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Targeting the TLR4 signaling pathway by polyphenol: A novel therapeutic strategy for neuroinflammation

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Highlights

► TLR4 has a crucial role in pathogen recognition and activation of innate immunity

► TLR4 may be implicated in the pathogenesis of neuroinflammation-related diseases

► Extensive evidences show the promising role of polyphenols on TLR4 signaling pathways

►TLR4 targeting by polyphenols may open therapeutic windows for mentioned diseases

Abstract

A wide array of cell signaling mediators and their interactions play vital roles in neuroinflammation associated with ischemia, brain trauma, developmental disorders and age-related neurodegeneration. Along with neurons, microglia and astrocytes are also affected by the inflammatory cascade by releasing pro-inflammatory cytokines, chemokines and reactive oxygen species. The release of pro-inflammatory mediators in response to neural dysfunction may be helpful, neutral or even deleterious to normal cellular survival. Moreover, the important role of NF-κB factors in the central nervous system (CNS) through toll-like receptor (TLR) activation has been well established. This review demonstrates recent findings regarding therapeutic aspects of polyphenolic compounds for the treatment of neuroinflammation, with the aim of regulating TLR4. Polyphenols including flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans, can target TLR4 signaling pathways in multiple ways. Toll interacting protein expression could be modulated by epigallocatechin-3-gallate. Resveratrol may also exert neuroprotective effects via the TLR4/NF-κB/STAT signaling cascade. Its role in activation of cascade via interfering with TLR4 oligomerization upon receptor stimulation has also been reported. Curcumin, another polyphenol, can suppress overexpression of inflammatory mediators via inhibiting the TLR4-MAPK/NF-κB pathway. It can also reduce neuronal apoptosis via a mechanism concerning the TLR4/MyD88/ NF-κB signaling pathway in microglia/macrophages. Despite a symphony of *in vivo* and *in vitro* studies, many molecular and pharmacological aspects of neuroinflammation remain unclear. It is proposed that natural compounds targeting TLR4 may serve as important pharmacophores for the development of potent drugs for the treatment of neurological disorders.

Key words: Central nervous system; Neuroinflammation; Toll-like receptor 4; NF-κB; Polyphenol.

1. Introduction

Inflammation is defined as an interaction between the immune system and injured tissues, for restoring homeostasis by complex signaling pathways (Medzhitov, 2008, Devi et al. 2015). A number of contributing factors such as infection, traumatic brain injury, drug abuse, autoimmunity or toxic

metabolites in the nervous tissue can induce neuroinflammation (Gendelman, 2002, Maqbool et al., 2015). If such conditions persist for a long duration, then it can lead to the development of several degenerative diseases, including multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) (Lucin and Wyss-Coray, 2009). The aim of the neuroinflammatory response is initially protective for omitting damaged tissue and supporting regeneration of damaged cells, thus finally limiting the occurrence of the disease ratio in the body. Neuroinflammation may also induce cellular dysfunction in the central nervous system (CNS), whilst at the same time, it presents as a protective factor for the removal of compact extracellular protein aggregates such as amyloid beta plaques in AD (Sha et al., 2014). Therefore, inflammation can act as a double-edged sword and has both protective and/or destructive roles.

Chronic injury and inflammation can impair brain repair pathways which normally attenuate damage to the neural network and synaptic transmission. This process may be partially toxic due to the migration of leukocytes across the blood brain barrier (BBB) (Gendelman, 2002). When infection or other neural injuries occur, the innate immune system including astrocytes and microglia are activated by toll like receptors (TLR).

In some cases, the term "neuroinflammation" is replaced with "microglial activation" owing to its key role in the absence of T cells to remove cell debris during CNS damage (Graeber et al., 2011). These cells have the same role of neutrophils and monocytes outside of the CNS, and can produce a wide variety of pro-inflammatory cytokines such as IL-β, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and chemokines in response to neural dysfunction (Donnelly and Popovich, 2008). Recent studies have shown various inconsistent observations; in some cases, inhibition of cytokines may exert neuroprotective roles in brain injury models, while on the other hand, other studies have shown that inhibition of cytokine signaling can enhance neural injury by limiting the efficiency of repair mechanisms (Hailer, 2008, McCoy and Tansey, 2008). These variables arise from different receptors and mediators which

have various interactions in inflammatory pathways and oxidative stress (Saeidnia and Abdollahi, 2013a,b).

