Alzheimer’s disease: natural products as inhibitors of neuroinflammation

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Abstract
Alzheimer’s disease (AD) is the most common form of dementia and affects 44 million people worldwide. New emerging evidence from pre-clinical and clinical investigations shows that neuroinflammation is a major pathological component of AD suggesting that anti-inflammatory strategies are important in delaying the onset or slowing the progression of the disease. However, efforts to employ current anti-inflammatory agents in AD clinical trials have produced limited success. Consequently, there is a need to explore anti-inflammatory natural products, which target neuroinflammatory pathways relevant to AD pathogenesis. This review summarises important druggable molecular targets of neuroinflammation and presents classes of anti-neuroinflammatory natural products with potentials for preventing and reducing symptoms of AD.

Keywords  Alkaloids · Marine natural products · Polyphenols · NF-κB · Terpenes

Introduction
Alzheimer’s disease (AD) is the most common form of dementia. AD has been reported to affect about 44 million people globally, and is estimated to triple by 2050 due to general population ageing (Prince et al. 2014). The main pathological features of AD include extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (Bloom 2014). Studies have established that there is a strong correlation between symptoms of AD and the accumulation of these plaques and tangles due to their ability to induce neurodegeneration that mediates loss of memory and cognition.

Interestingly, new emerging evidence continues to demonstrate that neuroinflammation is also a major pathological component of AD (Webers et al. 2020). Several reports of animal experiments and clinical studies have provided strong links between neuroinflammation and AD pathogenesis. Increasing evidence from several studies revealed that inflammatory responses in the brain are a major contributor to the pathogenesis of AD (Heppner et al. 2015; Fu et al. 2019). In fact, high levels of pro-inflammatory mediators have been detected in the brain of AD patients (Hesse et al. 2016). Furthermore, neuroinflammation which is characterised by activation of brain-resident macrophages with the resultant hyper-secretion of pro-inflammatory cytokines and chemokines such as interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNFα), interleukin-8 (IL-8), transforming growth factor-β (TGF-β) and macrophage inflammatory protein-1α (MIP-1α) is a well-documented consequence of high levels of insoluble forms of Aβ (Akiyama et al. 2000). Consequently, anti-inflammatory strategies have the potential to delay the onset or slow the progression of the disease.

It is now well-established that the transcription factor nuclear factor-kappa B (NF-κB) plays a major role in neuroinflammation-mediated AD. NF-κB is a master regulator of inflammatory gene transcription and has been shown to be expressed in the brains of AD patients (Boissière et al. 1997; Liao et al. 2016). NF-κB has also been proposed as a molecular mechanism underlying the development of some sporadic cases of AD (Chen et al. 2012). These reports linking NF-κB to AD strengthen the role of neuroinflammation in AD.
A number of molecular mechanisms and cellular signalling pathways have been proposed to contribute to neuroinflammation in AD. Some of these mechanisms are known to be under the direct influence of NF-kB, while others have been reported to cross-talk with this transcription factor in a manner that makes them a molecular target for drug action in AD therapeutics.

The signalling pathways involving the mitogen activated protein kinases (MAPKs) have been strongly linked to neuroinflammation and AD. Of the MAPKs, the p38 MAPK has been implicated in neuroinflammation. Evidence linking p38 MAPK to neuroinflammation was put forward by Kim and Choi (2015), who suggested that exposure of microglia to Aβ induces microglial activation with the subsequent production of pro-inflammatory cytokines and reactive oxygen species, which in turn activate p38 MAPK signalling. Further reports show that Aβ-induced oxidative stress results in the activation of p38 MAPK with the resultant tau hyperphosphorylation (Giraldo et al. 2014). Recent reports have also suggested that p38 MAPK plays a role in neuroinflammation and AD due to its ability to activate NF-κB (Kheiri et al. 2018), thus making it a potential molecular target for novel AD treatment.

The nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that regulates phase II antioxidant response mechanisms in response to oxidative stress. Emerging evidence links activation of the Nrf2 protective mechanism to anti-inflammatory effects involving NF-κB (Nair et al. 2008; Sandberg et al. 2014). Specifically, NF-κB is a known negative regulator of Nrf2 (Liu et al. 2008; Kim et al. 2010a, b; Yu et al. 2011). Rojo et al. (2010) demonstrated that an activation of the microglia in Nrf2-deficient animals is accompanied by increased levels of pro-inflammatory cyclooxygenase-2 (COX-2), inducible nitric oxide synthases (iNOS), IL-6, and TNFα. To confirm these observations, Ramsey et al. (2007) reported that brains from AD patients have decreased levels of Nrf2 in the hippocampus. Consequently, there is an increasing interest in pharmacological activators of Nrf2 to activate or restore its protective mechanisms (Sandberg et al. 2014).

Research findings implicating neuroinflammation in AD have resulted in pre-clinical and clinical investigations of NSAIDs and other anti-inflammatory agents as potential therapeutic strategies for AD (McGeer et al. 2016; Cuello, 2017). However, efforts to use current anti-inflammatory agents in AD clinical trials have not been successful. Investigations showed that anti-inflammatory drugs failed to delay or reduce the pathological symptoms of patients with mild cognitive impairment or AD (Fu et al. 2019). Most of the anti-inflammatory drugs which have been investigated in clinical trials for AD are known to target specific single inflammatory mechanisms. It was therefore not surprising that these drugs failed in clinical trials, given the multi-faceted nature of AD pathology. The multi-target approach is an alternative strategy in evaluating anti-inflammatory drugs for effectiveness in slowing the progression of AD.

Some natural products are able to produce multi-target anti-inflammatory activity in AD through modulation of multiple signalling pathways. It has been proposed that the multi-pharmacological actions of black and green tea polyphenols could be valuable in the treatment of neurodegenerative disorders including AD (Mandel et al. 2011, 2012). Inhibition of neuroinflammation by natural products has also been linked to their ability to produce anti-amyloid effect. Apigenin is an anti-inflammatory natural product which showed effects on APP processing and preventing Aβ burden through down-regulation of BACE1 levels, the relief of Aβ deposition, and the decrease of insoluble Aβ levels (Zhao et al. 2013). It is worth evaluating other anti-inflammatory natural products with multi-target anti-inflammatory activity as potential candidates for AD therapeutics.

**Natural product inhibitors of neuroinflammation**

Several natural products have been reported to produce anti-neuroinflammatory activity through mechanisms involving inhibition of microglia activation, reduction of the release of pro-inflammatory cytokines from activated microglia, or through inhibition of NF-κB and p38 MAPK activation. Other natural products produce marked activation of Nrf2, a mechanism which has been shown to contribute at least in part to their anti-neuroinflammatory activity. This review will highlight some of our investigations and those reported by other investigators on the main classes of natural products with promising therapeutic potentials for inhibiting neuroinflammation.

**Alkaloids**

Alkaloids are pharmacologically-active secondary metabolites consisting of nitrogen, often as an integral part of the ring (Ziegler and Facchini 2008; Nahar and Sarker 2019) and exist as either proto-alkaloids (nitrogen-containing but not heterocyclic in structure) or true alkaloids (nitrogen-containing heterocyclic compounds) (Rosa et al. 2007). Alkaloids (Fig. 1) have been linked to a wide variety of pharmacological activities, including anti-inflammatory effects.

