, it prevented microglia-mediated death of pre-oligodendrocytes by inhibiting the expression of iNOS and ROS generation in activated microglia (Fig. 3 (I) (II)) (He et al. 2010). Curcumin has been shown to downregulate the expression levels of COX-2 and pro-inflammatory cytokines, TNFα, IL-1β and IL6 in activated microglia by inhibiting the nuclear translocation of the NFκB p65 subunit (Fig. 3 (II)) (C.-y. Jin et al. 2007). In a similar study, curcumin was shown to inhibit the JNK and p38 MAPK pathways as well as the DNA binding ability of NFκB and AP1 (Fig. 3 (VII)) transcription factors which regulate the expression of pro-inflammatory mediators (Jung et al. 2006). Curcumin mitigated the microglial expression of ICAM-1, a cell adhesion molecule and monocyte chemoattractant protein-1 (MCP-1), a crucial molecule for microglial migration. These genes contain STAT binding elements in their promoters and curcumin was found to shut down the JAK-STAT pathway thereby, repressing the expression of these genes (Fig. 3 (V)) (H. Y. Kim et al. 2003). A recent transcriptomic analysis of LPS-activated microglial cells treated with curcumin revealed newer, unknown targets of curcumin. Apart from downregulating pro-inflammatory genes such as STAT-1, IL-6 and iNOS, curcumin was found to inhibit the expression of toll-like receptor-2 (TLR-2) (Fig. 3 (II)), a cell membrane receptor which acts as a pathogen sensor in microglia and CSF-1, a cytokine involved in microglial proliferation. Further, curcumin induced anti-inflammatory gene Interleukin 4 (IL-4), antioxidant gene Peroxisome proliferator-activated receptor a (PPARα), and genes known to be involved in cell adhesion and migration such as Netrin G1, Delta-like 1, Platelet endothelial cell adhesion molecule 1 (PECAM1) and Plasma cell endoplasmic reticulum protein 1 (Karlstetter et al. 2011).

Future direction and conclusions

This review summarizes the mechanism of action and the molecular targets of four plant phenols in mitigating microglia-mediated neuroinflammation in CNS pathologies. While the anti-inflammatory and antioxidant properties of these natural phenols have been well established, in vivo studies showing the ability of these compounds to specifically mitigate the neurotoxic effects of activated microglia without compromising the phagocytic ability of microglia which is essential in the inflammatory response to brain injury and insult are lacking. In addition, an important aspect in development of these polyphenols as "nutraceutical" formulations is to determine the bioavailability and physiological stability of these compounds in vivo (Dhawan et al. 2011; Amri et al. 2012; Cheng et al. 2013; Nazari et al. 2014). While dietary supplements of vitamins and nutrients have gained popularity as "nutraceutical" formulations, further studies are crucial in understanding if the regular consumption of plant-based polyphenols can delay or prevent the onset of neurological disorders, without eliciting undesirable side-effects. Directing the specificity of these compounds toward the deleterious functions of chronically activated microglia while reinforcing the critical neuroprotective functions of microglia is a challenging task. One possible way of achieving specificity and maximizing efficacy could be through the development of microglia-directed drug delivery systems (Sun et al. 2010) and combinatorial therapies (Kelso et al. 2011), i.e., use of these natural phenols with drugs specifically targeting different phenotypes of microglia. For this purpose, it is essential to catalogue molecular and epigenetic profiles that are specific to different phenotypes of microglia in health and CNS disorders.

Several studies have focused on the transcriptomic and epigenomic signatures of microglia to understand their functions in healthy brain and neuropathologies (Albright and González-Scarano 2004; Parakalan et al. 2012; Hickman et al. 2013). These studies not only unraveled the

molecular mechanisms of microglia-mediated neuroinflammation, but also revealed the diverse novel roles of microglia in health and disease. Series of these studies would eventually assist in devising microglia-targeted therapies to mitigate neuroinflammation that contributes to progression of CNS disorders. With transcriptomic signatures of microglia well established (Albright and González-Scarano 2004; Moran et al. 2004; Parakalan et al. 2012), screening and validation of changes in epigenetic machineries such as histone and chromatin modifications, DNA methylation, microRNAs and other non-coding RNAs (piRNA, circRNA, lncRNA) in microglial cells from in vivo and in vitro systems of CNS disease models are currently being catalogued to provide deeper insights into the microglial epigenome (Hickman et al. 2013; Satoh et al. 2014). Since epigenetic changes are reversible, undesirable neurotoxic effect of activated microglia could be reverted to a neuroprotective behavior through the alteration of microglial epigenome. Hence, future research aimed at discovering epigenetically active compounds would lead to development of "pharmacoepigenomic" drugs for the treatment of CNS diseases.

From the studies conducted thus far, it is clear that dietary phenols are potent anti-inflammatory and antioxidant compounds that can mitigate microglial activation in both animal models of CNS disease and in vitro systems. Figure 3 shows the molecular mechanisms targeted by dietary phenols in microglia. Recent studies have explored the potential of dietary phenols in epigenetically regulating cellular machinery. Luteolin was found to induce miRNA-132 expression in neurons, thereby regulating neurite outgrowth in vitro (Lin et al. 2012). Luteolin was also found to exert its anti-inflammatory effects in human monocytes through the inhibition of CREB-binding protein/p300, a histone acetyltransferase (HAT) known to function as an NFκB coactivator (H. J. Kim et al. 2014). Similarly curcumin is able to transrepress oncogenes and oncomiRNAs by exerting a strong inhibitory effect on histone acetylation in tumor cells (Teiten et al. 2013), thereby underscoring the importance of phenolic compounds in epigenetically regulating gene expression. Resveratrol causes epigenetic alteration of tumor cell proliferation by functioning as an inhibitor of class I, II and IV histone deacetylases (Venturelli et al. 2013). Other polyphenols (not discussed in this review) such as fisetin and myricetin were found to epigenetically alter gene expression by inhibiting DNA methylation at specific gene promoters (Busch et al. 2015). These studies may illustrate the ability of dietary phenols to alter the epigenetic status of microglia and hence future studies can focus on developing these dietary phenols as therapeutic drugs in the context of CNS health and disease.

Compliance with ethical standards

Conflict of interest The authors confirm that this article content has no conflict of interest.

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