Astrocytes and microglia also have potential to release reactive oxygen species (ROS). The main sources of ROS production in CNS are microglial cells and astrocytes (Sheng et al., 2013). Previous studies have shown that increased levels of ROS can induce neurodegeneration (Tabner et al., 2001). Therefore, potent anti-oxidant compounds may exert neuroprotective effects by lowering the levels of highly volatile ROS, and inducing anti-inflammatory cascades (Rahimifard et al., 2015). Furthermore, several animal models have shown that activation of microglial cells is a key step in the pathogenesis of neurodegenerative diseases, and is triggered by excessive activation of ion channels or hypersecretion of excitotoxic neurotransmitters, leading to a decline in ATP and essential growth factors in injured neurons (Hanisch and Kettenmann, 2007). Upon activation, different types of microglial cells have differing responses, including secretion of toxic factors to kill microbes, secretion of anti-inflammatory cytokines for attenuating stress, and increased clearance of apoptotic cells or abnormal molecules (Gendelman, 2002; Saeidnia and Abdollahi, 2013a,b).

2. Molecular aspects of neuroinflammation

An interesting aspect discussed in this part is, how neuroinflammation involves CNS diseases and neuronal disorders. Different cells and mediators play major roles in the neuroinflammatory process and complex events at various steps. At first, pathogens that attack or injure neural tissue cause activation in molecular pathways resulting in the release of ATP, heat-shock protein, amyloid-β, oxidized lipids, histones and box-1 proteins. Then TLRs become active, and recruit microglial cells, which contain 10 percent of the brain cells, and starts different cascades. Also, in this process astrocyte activation inhibits penetration of T-cells into CNS by inducing apoptosis (Jacobs and Tavitian, 2012).

Different mediators regulate inflammation, including nuclear factor-kappa B (NF-κB) proteins, TNF-α, TNF-β, ILs, adhesion molecules and proinflammatory enzymes such as 5-lipoxygenase (5-LOX), 12-LOX and cyclooxygenase 2 (COX-2) (Aggarwal, 2004, Thomson, 2011). Among these factors, the NF-κB family has the key role in the regulation of inflammation by mediating synthesis of above proteins and activating genes which regulate inflammatory responses (Lin and Karin, 2007, Gupta et al., 2010). Previous studies have shown that the NF-κB is the critical signal transformer which regulates endocytosis, cellular permeability, and intracellular interactions (Stone et al., 2011). Previous studies on neurodegenerative diseases have highlighted the critical roles of NF-κB in both neurons and microglia (Kaltschmidt et al., 2005). If the NF-κB pathway is activated in microglia, it will regulate the inflammatory pathway by stimulating the secretion of ROS and proinflammatory cytokines including TNF-α, IL-1 and interferon-γ, and thus play secondary neurotoxicity effects (Block et al., 2007). In one study, Yakovleva et al. showed that exposing mice to acute alcohol can induce neuroinflammation by activating NF-κB (Yakovleva et al., 2011). Another study by El-Hage et al showed that exposure to HIV and other viral infections may activate NF-κB, and induce neuro-acquired immune deficiency syndrome (neuroAIDS) (El-Hage et al., 2008). As well, bacterial infections due to their lipopolysaccharide (LPS) content, can regulate the transport of TNF-α, express cytokine receptors, activate COX-2 protein and prostaglandin E2 (PGE-2), and finally induce cerebral inflammation (Pan et al., 2010).

Further studies have shown that cyclic adenosine monophosphate (cAMP) mediates the function of NF-κB transcription factors as a result of increasing level of IkB (Kamthong And Wu, 2001) or blocking IKK activity via cAMP/PKA (Minguet et al., 2005). It can be activated by cytokines, oxidative stress, pathogen associated molecular patterns (PAMP), glucose, amyloidogenic peptides and increased levels of NF-κB (Gerlo et al., 2011). In this scenario, cyclic guanosine monophosphate (cGMP) plays a vital role in the CNS by mediating the action of nitric oxide (NO) and regulating NF-κB expression. NO in micromolar concentration exhibits proinflammatory and cytotoxic effects, and in nano molar concentrations, exerts anti-inflammatory properties (Rizzo et al., 2010). The NO/cGMP/PKG cascade

inhibits pro-apoptotic pathways and increases viability of neural cells in response to brain inflammation, ischemia or brain trauma (Fiscus, 2002). All of the above studies indicate the importance of NF-κB factors which can activate the TLR family in the CNS.