With regards to anti-inflammatory activity in the CNS, our investigations revealed that the alkaloid cryptolepine found in *Cryptolepis sanguinolenta* produced a reduction in the levels of TNFα, IL-6, IL-1β, NO, and PGE2 in LPS-stimulated rat microglia. There are currently no studies to determine demonstrating anti-inflammatory effects of
Cryptolepine on microglia stimulated with either amyloid beta. We also observed reductions in protein and mRNA levels of COX-2 and iNOS and further demonstrated that the effects of the compound are mediated through blocking activation of NF-κB, p38 MAPK in the microglia (Olajide et al. 2013). The effects of cryptolepine in animal models of neuroinflammation or AD are yet to determined. However, we have shown that this alkaloid produced anti-inflammatory activity in animal models of peripheral inflammation (Olajide et al. 2009). A major limitation in the development of this alkaloid in the treatment of AD is related to its cytotoxicity due to its ability to cause DNA damage (Gopalan et al. 2011).

In similar fashion, tetrandrine (a bisbenzylisoquinoline alkaloid isolated from Radix Stephania tetrandra) has shown promising NF-κB-mediated anti-inflammatory activity in BV-2 microglia activated with fibrillar amyloid beta and reduced hippocampal neuroinflammation by inhibiting NF-κB activation in a rat model of AD induced by amyloid beta (He et al. 2011a, b). While there are no studies demonstrating the clinical efficacy of tetrandrine in AD, it has been suggested that this alkaloid is able to permeate the blood–brain barrier to provide benefits in stroke, due to its lipophilic nature (Chen et al. 2011). A related glycosidic flavonoid to kaempferol, tiliroside (contained in plants such as rosehip, linden and strawberry) was demonstrated in our studies to inhibit neuroinflammation in BV-2 microglia through multiple mechanisms including attenuation of NF-κB and p38 MAPK, in addition to activating Nrf2 (Velagapudi et al. 2014, 2018a, b). Neither kaempferol nor tiliroside has been investigated for clinical efficacy in humans. Apigenin (4′,5,7-trihydroxyflavone), structurally similar to kaempferol with just one less –OH group at C-3 is a flavone found in chamomile, celery and parsley, and many other plants. Studies reported by Rezai-Zadeh et al. (2008) showed that treatment of interferon gamma-activated microglia with apigenin resulted in a decrease in the production of pro-inflammatory IL-6 and TNFα through mechanisms involving STAT1. Further evidence of the anti-inflammatory activity of this flavonoid was provided in investigations showing reductions in iNOS/NO and PGE2/COX-2 in activated microglia (Choi et al. 2014). Animal studies have also suggested that the anti-inflammatory activity of apigenin may contribute to its neuroprotective activity in models of AD. Treatment of mice with apigenin improved spatial learning and memory following amnesia induction with Aβ25–35 (Liu et al. 2011). It is widely known that one of the mechanisms involved in Aβ-induced neurodegeneration involves neuroinflammation (Ralay Ranaivo et al. 2006), suggesting that the neuroprotective activity

**Flavonoids and other polyphenols**

Flavonoids are naturally occurring phenolic compounds that can be structurally classified as anthocyanins, catechins, flavones, flavonols, flavanols, flavanones, and isoflavonoids. They are found in abundance in flowers, fruits, barks, roots, stems, tea, wine and vegetables (Nahar and Sarker 2019). Several flavonoids and polyphenolic compounds have been shown to possess anti-neuroinflammatory activity (Fig. 2).

Kaempferol is a flavonol which has been shown to inhibit neuroinflammation by reducing LPS-induced production of pro-inflammatory mediators in BV2 microglial cells through mechanisms involving NF-κB and p38 MAPK (Park et al. 2011). A related glycosidic flavonoid to kaempferol, tiliroside (contained in plants such as rosehip, linden and strawberry) was demonstrated in our studies to inhibit neuroinflammation in BV-2 microglia through multiple mechanisms including attenuation of NF-κB and p38 MAPK, in addition to activating Nrf2 (Velagapudi et al. 2014, 2018a, b).
Fig. 2 Examples of some anti-neuroinflammatory flavonoids and polyphenols
Alzheimer's disease: natural products as inhibitors of neuroinflammation

Fig. 2 (continued)
reported by Liu et al. (2011) may be related to anti-inflammatory action of the compound.

Quercetin, a similar flavonol to kaempferol with an extra hydroxyl group at C-3′ (B ring) is a ubiquitous anti-inflammatory and antioxidant natural product that is found in many fruits, vegetables, and seeds. Treatment with quercetin reduced iNOS-mediated NO production in LPS-stimulated BV-2 microglia through mechanisms involving suppression of NF-κB activation (Kang et al. 2013). These authors further demonstrated that the antioxidant transcription factor, Nrf2 is required for the anti-inflammatory effect of quercetin (Kang et al. 2013). These observations were supported by studies linking inhibition of neuroinflammation by quercetin to potential cross-talk between MAPKs and Nrf2 (Sun et al. 2015).

The anti-inflammatory activity of quercetin has been linked to its effect on cognitive function in APP/PS1 mouse model of AD. Investigations by Lv et al. (2018) demonstrated that quercetin treatment of APP/PS1 mice significantly reduced Aβ plaques, p-Tau and neuroinflammation.
The antioxidant activity of quercetin, through activation of Nrf2 and the subsequent anti-inflammatory effect in the microglia are significant in neuroprotection and therapeutic benefits in AD. There are no studies showing clinical efficacy of quercetin in AD. This may be due to its poor permeation of the BBB. Similar anti-inflammatory/neuroprotective profiles have been reported for the related flavone luteolin (Burton et al. 2016; Yao et al. 2018).

Epigallocatechin-3-gallate (EGCG) is a flavanol found mainly in green tea (Camellia sinensis). Studies have suggested that the anti-amyloidogenic and neuroprotective actions of this flavonoid are due to its ability to inhibit neuroinflammation. Experiments conducted in vitro showed that EGCG could reduce TNFα, IL-1β, IL-6, iNOS levels in Aβ-stimulated EOC13.31 microglia through mechanisms involving NF-κB (Wei et al. 2016). In animals, Lee et al. (2013) reported that EGCG prevented memory impairment and reduced the levels Aβ generation and neurotoxicity in mice following systemic injection of lipopolysaccharide (LPS). Similar observations were made in studies reported by Seong et al. (2016) who further linked the anti-neuroinflammatory activity of this compound to inhibition of NF-κB activation. In vivo experiments have also shown that EGCG produced neuroprotection in animal models of AD. For example, intraperitoneal injection of 12-month-old Tg2576 mice with 20 mg/kg EGCG resulted in decreased levels of Aβ as well as plaque load in the brain. Similar observations were made following oral administration of the compound to TgCRND8 (Tg) mice (Walker et al. 2015).