3. TLR4 signaling pathways

TLRs can be activated by various types of stimuli. These could be categorized as pathogens, different cytokines or even stress that is induced in the cells (Medzhitov et al., 1997, Akira et al., 2006, Koedel et al., 2007). These stressors can be mainly induced by a disease, engaging neural cells. As reported previously, the first and most important factor that can increase the expression of TLRs is pathogens. Pathogens are either extracellular or molecules that are released from damaged cells. These outcomes are followed by tissue injury. It is important to mention that a well-known extracellular pathogen that can induce the activation of TLRs are LPS from a group of gram negative bacteria (Takeuchi and Akira, 2001) called Enterobacteriaceae (i.e., *Escherichia coli*) (Gárate et al., 2013), as well as fungal and viral products (Schaefer et al., 2004). The main pathway activated by lipopolysaccharide (LPS) is the myeloid differentiation primary response protein 88 (MyD88) dependent and independent pathways. The common step to both pathways is the recognition of the lipid A-region of LPS by TLR4. LPS binds to LPS binding protein (LBP) and the resulting complex attaches to another protein known as cluster of differentiation 14 (CD14) (Poltorak et al., 1998). The latter protein serves as a membrane-bound protein in innate immune cells or circulates in plasma in a soluble form. It has been shown that the main role of CD14 is to enhance TLR4 signaling by facilitating its transport to lipid rafts in the cellular membrane. Afterwards, the co-receptor myeloid differentiation factor-2 (MD-2) is recruited to promote the translocation of TLR4 to the cell membrane (Shimazu et al., 1999). This essential process is followed by endocytosis of the TLR4/MD2 complex. The recognition of the heterotrimer CD14/TLR4/MD-2 to LPS induces the activation of the MyD88-dependent and the MyD88-independent pathways. A general schema of the TLR4 pathway is shown in Figure 1.

3.1. MyD88-dependent pathway

The first and most important pathway is the MyD88 dependent. Studies have shown that MyD88 knockout mice are not responsive to TLR ligands (Kawai et al., 1999). In this mechanism, after stimulation, TLR4 binds to MyD88 at the toll-interleukin1 (IL-1) receptor TIR cytoplasmic domain (Laird et al., 2009) leading to the recruitment of the IL-1 receptor-associated kinase IRAK4 (Takeda and Akira, 2004). Activated IRAK4 dissociates from MyD88, binds to and activates the TNF receptor associated factor 6 (TRAF6), leading to the formation of Complex-1. This triple association then dissociated from TLR4 and stimulates the recruitment of several proteins, including TGFα related kinase (TAK-1), and TAK1 binding protein (TAB) 1-3, forming core components of Complex-2. These processes lead to the activation of two sub pathways: (1) Phosphorylation of TAK-1 induces the activation of IκB kinases complex (IKK) which in turn phosphorylates inhibitor of kappa B (IκB) protein. This leads to their proteosomal-mediated degradation, and stimulates the translocation of NF-κB to the nucleus (Delaney and Mlodzik, 2006). NF-κB will subsequently activate pro inflammatory mediators, which are highly effective in activating inducible nitric oxide synthase (iNOS), inducible COX-2, and stimulate the release of major inflammatory cytokines, such as IL-1β, IL-6, and TNF-α (Saha and Pahan, 2006). (2) Alternatively, TRAF6 activates Mitogen-activated protein kinases (MAPKs) ERK1/2, p38, and JNK via phosphorylation, which in turn modulate the activation of several transcription factors, including activator protein-1 (AP-1) (Takeda and Akira, 2004).

3.2. *MyD88-independent pathways*

On the other hand, another study has shown that in MyD88 knockout mice, following stimulation of TLRs, JNK and NF-κB are produced. This leads to the hypothesis that there are other MyD88-independent pathways may also be present (Kawai et al., 2001). After TLR4 stimulation by its ligand, TLR recruits TIR-domain-containing adaptor-inducing interferon-β (TRIF) and translocating chain-associated membrane protein (TRAM). The dimerisation of these two proteins activates the TRAF6-TAK1-IKK pathway described above. This interaction destructs IkappaBs and activates NF-κB (Okun et

al., 2009). Alternatively, TBK1 kinase phosphorylates interferon regulatory factor 3 (IRF3), and this phosphorylation makes it active. Activated IRF3 can be translocated to the nucleus where it acts as a transcription factor. Interferon 1β (IFN-1β) binds to activated IRF3, and activates the transcription factor, Signal transducer and activator of transcription (STAT). Overactivation of TLR4 is regulated by several endogenous inhibitors, including the ubiquitin ligase TRIAD3A, which enhances the ubiquitination and hence degradation of TLR4 (Chuang and Ulevitch, 2004). As well, RP105, a homologue of the TLR4 protein can antagonize TLR4 signaling on the cell membrane (Divanovic et al., 2005). Recently, acetylation of lysine residues has been shown to alter the post-translational modification of TLR4 signaling (Hu et al., 2013).