Human trials to evaluate the efficacy of EGCG in improving cognitive function have not reflected results achieved in vitro and in animal models of AD. For example, administration of 300 mg EGCG to healthy volunteers was shown to increase cerebral activity (as evidenced by an increase in alpha, beta and theta activities in the brain) without a corresponding effect on task performance (Scholey et al. 2012). Furthermore, a double-blind, placebo-controlled, crossover investigation of a single oral dose of 135 mg EGCG on cognitive performance, mood and cerebral blood flow (CBF) in healthy human adults did not show any significant effects on mood and cognition, in comparison with placebo (Wightman et al. 2012). The translational gap between bioactivity of EGCG in vitro and in animal studies and its effects in human trials is possibly associated with low oral bioavailability of the compound on the one hand, as well as different metabolism between animals and humans on the other hand (Mühl et al. 2013). More long-term human trials are necessary to establish the effects of EGCG on cognitive performance. Investigations to compare oral bioavailability and BBB penetration of EGCG in mice and human subjects will throw more light on the apparent lack of efficacy in human studies. EGCG consumption has been associated with hepatotoxicity (Navarro et al. 2013; Hu et al. 2018). This effect of the compound needs to be taken into consideration in future clinical development for AD therapeutics.

Investigations on the pomegranate fruit polyphenol punicalagin revealed that the compound produced significant inhibition of neuroinflammation in LPS-activated rat primary microglia through interference with mechanisms resulting in activation of NF-κB (Olajide et al. 2014). Interestingly, one of its gut-derived metabolites urolithin A, showed similar effects on LPS-activated BV-2 microglia (Velasagudi et al. 2019). Urolithin A has also produced neuroprotection by blocking memory impairment and neuroinflammation in APP/PS1 mice (Gong et al. 2019) and in a Caenorhabditis elegans model (Yuan et al. 2016; Fang et al. 2019). Based on the published literature no studies in humans have been conducted on pomegranate polyphenols or their gut-derived metabolites with respect to cognitive performance or other therapeutic measures of AD.

Mangiferin is a naturally occurring glucosylxanthone found in the stem bark and leaves of mango plant (Mangifera indica). Investigations in rat primary microglia revealed that mangiferin could inhibit COX-2 expression and prostaglandin E2 (PGE2) production following activation with LPS (Bhatia et al. 2008). In vivo experiments showed that mangiferin diminished neuroinflammation and improved cognitive deficits in APP/PS1 mice (Infante-Garcia et al. 2017). Based on published literature no human studies have demonstrated the efficacy of mangiferin in therapeutic endpoints of AD.

Resveratrol is a polyphenol found in grapes and berries. This stilbene is reputed with various pharmacological activities and has been widely studied as potential treatment for diverse disorders. Several pharmacological studies have demonstrated anti-neuroinflammatory/neuroprotective effects of resveratrol in vitro and in animal models. The first indication of inhibition of neuroinflammation by resveratrol was reported by Candelario-Jalil et al. (2007) who provided evidence that this compound inhibited PGE2 production and free radical formation in LPS-activated primary rat microglia. This study further revealed that resveratrol was the first known inhibitor which specifically prevents microsomal prostaglandin E synthase-1 (mPGES-1) expression without affecting COX-2. Subsequent studies by Abraham and Johnson (2009) demonstrated that resveratrol consumption resulted in reduction of LPS-induced IL-1β in plasma and IL-1β mRNA in the hippocampus of aged mice, as well as in cultured BV-2 microglia. Other studies over the last few years have increased the evidence demonstrating inhibition of neuroinflammation and neuroinflammation-mediated neuronal damage by resveratrol (Lu et al. 2010; Zhang et al. 2013; Potter et al. 2013; Wang et al. 2015; Yao et al. 2015). It is noteworthy that a recent study by Sun et al. (2019) provided a new evidence linking inhibition of neuroinflammation by resveratrol to its ability to rescue tau-induced...
cognitive deficits and neuropathology in a mouse model of AD. In that study, treatment with resveratrol rescued cognitive deficits, reduced levels of phosphorylated tau, prevented neuroinflammation and synapse loss in the brains of mice. These pre-clinical reports on resveratrol are promising and warrant further clinical evaluation.

In a clinical trial, treatment of mild to moderate AD patients with resveratrol resulted in the decline of cerebrospinal fluid amyloid beta, which is an AD biomarker. This was accompanied by reduction in biomarkers of neuroinflammation (Moussa et al. 2017). However, a pilot study to study the effects of chronic resveratrol use on cognitive function in elderly subjects revealed selectively improved psychomotor speed without significantly affecting other domains of cognitive function (Anton et al. 2018). These findings providing modest clinical evidence for the efficacy of resveratrol in AD is possibly connected to low oral bioavailability of the compound. Larger placebo-controlled, randomised trials with bioavailable formulations of resveratrol are required to throw more light on the efficacy of the compound in humans.

Curcumin found in Curcuma longa (turmeric) is perhaps the most investigated natural neuroprotective polyphenol for treating AD. It has been linked to a diverse range of pharmacological activities and therapeutic benefits including anti-inflammatory, anticancer, antimicrobial, antioxidant, and wound healing effect (Williams et al. 2011). In particular, curcumin has been widely investigated in cellular and animal models of neuroinflammation. Experiments using BV-2 microglia revealed that this diarylheptanoid inhibited neuroinflammation in LTA-activated microglial cells through reduction in the production of TNFα, PGE2, and nitric oxide (NO), as well as inhibition of NF-κB and MAPK activation (Yu et al. 2018). Similar observations were made in BV-2 microglia stimulated with LPS (Porro et al. 2019; Zhang et al. 2019). These observations in the microglia have been confirmed by results of experiments in animal models of AD which showed that curcumin treatment ameliorated cognitive decline and neuroinflammation following exposure to LPS, and in p25 transgenic mice (Sundaram et al. 2017; Sorrenti et al. 2018). Curcumin also inhibited formation of amyloid beta oligomers and fibrils and reduced amyloid in mouse models of AD (Yang et al. 2005).

Interestingly, a clinical trial with curcumin did not demonstrate efficacy in AD in a 24-week placebo-controlled trial (Ringman et al. 2012). The authors suggested that the lack of efficacy could be related to bioavailability of the product used or differences in the biology of rodent models of AD and human AD. However, a subsequent randomised, double-blind, placebo-controlled study in healthy older population which employed 400 mg/day of a highly bioavailable curcumin preparation (Longvida), reported a significantly improved working memory and mood after a 4-week treatment (Cox et al. 2015). These studies suggest that the clinical efficacy of curcumin in AD would be increased by approaches which enhance its bioavailability.

Our investigations revealed that other polyphenols such as formononetin, an isoflavone in Trifolium pratense (red clover) inhibited neuroinflammation through mechanisms involving attenuation of NF-κB activation in LPS-activated BV-2 microglia (El-Bakoush and Olajide 2018). Similar results were obtained in experiments on agathisflavone, a biflavonoid isolated from Anacardium occidentale (Vela-gapudi et al. 2018a, b). These observations have not been confirmed in animal experiments. It is expected that future animal experiments to establish in vivo activities of these compounds would be valuable in determining their potentials for follow-up clinical studies.

Flavonoids remain one of the important groups of natural products for inhibiting neuroinflammation in AD due to their fundamental inhibitory actions on pro-inflammatory transcription factors. Furthermore, this group of compounds activate antioxidant/anti-inflammatory transcription factors. While flavonoids have proven to be promising therapeutic natural products in pre-clinical models of AD, it is important to note that the overall bioavailability of parent flavonoids are usually low. Furthermore, flavonoids do not cross the blood–brain barrier easily due to their high polarity.

**Terpenes**

Terpenoids are a large and structurally diverse group of compounds formed biosynthetically from a combination of two or more isoprene units (a five carbon unit, chemically known as 2-methyl-1,3-butadiene) (Nahar and Sarker 2019). Terpenoids (Fig. 3) have been widely reported to inhibit neuroinflammation in animal models and in vitro.

Parthenolide, a biologically-active sesquiterpene lactone present in Tanacetum parthenium has been reported to improve cognitive function and decrease levels of TNF-α and IL-6 in the cortical and hippocampal regions of rats (Khare et al. 2017). Recently, this compound was reported to inhibit neuroinflammation in intracerebral haemorrhage-induced brain injury in rats through TLR4/NF-κB-mediated reduction in the levels of TNF-α, interleukin IL-6, IL-17 in the ipsilateral hemispheres of the brain (Wang et al. 2020). It appears that the NF-κB inhibitory action of parthenolide is responsible for its versatile inhibitory actions in different neuropathologies involving inflammation. Neurprotection by this sesquiterpene lactone needs to be further confirmed in AD clinical trials.

Artemisinin is a sesquiterpene lactone found in the Chinese herb Artemisia annua (Qinghao) of the family Asteraceae, and was originally developed for the treatment of multi-drug resistant malaria. Recently, this compound and some of its synthetic analogues have been reported.
to possess potential neuroprotective activity in AD, partly through their anti-inflammatory activity. Studies reported by Zhu et al. (2012) revealed that artemisinin inhibited LPS-induced release of TNFα, IL-6, MCP-1 and NO in BV-2 microglia. These authors further suggest that the observed inhibition of neuroinflammation by artemisinin was related to its modulatory effects on the NF-κB signalling pathway in the microglia. Subsequent studies showed that this compound was neuroprotective in a mouse model of AD through reduction in the levels of IL-1β, IL-6 and TNF-α in the hippocampus and the cortex (Qiang et al. 2018). Similarly, we have reported that artemisinin analogues, artesunate and artemether inhibited neuroinflammation by targeting NF-κB signalling in BV-2 microglia (Okorji and Olajide, 2014; Okorji et al. 2016). Artemisinin and its synthetic derivatives have been shown to cross the blood–brain
barrier due to their lipophilicity (Navaratnam et al. 2000). However, experiments in animals have suggested that the compounds are neurotoxic (Meshnick 2002; Genovese and Newman, 2008), which may be discouraging their investigation in AD clinical trials.

Our investigations have shown that thymoquinone (the main bioactive constituent of *Nigella sativa*) is a potent inhibitor of neuroinflammation. In LPS-activated BV-2 microglia, thymoquinone treatment resulted in significant reduction in TNFα, IL-6, PGE2, and NO protein and mRNA through mechanisms involving inhibition of the pro-inflammatory NF-κB and activation of the anti-inflammatory Nrf2 pathways (Velagapudi et al. 2017b). We further showed that inhibition of neuroinflammation by this compound was partially related to activation of both sirtuin 1 (SIRT-1) and 5′ adenosine monophosphate-activated protein kinase (AMPK) in the microglia (Velagapudi et al. 2017a). Similar observations showing inhibition of neuroinflammation by thymoquinone were made in recent investigations reported by Cobourne-Duval et al. (2018). Recently, thymoquinone was shown to improve cognitive decline in a rat model of AD, while decreasing Aβ formation and accumulation, as well as TNF-α and IL-1β (Abulfadl et al. 2018).

Carnosic acid and carnosol are brain-permeable natural diterpenes found in *Rosmarinus officinalis*, and have shown significant neuroprotective activity (de Oliveira, 2016). Studies by Foresti et al. (2013) showed that carnosol could inhibit neuroinflammation in BV-2 microglia by reducing levels of TNF-α, PGE2, and nitric oxide following activation with either LPS or interferon gamma (IFNγ). In addition, carnosic acid was reported to produce anti-inflammatory effect in paraquat-induced increase in the levels of IL-1β, TNFα, and cyclooxygenase-2 (COX-2) in SH-SY5Y cells by targeting Nrf2/HO-1 and NF-κB signalling pathways (de Oliveira et al. 2018). It appears that inhibition of neuroinflammation by carnosol and carnosic acid could be related to Nrf2 activation, which is known to result in an anti-inflammatory outcome (Innamorato et al. 2008). Ginkgolides are pharmacologically-active diterpenes found in *Ginkgo biloba* (*Ginkgoaceae*). In a study reported by Zhou et al. (2012), ginkgolides were shown to inhibit neuroinflammation by reducing levels of IL-1β, IL-6, IL-8, TNF-α in BV-2 microglia activated with oxygen–glucose deprivation and re-oxygenation through mechanisms involving TLRs/MyD88/ NF-κB signalling pathways. Anti-inflammatory activity has also been reported to contribute to the neuroprotective actions of ginkgolides in models of cerebral ischemia and reperfusion injury (Gu et al. 2012; Jiang et al. 2014).

There are no reports in literature indicating the benefits of ginkgolides in clinical trials for AD treatment. Clinical studies on standardised *Ginkgo biloba* extracts have shown conflicting results. Results of a randomised controlled trial to evaluate the efficacy of *Ginkgo biloba* extract (240 mg) in patients diagnosed with mild to AD or vascular dementia showed that the extract improved cognitive function, neuropsychiatric symptoms and functional abilities (Ihl et al. 2012). However, in another study to assess the efficacy of long-term use of *Ginkgo biloba* extract (120 mg) for the reduction of incidence of AD in elderly adults with memory complaints, the extract did not reduce the risk of progression to AD when compared with placebo (Vellas et al. 2012). A systematic review and meta-analysis of randomised controlled trials of *Ginkgo biloba* extract in mild cognitive impairment and AD attributed the conflicting outcomes of the trials to limited sample size, inconsistent findings and methodological quality of included trials (Yang et al. 2016). Furthermore, the effectiveness of *Ginkgo biloba* extract in treating established AD without preventing its incidence warrants further investigation.

**Carotenoids from *Crocus sativus* (Saffron)**

*Crocus sativus* (Saffron) is a spice that is widely reputed for a wide variety of therapeutic applications, including neurodegenerative disorders, depression, diabetes mellitus, atherosclerosis and cancer (Leone et al. 2018). Evidence from in vitro experiments, animal models of AD and clinical trials have shown that carotenoids in saffron flowers, crocin and crocetin are neuroprotective natural products with therapeutic potentials in AD. Studies in BV-2 microglia showed that crocin and crocetin inhibited LPS-induced production of NO/iNOS, TNF-α, IL-1β and ROS in BV-2 microglial cells through mechanisms linked to NF-κB (Nam et al. 2010; Zhang et al. 2018). These anti-inflammatory carotenoids have been reported to produce promising activities in animal models of AD through their ability to improve cognitive function (Hosseinizadeh et al. 2012; Asadi et al. 2015). A study published by Mazumder et al. (2017) appears to provide a link between the anti-inflammatory and antioxidant activities of crocin and its ability to enhance cognitive abilities in mice. This hypothesis needs to be further investigated to provide a better understanding of how anti-inflammatory natural products promote cognitive abilities.

There are no clinical studies to demonstrate the benefits of crocin and crocetin in AD. However, results of single- and double-blind, placebo controlled clinical trials on saffron have shown promising effects in patients with moderate to severe Alzheimer’s disease (Akhondzadeh et al. 2010a, b; Farokhnia et al. 2014; Tsolaki et al. 2016).