3.3. Expression of TLR4 in healthy and disease state

As previously mentioned, inflammation can be destructive in several levels and also plays a crucial role in the immune system of the body. The main role of TLRs during neuroinflammation is the regulation of pathways which activate glial cells, several different enzymes and cytokines during the inflammatory process. One study showed that mice with TLR deficiency demonstrated lower levels of cellular damage following exposure to stress (Gárate et al., 2013). AD and depression represent two well-known examples of neurological disorders where neuroinflammation is prevalent in the pathobiology of disease (Giovannini et al., 2003, Hunot and Hirsch, 2003). In these diseases, stress induced within cells activates factor kB and increases the expression of pro inflammatory enzymes such as COX-2 and NO synthase. These two enzymes can play an important role in brain prefrontal cortex and regulate gut barrier, function and permeability. A study, which reported the protective effects of antibiotics in patients with depression, attests to these claims (Gárate et al., 2011). Another study has shown that the secretion of anti-inflammatory and pro inflammatory cytokines increases in age-related diseases, so it can be said that TLRs play an important role in many age-related diseases associated with alterations in pro-inflammatory or anti-inflammatory cytokines (Okun et al., 2009).

It is thought that TLRs are expressed on various immune-related cells, including microglia, astrocytes, oligodendrocytes, neurons and cerebral vascular endothelium. On the other hand, any stimuli of tissue injury can induce activation of immune-related cells and activate TLRs. This activation plays a pivotal role in the inflammatory response. For instance, in chronic fatigue syndrome, AD or depressive disorders, selected neural tissues are vulnerable to stress, leading to activation of TLRs and inflammation in these disease states (Maes et al., 2007). Stress related factors can make a fundamental increment in the expression of TLRs. These increments are associated with the inflammatory component of disease (Mass et al., 2008, Leonard and Maes, 2012). Another neural disease which is related to TLRs activation is ALS. A study has elaborated that TLR4 protein expression is up regulated by up to 3 fold during the last stage of disease in a transgenic rodent model compared to WT (Wild type) mice. This is suggestive of the crucial role of TLRs in the pathophysiology of ALS (Lee et al., 2015).

Activated TLRs can also regulate brain responses (Caso et al., 2008, Gárate et al., 2011). Studies have shown that these pathways are regulated by TLRs in the brain prefrontal cortex of rodents which are vulnerable to stress (Madrigal et al., 2001, García-Bueno et al., 2008, Gárate et al., 2013). Significant expression levels of TLR4s have been reported in regions of the CNS where there is an absence of the blood brain barrier (BBB), circumventricular organs, plexus choroideus, and leptomeninges. It is likely that TLR4 may serve as an important immunosurveilance in these regions. Moreover, TLR4 appears to be involved in neuronal/astrocytic signalling, which leads to activation of brain endothelial cells, and stimulates the neutrophil transmigration in the presence of LPS *in vitro*.

Additionally, one study showed that mutations in the TLR4 gene can cause noticeable reduction in microglial function leading to a lower release of inflammatory products (Walter et al., 2007). TLR4 also plays a key role in brain damage. If TLR4 are antagonised, microtubule-associated protein kinase and NF-κB pathways remain inactive, and the inflammatory mediators will not be produced and secreted by astrocytes (Alfonso-Loeches et al., 2010). TLR4 is also activated in other inflammatory diseases such as

intestinal ischemia in response to over-activation of the immune system and increasing levels of TNF-α (Mozaffari and Abdollahi, 2013).

4. TLR4 Signaling and Polyphenols

Brain response to infection, trauma and ischemia share many similarities. These, along with some other circumstances within the CNS are synchronized with immune response prominently via activation of microglia, resembling the action of macrophage cells in the nervous system. TLR4 is one of the vital contributors to microglial activation. This pathogen linked molecular receptor is recognized to potentiate an inflammatory cascade pathway in reaction to different CNS stimuli (Buchanan et al., 2010).

Polyphenols comprise extensive diversity of molecules that share a similar basic polyphenolic structure (*e.g*numerous hydroxyl groups of aromatic rings) as well as molecules with a single phenol ring, including phenolic acids and phenolic alcohols. The classification of polyphenols is based either on the number of phenol rings or the type of the structural elements that join rings to one another. Some of the chief groups are: flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans (Archivio et al., 2007). Active ingredients in plants, including polyphenols, have numerous therapeutic effects due to their potent anti-oxidant, and anti-inflammatory features (Hasani-Ranjbar et al., 2008, Hasani-Ranjbar et al., 2010; Khan et al., 2016; Saeidnia and Abdollahi, 2013a,b).