**Marine natural products**

The most investigated neuroprotective marine natural product is astaxanthin (3,3′-dihydroxy-β,β′-carotene-4,4′-dione), a xanthophyll carotenoid found in *Haematococcus pluvialis*, *Chlorella zofingiensis*, *Chlorococcum*, and *Phaffia*...
rhodomyza. In LPS-stimulated BV-2 microglia, astaxanthin was reported to inhibit NO/iNOS and COX-2 (Choi et al. 2008). In a separate study, Kim et al. (2010a, b) showed that the compound attenuated LPS-induced production of IL-6 in BV-2 microglia through mechanisms involving ERK1/2-MSK-1 and NF-xB activation.

Inhibition of neuroinflammation has also been reported for astaxanthin in animal models of neurodegeneration. In a study reported by Zhou et al. (2015), treatment of diabetic mice with astaxanthin alleviated alleviated cognition deficits with accompanying inhibition in NF-xB mediated neuroinflammation. Inhibition of neuroinflammation was also proposed to be responsible for the neuroprotection by astaxanthin in experimental subarachnoid haemorrhage (Zhang et al. 2014). Interestingly, clinical trials on the benefits of astaxanthin in improving cognition have shown promising results (Satoh et al. 2009; Katagiri et al. 2012), suggesting that this marine natural product holds significant promise in the development of novel therapeutics for neurodegenerative disorders such as AD.

**Challenges in the delivery of natural products to the brain: novel delivery technologies**

Treatment of AD is challenging partly due to the presence of physical barriers such as the blood–brain barrier (BBB) in the brain. The BBB is the critical barrier that needs to be overcome to transport natural compounds from the blood into brain. The challenges posed by the BBB is important in the activity of neuroprotective natural products because their benefit is significantly affected by low bioavailability and sometimes poor pharmacokinetic profile (Manach et al. 2004; Soares et al. 2018).

The bioavailability of some anti-inflammatory natural products is attributed to their metabolism. Curcumin is a widely-studied anti-inflammatory and antioxidant polyphenol. However, the pharmacological potential is restricted because of its low bioavailability following oral administration (Aggarwal and Sung 2009; Kumar et al. 2010; Di Meo et al. 2019). Resveratrol is a polyphenol with antioxidant, anti-inflammatory and neuroprotective actions. However, in spite of its lipophilicity resveratrol is extensively metabolised and rapidly eliminated resulting in poor bioavailability (Chimento et al. 2019). The poor bioavailability profiles of these polyphenols have triggered the synthesis of more bioavailable derivatives.

Delivery technologies involving mostly lipid-based nanocarriers have been explored to enhance the bioavailability and BBB penetration of neuroprotective natural products. For example, liposomes are formed by amphiphilic substances such as phospholipids that self-assemble as vesicles which compose of lipid bilayers (Lúcio et al. 2010). Over the years, lipid nanoparticles have become more popular and have the advantage of protecting active compounds (Soares et al. 2018). Solid lipid nanoparticles (SLNs) are a new generation of submicron-sized lipid emulsions in which the liquid lipid (oil) has been substituted by a solid lipid with an ability to penetrate the BBB and produce a pharmacological action in the CNS (Mutoh et al. 2016). Table 1 summarises the novel delivery strategies which have been applied in enhancing the permeability of some anti-inflammatory natural products into the brain.

**Conclusion and future direction**

Natural products exhibit promising health-promoting effects in neurodegenerative diseases partly due to their anti-inflammatory property. The emerging research data on the possible therapeutic effects of natural products as neuroprotective agents is particularly exciting due to the steadily increasing population with AD.

In spite of the overwhelming evidence suggesting the potentials of anti-inflammatory natural products in treating AD, further investigations are required to assess their clinical efficacy in properly-controlled human trials. Studies have shown that in vitro data demonstrating efficacy do not always translate into in vivo effects. Furthermore, extrapolating data from animal models to humans in the search for new treatment for AD is not reliable due to significant species differences. To overcome this challenge, pre-clinical investigations on anti-inflammatory natural products need to focus on employing new cutting-edge tools. One of such approaches is the use of a tri-culture including human neurons, astrocytes and microglia to evaluate neuroinflammation and neuroprotection in vitro.

![Image](image-url)
Small molecules for AD must be bioavailable and overcome the challenges posed by the BBB to act in the brain. Published articles have shown the potential values of nano-carriers in delivering natural products to the brain. More research efforts need to focus on new delivery methods to achieve significant therapeutic concentrations of polar phytochemicals (such as the anti-inflammatory/antioxidant polyphenols) in the brain.

With regards to molecular target-driven discovery of novel natural products for AD, focusing on a single gene is not the best disease model; as most pharmacologically-active natural products identified using this approach have not resulted in new treatments, mainly due to the complex mechanisms involved in AD. Investigations need to focus on the two principal transcription factors, NF-κB and Nrf2, which control key molecular players in producing inflammation or anti-inflammation (Fig. 4). Furthermore, pre-clinical investigations on AD should focus more on experimental models which combine stress reduction (neuroinflammation, oxidative stress), neuroprotection, and regeneration.

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References
Abraham J, Johnson RW (2009) Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and
deficits in working memory in aged mice. Rejuvenation Res 12:445–453
Abulfadl YS, El-Maraghy NN, Ahmed AE, Nofoal S, Abdel-Mottaleb Y, Badary OA (2018) Thymoquinone alleviates the experimentally induced Alzheimer’s disease inflammation by modulation of TLRs signaling. Hum Exp Toxicol 37:1092–1104
Aggarwal BB, Sung B (2009) Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci 30:85–94
Ahmad N, Ahmad R, Alam MA, Samim M, Iqbal Z, Ahmad FJ (2016) Quantification and evaluation of thymoquinone loaded mucosal-hesive nanoemulsion for treatment of cerebral ischemia. Int J Biol Macromol 88:320–332
Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Chergahmakan H, Razaeghi S, Hejazi SS, Yousefi MH, Alimardani R, Jamshidi A, Zare F, Moradi A (2010a) Saffron in the treatment of patients with mild to moderate Alzheimer’s disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther 35:581–588
Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Chergahmakan H, Razaeghi S, Hejazi SS, Yousefi MH, Alimardani R, Jamshidi A, Rezagadeh SA, Yousefi A, Zare F, Moradi A, Vossoughi A (2010b) A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer’s disease. Psychopharmacology 207:637–643
Akiyama H, Barger S, Barnum S et al (2000) Inflammation and Alzheimer’s disease. Neurobiol Aging 21:383–421
Anton SD, Ebner N, Dzierzewski JM, Zlatar ZZ, Gurka MJ, Dotson VM, Kirton J, Mankowski RT, Marsiske M, Manini TM (2018) Effects of 90 days of resveratrol supplementation on cognitive function in elders: a pilot study. J Altern Complement Med 24:725–732
Asadi F, Jamshidi AH, Khodagholi F, Yans A, Azimi L, Faizi M, Vali L, Abdollahi M, Ghaehremani MH, Sharifzadeh M (2015) Reversal effects of crocin on amyloid-β-induced memory deficit: Modificaiton of autophagy or apoptosis markers. Pharmacol Biochem Behav 139:47–58
Barras A, Mezzetti A, Richard A, Lazzaroni S, Roux S, Melnyk P, Betbeder D, Monflilliette-Dupont N (2009) Formulation and characterization of polyphenol-loaded lipid nanocapsules. Int J Pharm 379:270–277
Bhatia HS, Candelario-Jalil E, de Oliveira AC, Olajade OA, Martínez-Sánchez G, Fiebich BL (2008) Mangierin inhibits cyclooxygenase-2 expression and prostaglandin E2 production in activated rat microglial cells. Arch Biochem Biophys 477:253–258
Bloom GS (2014) Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathology. JAMA Neurol 71:505–508
Bosissière F, Hunot S, Faucheux B, Duyckaerts C, Hauw JJ, Agid Y, Hirsch EC (1997) Nuclear translocation of NF-kappaB in cholinergic neurons of patients with Alzheimer’s disease. Nat Neurosci 22:401–412
Cobourne-Duval MK, Taka E, Mendonca P, Soliman KFA (2018) Thymoquinone increases the expression of neuroprotective proteins while decreasing the expression of pro-inflammatory cytokines and the gene expression NFκB pathway signaling targets in LPS/IFNγ-activated BV-2 microglia cells. J Neuroimmunol 320:87–97
Cox KH, Pippigas A, Scholey AB (2015) Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J Psychopharmacol 29:642–651
Cuello AC (2017) Early and late CNS inflammation in Alzheimer’s disease: two extremes of a continuum? Trends Pharmacol Sci 38:956–966
Dang H, Meng MHW, Zhao H, Jai D, Deng Y, Ly F (2014) Luteolin-loaded solid lipid nanoparticles synthesis, characterization, & improvement of bioavailability, pharmacokinetics in vitro and vivo studies. J Nanopart Res 16:1–10
de Oliveira MR (2016) The dietary components carnosic acid and carnosol as neuroprotective agents: a mechanistic view. Mol Neurobiol 53:6155–6168
de Oliveira MR, de Souza ICC, Fürstenau CR (2018) Carnosic acid induces anti-inflammatory effects in paraquat-treated SH-SY5Y cells through a mechanism involving a crosstalk between the Nrf2/HO-1 Axis and NF-κB. Mol Neurobiol 55:890–897
Di Meo F, Margarucci S, Galdieri U, Crispi S, Peluso G (2019) Curcumin, gut microbiota, and neuroprotection. Nutrients 11:2426
El-Bakoush A, Olajade OA (2018) Formononetin inhibits neuroinflammation and increases estrogen receptor beta (ERβ) protein expression in BV2 microglia. Int Immunopharmacol 61:325–337
Fang EF, Hou Y, Palikaras K (2019) Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer’s disease. Nat Neurosci 22:401–412
Farokhnia M, Shaftee Sabet M, Iranpour N, Gouglou A, Yektehtza H, Alimardani R, Farsad F, Kamalipour M, Akhondzadeh S (2014) Comparing the efficacy and safety of Crocus sativus L. with memantine in patients with moderate to severe Alzheimer’s disease: a double-blind randomized clinical trial. Hum Psychopharmacol 29:351–359
Foresti R, Bains SK, Pitchumony TS, de Castro Brás LE, Dragó F, Dubois-Rande JL, Bucolo C, Motterlini R (2013) Small molecule activators of the Nrfl2/HO-1 antioxidant axis modulate heme metabolism and inflammation in BV2 microglia cells. Pharmacol Res 76:132–148
Fu WY, Wang X, Ip NY (2019) Targeting neuroinflammation as a therapeutic strategy for Alzheimer’s disease: mechanisms, drug candidates, and new opportunities. ACS Chem Neurosci 10:872–879
Genovese RF, Newman DB (2008) Understanding artemisinin-induced brainstem neurotoxicity. Arch Toxicol 82:379–385
Giraldo E, Lloret A, Fuchsberger T, Vina J (2014) Abeta and tau toxicities in Alzheimer’s are linked via oxidative stress-induced p38 activation: protective role of vitamin E. Redox Biol 2:873–877
Gong Z, Huang J, Xu B et al (2019) Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. J Neuroinflammation 16:62
Gopalan RC, Emerse E, Wright CW, Karahalil B, Karakaya AE, Anderson D (2011) Effects of the anti-malarial compound cryptolepine and its analogues in human lymphocytes and sperm in the Comet assay. Toxicol Lett 207:322–325

Gu JH, Ge JB, Li M, Wu F, Zhang W, Qin ZH (2012) Inhibition of NF-κB activation is associated with anti-inflammatory and anti-angiogenic effects of Ginkgolide B in a mouse model of cerebral ischemia/reperfusion injury. Eur J Pharm Sci 47:652–660

Hagl S, Kocher A, Schiborr C, Kolesova N, Frank J, Eckert GP (2015) Curcumin micelles improve mitochondrial function in neuronal PC12 cells and brains of NMRI mice - impact on bioavailability. Neurochem Int 89:234–242

He FQ, Qiu BY, Li TK, Xie Q, Cui DJ, Huang XL, Gan HT (2011a) Tetrandrine suppresses amyloid-β-induced inflammatory cytokines by inhibiting NF-κB pathway in murine BV2 microglial cells. Int Immunopharmacol 11:1220–1225

He FQ, Qiu BY, Zhang XH, Li TK, Xie Q, Cui DJ, Huang XL, Gan HT (2011b) Tetrandrine attenuates spatial memory impairment and hippocampal neuroinflammation via inhibiting NF-κB activation in a rat model of Alzheimer’s disease induced by amyloid-β (1–42). Brain Res 1384:89–96

Heppner FL, Ransohoff RM, Becher B (2015) Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci 16:358–372

Hesse R, Wahler A, Gumert P et al (2016) Decreased IL-8 levels in CSF and serum of AD patients and negative correlation of MMSE and IL-1β. BMC Neurol 16:185

Hosseinzadeh H, Sadeghnia HR, Ghaeni FA, Motamedshariyat VS, Mohajeri SA (2012) Effects of saffron (Crocus sativus L.) and its active constituent, crocin, on recognition and spatial memory after chronic cerebral hypoperfusion in rats. Phytother Res 26:381–386

Hu J, Webster D, Cao J, Shao A (2018) The safety of green tea and green tea extract consumption in adults—results of a systematic review. Regul Toxicol Pharmacol 95:412–433

Ihl R, Tribanek M, Bachinskaya N, GOTADAY Study Group (2012) Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761® in Alzheimer’s disease and vascular dementia: results from a randomised controlled trial. Pharmacopsychiatry 45:41–46

Infante-Garcia C, Ramos-Rodriguez JJ, Delgado-Olmos I, Gamero-Arana L, Jerez-Gonzalez A, Carmona-Martín N, Recio-Gonzalez F, Manchón-Conde R, Buñuel-Montero A (2016) Neuroprotective effects of bilobalide in a mouse model of cerebral ischemia-reperfusion injury. Mitochondrion 27:279–312

Jiang M, Li J, Peng Q et al (2014) Neuroprotective effects of bilobalide in a mouse model of cerebral ischemia-reperfusion injury. Mitochondrion 27:279–312

Kakkar V, Kaur IP (2011) Evaluating potential of curcumin loaded solid lipid nanoparticles in aluminium induced behavioural, biochemical and histopathological alterations in mice brain. Food Chem Toxicol 49:2906–2913

Kang CH, Choi YH, Moon SK, Kim WJ, Kim GY (2013) Quercetin inhibits lipo polysaccharide-induced nitric oxide production in BV2 microglial cells by suppressing the NF-κB pathway and activating the Nrf2-dependent HO-1 pathway. Int Immunopharmacol 17:808–813