The protective effect of polyphenols against inflammation by targeting the TLR4 signaling pathway has been investigated in several models. One study examined the effects of tea polyphenols on the secretion and expression of TLR4 in human periodontal ligament cells stimulated by LPS (Ning-jing et al., 2015). The study showed the tea polyphenols significantly attenuated the increase in secretion and expression of TLR4 at both the mRNA and protein level up to 72 hours following exposure to pathophysiological concentrations of LPS. Similarly, a recent study showed that green tea extract can restore neutrophil effector/inflammatory function in obesity induced by cafeteria diet (Albuquerque et al., 2016). The study

reported a decrease in chemotaxis, release of hydrogen peroxide and hypochlorous acid, and reduced myeloperoxidase activity. Improved immunomodulatory effects were reported with treatment of green tea extract, including restoration of normal hydrogen peroxide and hypochlorous acid production, and reduction in the mRNA expression of TLR4 and IκK, and the production and release of inflammatory cytokines. Taken together, these studies suggest that tea polyphenols can reduce inflammation via modulation of the TLR4 signaling pathway. Another study showed that tea polyphenols can protect against renal ischemia/reperfusion injury in a rat model by inhibiting the activation of the TLR4/NF-κB p65 signaling pathway (Li et al., 2014). In this study, treatment with a mixture of tea polyphenols (100, 200 and 300 mg/kg body weight) once daily for 10 days prior to induction of ischemia, significantly suppressed free radical generation, and reduced the levels of urea nitrogen and serum creatinine Moreover, tea polyphenol pretreatment significantly decreased TLR4 and NF-κB p65 protein expression levels and attenuated the increased level of serum IL-1β, IL-6, ICAM-1 and TNF-α, enhanced IL-10 production, and reduced renal epithelial tubular cell apoptosis induced by renal ischemia/reperfusion injury rats. Pretreatment with tea polyphenols may represent a potential and effective therapeutic strategy for the prevention of ischemic/reperfusion injury via suppression extrinsic apoptotic signal pathway as a consequence of the activation of the TLR4/NF-κB p65 signal pathway.

An important polyphenol, epigallocatechin-3-gallate (EGCG), is a vital constituent of green tea (Tabatabaei-Malazy et al., 2015, de Oliveira et al., 2016), with potent anti-oxidant and anti-inflammatory properties (Hasani-Ranjbar et al., 2013). It has been previously reported that this EGCG causes downregulation of the inflammatory response in macrophages, but the exact mechanism remains unclear. Recent findings suggest that the 67-kDa laminin receptor (67LR) works as a cell surface EGCG receptor and mediates the anticancer effects of EGCG at a particular concentration (0.1-1mM) (Byun et al., 2010). Moreover, Byun et al. (2012) further showed that EGCG-treated dendritic cells inhibited lipopolysaccharide (LPS)-induced production of TNF-α, IL-1β, and IL-6, and activation of MAPK, ERK1/2, p38, JNK, and NF-κB, and p65 translocation through 67LR (Byun et al., 2012). The study

demonstrated that 67LR plays a vital role in mediating the anti-inflammatory action of a physiologically relevant EGCG, by upregulating the expression of Toll interacting protein (Tollip) expression, a negative regulator of TLR4 signaling through 67LR.

EGCG can inhibit the activity of IKK an important kinase in NF-κB activation (Youn et al., 2006a). EGCG also inhibits IRF3 that is promoted by LPS, and also the overexpression of TRIF, by stopping kinase activity of TBK1. Though, EGCG does not inhibit activation of IRF3 resulted from overexpression of constitutively active IRF3. Thus TBK1 seems the key molecular target of EGCG in the TRIF-dependent signaling pathways of TLR4. In addition, we can come to the idea that EGCG applies its anti-inflammatory effects via modulation of both the MyD88- and TRIF dependent signaling pathways of TLR4. EGCG can also inhibit anti-β2-glycoprotein I (β2GPI)/β2GPI-induced tissue factor (TF) and TLR4/TNF-α protein expression reported in human acute monocytic leukemia cells. This suggests that inhibition of the intracellular signal transduction pathway of TLRs-MAPKs-NF-κB axis may represent an important therapeutic target for the treatment and prevention of antiphospholipid syndrome (APS) (Wang et al., 2014).

In addition, resveratrol (trans-3,5,4-trihydroxystilbene), a polyphenol found in red grapes and in several other plant sources, has demonstrated chemopreventative effects and potent anti-inflammatory properties. The therapeutic effects of resveratrol have been shown in several diseases such as inflammatory bowel disease by down-regulation of enzymes and cytokines which play role in inflammatory signaling pathways (Farzaei et al., 2015). Capiralla et al. showed that resveratrol exhibited potent anti-inflammatory effects through a mechanism involving the TLR4/NF-κB/signal transducer pathway and activation of transcription (STAT) cascade *in vitro*. It was also reported that resveratrol played a role in the activation cascade and receptors are regulated by interaction with TLR4 oligomerization. Resveratrol has also been shown to reduce tumor growth and survival in TLR4 competent C3H/HeN mice compared to TLR4 deficient mice, when both are exposed to a DMBA-induced skin carcinogenesis protocol (Yusuf et al.,

2009). Resveratrol treatment also inhibited angiogenesis more significantly in TLR4 competent mice, compared to TLR4 deficient mice. TLR4 competent mice also exhibited greater levels of IL-2 and IFN-γ compared to TLR4 deficient mice, and TLR4 competent C3H/HeN mice exhibited a greater propensity to induce cell-mediated immune response following exposure to pathological concentrations of DMBA. These results suggest that TLR4 is the main mediator of resveratrol induced chemoprevention in DMBA skin tumorigenesis.

As well, another study showed that resveratrol can prevent the initiation of murine RAW 264.7 macrophages and cells of microglial BV-2 targeted with a TLR4 ligand and LPS (Capiralla et al., 2012). Resveratrol has also been to reduce the levels of IL-6, NO, and TNF-α in RAW264.7 cells exposed to pathophysiological concentrations of LPS (Yang et al., 2014). mRNA and protein expression levels of high mobility group box 1 (HMGB1) (mRNA and protein) and TLR4 were also significantly lowered in cells treated with LPS and resveratrol compared to cells treated with LPS alone, in that study. Similarly, resveratrol treatment (5-20μM) attenuated the increase in TLR4 expression, inhibited NF-κB activation, and reduced the levels of TNF-α and IL-1β in cardiomyocytes exposed to anoxia/reoxygenation injury (Zhang et al., 2012; Azimi et al., 2015). Treatment with resveratrol after the onset of reoxygenation also improved cell survival and suppressed the immune response to anoxia/reoxygenation injury. This provides further evidence for the involvement of the TLR4/NF-κB signaling pathway in resveratrol-mediated protection. This suggests that resveratrol may mediate anti-inflammatory effects by modulating TLR4 expression in the HMGB1-TLR4 signaling pathway.

Recently, one study demonstrated that the protective effects of resveratrol against LPS induced acute lung injury may be due to inhibition of the MyD88 gene (Zhang et al., 2014). The study showed that resveratrol can suppress the edema, inflammatory cell infiltration and alveolar structure damage of lungs in mice, and reduce the lung wet to dry ratio following LPS-mediated acute lung injury. These effects occurred parallel to a significant decrease in the levels of the pro-inflammatory cytokines, IL-6,

and the expression of TLR4, myd88, andNF-κB. Therefore, it is likely that resveratrol mediated protective effects against LPS, may be at least in part, mediated by inhibition of the MyD88-dependent TLR4 signaling pathway.

Curcumin (Cur), another important polyphenolic compound extracted from the rhizome *Curcuma longa*, exerts potent antiviral, antioxidant, anti-diabetic and anti-inflammatory properties (Tabatabaei-Malazy et al., 2013, Nabavi et al., 2014, Nabavi et al., 2015, Tabatabaei-Malazy et al., 2015). In an *in vitro* study, it was shown that Cur suppresses the overexpression of inflammatory mediators via inhibiting the TLR4-MAPK/NF-κB pathway. Cur was also able to partly block of NADPH-linked intracellular ROS production (Meng et al., 2013). Another *in vitro* study showed that cur can suppress the activation of NF-kB induced by various pro-inflammatory stimuli by inhibiting IKKβ kinase activity in the MyD88-dependent pathway in 293T cells (Youn et al., 2006b). Cur also inhibits LPS-induced IRF3 activation, probably through interacting with both MyD88- and TRIF-dependent pathways. However, Cur did not inhibit IRF3 activation induced by overexpression of TRIF in 293T cells that proposes the key role of TLR4 receptor complex as well as IKKβ. Therefore, inflammatory consequences post activation of TLRs may be diminished by the use of polyphenols.