Katagiri M, Satoh A, Tsuji S, Shirasawa T (2012) Effects of astaxanthin-rich Haematococcus pluvialis extract on cognitive function: a randomised, double-blind, placebo-controlled study. J Clin Biochem Nutr 51:102–107

Khare P, Datusalia AK, Sharma SS (2017) Parthenolide, an NF-κB inhibitor ameliorates diabetes-induced behavioural deficit, neuro-transmitter imbalance and neuroinflammation in type 2 diabetes rat model. Neurochemical Int 20019:101–112

Kheiri G, Dolatshahi M, Rahmani F, Rezaei N (2018) Role of p38 MAPKs in Alzheimer’s disease: implications for amyloid beta toxicity targeted therapy. Rev Neurosci 30:9–30

Kim EK, Choi EJ (2015) Compromised MAPK signaling in human diseases: an update. Arch Toxicol 89:867–882

Kim JE, You DJ, Lee C, Ahn C, Seong JY, Hwang JI (2010a) Suppression of NF-kappaB signaling by KEAP1 regulation of IKKbeta activity through autophagic degradation and inhibition of phosphorylation. Cell Signal 22:1645–1654

Kim YH, Koh HK, Kim DS (2010b) Down-regulation of IL-6 production by astaxanthin via ERK-, JNK-, and NF-kB-mediated signals in activated microglia. Int Immunopharmacol 10:1560–1572

Kim YG, García ML, Himmel D, Reuben JP, Lam YK, Pan JX, Han GQ, Kaczorowski GJ (1988) Interaction of tetrandrine with slowly inactivating calcium channels. Characterization of calcium channel modulation by an alkaloid of Chinese herb origin. J Biol Chem 263:2238–2244

Kumar A, Ahuja A, Ali J, Baboota S (2010) Conundrum and therapeu tic potential of curcumin in drug delivery. Crit Rev Ther Drug Carrier Syst 27:279–312

Lee YJ, Choi DY, Yun YP, Han SB, Oh KW, Hong JT (2013) Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-neuroinflammatory properties. J Nutr Biochem 24:298–310

Leone S, Recinella L, Chiavaroli A, Orlando G, Ferrante C, Leporini L, Brunetti L, Menghini L (2018) Phytotherapeutic use of the Crocus sativus L. (Saffron) and its potential applications: a brief overview. Phytother Res 32:2364–2375

Liao Y, Qi XL, Cao Y, Wu FF, Ravid R, Winblad B, Pei JJ, Guan ZZ (2016) Elevations in the levels of NF-kB and inflammatory chemotactic factors in the brains with Alzheimer’s disease—one mechanism may involve 3 nicotinic acetylcholine receptor. Curr Alzheimer Res 13:1290–1301

Liu GH, Qu J, Shen X (2008) NF-kappaB/p65 antagonizes Nrf2-ARE pathway by depleting CBP from Nrf2 and facilitating recruitment of HDAC3 to MaIk. Biochim Biophys Acta 1783:713–727

Liu R, Zhang T, Yang H, Lan X, Ying J, Du G (2011) The flavonoid apigenin protects brain neurovascular coupling against amyloidβ25–35-induced toxicity in mice. J Alzheimers Dis 24:85–100

Lu X, Ma L, Ruan L et al (2010) Resveratrol differentially modulates inflammatory responses of microglia and astrocytes. J Neuroinflammation 7:46

Lúcio M, Lima JL, Reis S (2010) Drug-membrane interactions: significance for medicinal chemistry. Curr Med Chem 17:1795–1809

Lv M, Yang S, Cai L, Qin LQ, Li BY, Wan Z (2018) Effects of quercetin intervention on cognition function in appps1 mice was affected by vitamin D status. Mol Nutr Food Res 62:e1800621

Mähler A, Mandel S, Lorenz M et al (2013) Epigallocatechin-3-gallate: a useful, effective and safe clinical approach for targeted prevention and individualised treatment of neurological diseases? EPMA J 4:5

Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L (2004) Polyphenols: food sources and bioavailability. Am J Clin Nutr 79:727–747

Mandel SA, Amit T, Weinreb O, Youdim MB (2011) Understanding the broad-spectrum neuroprotective action profile of green tea polyphenols in aging and neurodegenerative diseases. J Alzheimer’s Dis 25:187–208
Mandel SA, Weinreb O, Amit T, Youdim MB (2012) Molecular mechanisms of the neuroprotective/neurorescue action of multi-target green tea polyphenols. Front Biosci (Schol Ed) 4:581–598

Mazumder AG, Sharma P, Patial V, Singh D (2017) Crocin attenuates kindling development and associated cognitive impairments in mice via inhibiting reactive oxygen species-mediated NF-κB activation. Basic Clin Pharmacol Toxicol 120:426–433

McGeer PL, Rogers J, McGeer EG (2016) Inflammation, antiinflammatory agents, and Alzheimer’s disease: the last 22 years. J Alzheimers Dis 54:853–877

Meesnick SR (2002) Artemisinin: mechanisms of action, resistance and toxicity. Int J Parasitol 32:1655–1660

Mouras S, Lazar AN, Markoutsa E, Duyckaerts C, Antimisiaris SG (2014) Multifunctional nanoliposomes with curcumin-lipid derivative and brain targeting functionality with potential applications for Alzheimer's disease. Eur J Med Chem 80:175–183

Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, Turner RS (2017) Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer’s disease. J Neuroinflammation 14:1

Mutoh T, Mutoh T, Taki Y, Ishikawa T (2016) Therapeutic potential of solid lipid nanoparticles encapsulated thymoquinone (TQ-SLNs) on 3-nitropropropionic acid induced Huntington’s disease-like symptoms in Wister rats. Chem Biol Interact 256:25–36

Navarrotam V, Mansor SM, Sit NW, Grace J, Li Q, Olliaro P (2000) Pharmacokinetics of artemisinin-type compounds. Clin Pharmacokinet 39:255–270

Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano KH, Park JH, Kang I, Hong JW, Lee EH (2010) Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. Eur J Pharmacol 648:110–116

Navaratnam V, Mansor SM, Sit NW, Grace J, Li Q, Olliaro P (2000) Pharmacokinetics of artemisinin-type compounds. Clin Pharmacokinet 39:255–270

Ojajide OA, Ajayi AM, Wright CW (2009) Anti-inflammatory properties of cryptopine. Phytother Res 23:1421–1425

Ojajide OA, Bhatia HS, de Oliveira AC, Wright CW, Fiebich BL (2013) Inhibition of neuroinflammation in LPS-activated microglia by cryptopine. Evid Based Complement Alternat Med 2013:459723

Ojajide OA, Kumar A, Velagapudi R, Okorji UP, Fiebich BL, Ojajide OA (2016) Antinaural drug arteether induces neuroinflammation in BV2 microglia through Nrf2-dependent mechanisms. Mol Neurobiol 53:6426–6443

Olajide OA, Bhatia HS, de Oliveira AC, Wright CW, Fiebich BL (2013) The effect of resveratrol on neurodegeneration and blood brain barrier stability surrounding intracortical microelectrodes. Biomaterials 34:7001–7015

Prince M, Albanese E, Guerchet M, Prina M (2014) World Alzheimer report 2014: dementia and risk reduction an analysis of protective and modifiable factors. Alzheimer’s Disease International (ADI), London