Cur pretreatment significantly reduced the expression levels of TLR2, TLR4 and TLR9 mRNA or protein in liver tissues in a mouse model. This suggests that Cur pretreatment can mediate protection against T cell-mediated hepatitis in mice (Han et al., 2012). In pericontusional tissue, the protein expression of TLR4 was maximal 24 hours after traumatic brain injury (TBI). TLR4 targeted mice showed attenuated functional impairment, brain edema and cytokine release post-TBI compared to WT mice. In another study, 100 mg/kg of Cur administration after TBI caused significant reduction in the number of TLR4-positive microglia/macrophages and release of inflammatory mediators with neuronal apoptosis of the WT mice. Taken together, these studies suggest that Cur administration after injury can improve patient outcomes and reduce morbidity and mortality by decreasing the acute activation of

microglia/macrophages and neuronal apoptosis *via* a mechanism concerning the TLR4/MyD88/ NF-κB signaling pathway in microglia/macrophages in TBI (Zhu et al., 2014).

Chlorogenic acid (CGA) is another type of polyphenol that has demonstrated potent anti-inflammatory, antioxidant activities (Nabavi et al., 2016). CGA has been shown to mediate several anti-inflammatory effects, although the specific underlying mechanism remains unclear. One study recently showed that CGA could attenuate the mRNA and protein expression levels of proinflammatory and profibrotic mediators, and reduced the levels of serum proinflammatory cytokines, such as TNF-α, IL-6 and IL-1β in male Sprague-Dawley rats, whereby liver inflammation and fibrosis was induced by carbon tetrachloride (CCl_4) (Shi et al., 2013). CGA treatment also suppressed CCl_4 induced NF-κB activation, and reduced the expression levels of TLR4, MyD88, iNOS and COX-2 in rats exposed to CCl_4. This suggests that CGA can ameliorate CCl_4-induced liver fibrosis in rats via inhibition of TLR4/MyD88/NF-κB signaling pathway.

5. Targeting TLR4 by polyphenols: a new therapeutic strategy for neuroinflammation

TLR are among important key elements in the innate immune response. Recent studies have highlighted their role in brain injury as well as neurodegeneration. Neuroinflammation is a key factor that can lead towards the development of neurodegenerative diseases. In fact, several inflammatory markers, such as chemokines, cytokines or proteins in acute phase are upregulated and lead to inflammation. Such inflammatory markers are also elevated in several neurodegenerative diseases including AD (Harold et al., 2009, Galimberti and Scarpini, 2010, Naj et al., 2011). Additionally, it has been reported that ethanol triggered neuroinflammation is mainly controlled by TLR4 signaling pathways. It was reported in a previous study that quercetin (another polyphenol) loaded into nanoparticles improved absorbance across blood brain barrier, and prevented AD progression and neuroinflammation through TLR4 linked mechanisms (Testa et al., 2014). It is likely that targeting TLR4 may represent an important therapeutic strategy in neuroinflammatory disorders (Alfonso-Loeches et al., 2010).

In a study conducted using a rat model for treating neuropathic pain also showed a positive relation between polyphenols and neurological problems *via* TLR4 cascade. In this study it was reported that EGCG was the best therapeutic strategy for alleviating neuropathic pain *via* TLR4 inhibition and further research is required regarding its clinical aspects as novel drug approach (Kuang et al., 2012). EGCG is one of the most potent polyphenolic flavonoid present in the green tea with special neuroprotective effects, but no clear understanding of the role of EGCG is available in adult neurogenesis after neuroinflammation. LPS-induced neuroinflammation caused inhibition of adult neurogenesis via destroying the differentiation and proliferation of neural stem cells, which was actually designated by the reduction in Bromodeoxyuridine (BrdU)-, Doublecortin (DCX)- as well as Neuronal Nuclei (NeuN)-positive cells. In addition to that, microglial cells were employed for stimulating TLR4-NF-κB signaling pathway in the hippocampus of adult mice following LPS injection. EGCG showed overall beneficial effects regarding impaired adult neurogenesis induced by LPS and neuroinflammation (Seong et al., 2016).

As previously mentioned, resveratrol a natural polyphenol with anti-inflammatory effects in clinical trials for AD, caused prohibition of murine RAW 264.7 macrophages and microglial BV-2 cells targeted by the TLR4 ligand, LPS. In addition, resveratrol-mediated inhibition of the downstream phosphorylation of the STAT1 and STAT3 upon LPS stimulus (Capiralla et al., 2012).

Cur, another food component in our diet has been used as a cooking ingredient for centuries. It has been demonstrated that Cur can cross the BBB and thus maintain increased biological activity (Yang et al., 2005). Recently, Cur has been shown to attenuate the homodimerization of TLR4, which is obligatory for triggering the downstream cascade pathways (Zhao et al., 2011). Likewise the supposition that Cur can reduce inflammatory damage through the TLR4 pathway has since been confirmed in experimental models of brain injury (Meng et al., 2013, Zeng et al., 2013; Farahani et al., 2015).

6. Future studies and conclusion

Neuroinflammation is a pathological condition that is associated with various inflammatory cascade pathways, toxic agents (Saeidnia and Abdollahi, 2013a), hormonal imbalance and autoimmune disturbances that are sometimes complicated because of observing controversial effects of antioxidants in such disorders (Saeidnia and Abdollahi, 2013b). Various contributing factors include the production and release of pro-inflammatory cytokines, chemokines and ROS, which cause neural dysfunction leading to cell death via energy restriction. Previous studies have elaborated on the significance of NF-κB in CNS, which can be regulated through TLRs. Recent findings to treat neuroinflammation via polyphenolic compounds are promising. Polyphenolic compounds have been shown to attenuate neuroinflammation via a variety of inter-related mechanisms, and provides a safe, non-invasive means to reduce morbidity and mortality due to acute and chronic inflammation. It is likely that modulation of TLR4 by polyphenols is the main target of polyphenols in an inflammatory setting.

While there is growing evidence for the involvement of TLR4 in the pathophysiology of neuropsychiatric diseases, the origin of TLR4 activation remains to be elucidated. For instance, two main mechanisms have been proposed to account for TLR4 activation: (1) translocation of gram-negative enterobacteria due to "leaky gut", and/or (2) prenatal infection induced maternal activation and subsequent production and release of high volatile ROS. As well, while the role of cytokines in the pathogenesis of neurological disorders is well documented, TLR4 dependent and independent cytokine effects, and the role of polyphenols, have not been investigated in these diseases.

At present, recent studies have shown that the anti-inflammatory effects of several naturally occurring polyphenolic compounds may be due to inhibition of the TLR4 pathway. Tea extracts, and other polyphenolic compounds such as resveratrol and CGA have been shown to reduce the mRNA expression of TLR4 and IκK, and/or enhance activation of the TLR4/NF-κB p65 signal pathway, which are a

MyD88-dependent process. Other polyphenols, such as EGCG have been shown to also upregulate the expression of Toll interacting protein (Tollip) expression, a negative regulator of TLR4 signaling through 67LR. Alternatively, EGCG and Cur have also been shown to induce anti-inflammatory effects through modulation of both the MyD88- and TRIF dependent signaling pathways of TLR4. However, our current findings on the involvement of TLR4 in neurodegenerative diseases remain descriptive, and are limited to a number of studies. Given the complex multi-faceted clinical phases of several neurodegenerative diseases, TLR4 may represent a compensatory or decisive pathway against cellular dysfunction. Therefore, the therapeutic potential for inhibition of TLR4 by polyphenols may represent a double–edged sword: while the innate immune response is fundamental to the pathobiology of several CNS conditions, activation of TLR4 may be protective. For example, TL4 appears to exhibit a neuroprotective role by regulating the phagocytic removal of amyloid beta plaques by microglial cells (Tahara, Kim et al. 2006), although TLR4 cytotoxicity to brain cells has also been reported (Trotta, Porro et al. 2014). Therefore, further research is necessary prior to translating preclinical findings to the clinic setting.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Figures Legends

Figure 1. TLR4 signaling pathway involved in TLR4 activation, and the signal transduction molecules targeted by polyphenols. Following binding of the ligand, LPS and subsequent homo- or heterodimerisation of the TLR4 receptor, MyD88 or TRIF are recruited by TIRAP and TRAM. This in turn leads to (A) MyD88 dependent processes. MyD88 associates with IRAKs/TRAF6 complex (Complex I) and TAK1/TABs complex (Complex II), leading to the activation of IKK. Activation of IKK phosphorylates IκBα which stimulates the nuclear translocation of NFκB where it stimulates the aactivation of proinflammatory cytokines and free radical production. TAK1 is also associated with the MAPK pathway and stimulates the activation of p38, JNK and ERK1/2. This leads to nuclear translocation of AP-1 and transcription of proinflammatory cytokines leading to cell death. (B) MyD88 independent process. After TLR4 stimulation by its ligand, TLR recruits TIR-domain-containing adaptor-inducing interferon-β (TRIF) and translocating chain-associated membrane protein (TRAM). The dimerisation of these two proteins activates the TRAF6-TAK1-IKK pathway described above. This interaction destructs IkappaBs and activates NF-κB. Alternatively, TBK1 kinase phosphorylates interferon regulatory factor 3 (IRF3), and this phosphorylation makes it active. The interaction between TRIF and TRAF3 induces the nuclear translocation of IRF3 and IRF7 and transcription of interferons which can activate STATs. Red arrow indicates activation of the pathway. Black arrow indicates inhibition of the TLR4 pathway by selected natural product.

Figure 1.