Puglia C, Frasca G, Musumeci T, Rizza L, Puglisi G, Bonina F, Chiecho S (2012) Curcumin loaded NLC induces histone hypoacetylation in the CNS after intraperitoneal administration in mice. Eur J Pharm Biopharm 81:288–293

Qiang W, Cai W, Yang Q et al (2018) Artemisinin B improves learning and memory impairment in ad dementia mice by suppressing neuroinflammation. Neuroscience 395:1–12

Raiy Ranaivo H, Craft JM, Hu W, Guo L, Wing KL, Van Eldik LJ, Watterson DM (2006) Glia as a therapeutic target: selective suppression of human amyloid-beta-induced upregulation of brain proinflammatory cytokine production attenuates neurodegeneration. J Neurosci 26:662–670

Ramachandran S, Thangarajan S (2016) A novel therapeutic application of solid lipid nanoparticles encapsulated thymoquinone (TQ-SLNs) on 3-nitropropropionic acid induced Huntington’s disease-like symptoms in Wister rats. Chem Biol Interact 256:25–36

Ramsey CP, Glass CA, Montgomery MB et al (2007) Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol 66:75–85

Rezai-Zadeh K, Ehrhart J, Bai Y, Sanberg PR, Bickford P, Tan J, Douglas RD (2008) Apigenin and luteolin modulate microglial activation via inhibition of STAT1-induced CD40 expression. J Neuroinflammation 5:41

Ringman JM, Frautschy SA, Teng E et al (2012) Oral curcumin for Alzheimer’s disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimers Res Ther 4:43

Rojo AI, Innamorato NG, Martin-Moreno AM, De Ceballos ML, Yamamoto M, Cuadrado A (2010) Nrf2 regulates microglial dynamics and neuroinflammation in experimental Parkinson’s disease. Glia 58:588–598

Rosa EAS, Bennett RN, Aires A (2007) Levels and potential health impacts of nutritionally relevant phytochemicals in organic and conventional food production systems. In: Cooper J, Niggli U, Elsevier, Amsterdam

Sandberg M, Patil J, D’Angelo B, Weber SG, Mallard C (2014) NRF2-regulation in brain health and disease: implication of cerebral ischemia. Neuropharmacology 79:298–306

Satoh A, Tsuji S, Okada Y et al (2009) Preliminary clinical evaluation of toxicity and efficacy of a new astaxanthin-rich Haematococcus pluvialis extract. J Clin Biochem Nutr 44:280–284

Schleyer A, Downey LA, Ciocciari J, Pipingas A, Nolidin K, Finn M, Wines M, Catchlove S, Terrens A, Barlow E, Gordon L, Stough C (2012) Acute neurocognitive effects of epigallocatechin gallate (EGCG). Appetite 58:767–770

Seong KJ, Lee HG, Kook MS, Ko HM, Jung JY, Kim WJ (2016) Epigallocatechin-3-gallate rescues LPS-impaired adult hippocampal neurogenesis through suppressing the TLR4-NF-κB signaling pathway in mice. Korean J Physiol Pharmacol 20:41–51

Smith A, Giunta B, Bickford PC, Fountain M, Tan J, Shytle RD (2010) Nanolipidic particles improve the bioavailability and alpha-secretase inducing ability of epigallocatechin-3-gallate (EGCG) for the treatment of Alzheimer’s disease. Int J Pharm 389:207–212

Soares TB, Loureiro L, Carvalho A, Oliveira MEC, Dias A, Sartoreno B, Lúcio M (2018) Lipid nanocarriers loaded with natural compounds: potential new therapies for age related neurodegenerative diseases? Prog Neurobiol 168:21–41
Sood S, Jain K, Gowthamarajan K (2014) Optimization of curcumin nanoemulsion for intranasal delivery using design of experiment and its toxicity assessment. Colloids Surf B Biointerfaces 113:330–337

Sorrenti V, Contarini G, Sut S, Dall’Acqua S, Confortin F, Pagetta A, Giusti P, Zuzso M (2018) Curcumin prevents acute neuroinflammation and long-term memory impairment induced by systemic lipopolysaccharide in mice. Front Pharmacol 9:183

Sun GY, Chen Z, Jasmer KJ, Chuang DY, Gu Z, Hannink M, Simonjy A (2015) Quercetin attenuates inflammatory responses in BV-2 microglial cells: role of MAPKs on the Nrf2 pathway and induction of heme oxygenase-1. PLoS ONE 10:e0141509

Sun XY, Dong QX, Zhu J, Sun X, Zhang LF, Qiu M, Yu XL, Liu RT (2019) Resveratrol rescues tau-induced cognitive deficits and neuropathology in a mouse model of tauopathy.Curr Alzheimers Res 16:710–722

Sundaram JR, Poore CP, Sulaimee NHB et al (2017) Curcumin ameliorates neuroinflammation, neurodegeneration, and memory deficits in p25 transgenic mouse model that bears hallmarks of Alzheimer’s disease. J Alzheimers Dis 54:129–133

Tsolaki M, Karathanasi E, Lazarou I, Dovas K, Verykouki E, Karacostas A, Georgiadis K, Tsolaki A, Adam K, Kompatsiaris I, Sinakos Z (2016) efficacy and safety of Crocus sativus L. in patients with mild cognitive impairment: one year single-blind randomized, with parallel groups, clinical trial. J Alzheimers Dis 54:129–133

Velagapudi R, Aderogba M, Olajide OA (2014) Tiliroside, a dietary glycoside flavonoid, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:5892–5901

Yang G, Wang Y, Sun J, Zhang K, Liu J (2016) Ginkgo biloba for mild cognitive impairment and Alzheimer’s disease: a systematic review and meta-analysis of randomized controlled trials. Curr Top Med Chem 16:520–528

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:5892–5901

Zhou X, Zhang F, Hu X et al (2015) Inhibition of inflammation by astaxanthin attenuates amyloid-β fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:5892–5901

Yao Y, Li J, Niu Y et al (2015) Resveratrol inhibits oligomeric Aβ-induced microglial activation via NADPH oxidase. Mol Med Rep 12:6133–6139

Zhang J, Zheng Y, Luo Y, Du Y, Zhang X, Fu J (2019) Curcumin inhibits neuroinflammation and improves cognitive dysfunction by inhibiting neuroinflammation. Neurochem Res 43:806–820

Yu M, Li H, Liu Q et al (2011) Nuclear factor p65 interacts with Keap1 to repress the Nrf2-ARE pathway. Cell Signal 23:883–892

Zhang LS, Shen Q, Lai Y, Park SY, Ou X, Lin D, Jin M, Zhang W (2018) Anti-inflammatory effects of curcumin in microglial cells. Front Pharmacol 9:386

Yuan T, Ma H, Liu W et al (2016) Pomegranates' neuroprotective effects against Alzheimer’s disease are mediated by urolithins, its ellagitannin-gut microbial derived metabolites. ACS Chem Neurosci 7:26–33

Zhang F, Wang H, Wu Q, Lu Y, Nie J, Xie X, Shi J (2013) Resveratrol protects cortical neurons against microglia-mediated neuroinflammation. Phytother Res 27:344–349

Zhang XS, Zhang X, Wu Q et al (2014) Astaxanthin offers neuroprotection and reduces neuroinflammation in experimental subarachnoid hemorrhage. J Surg Res 192:206–213

Zhang L, Previn R, Lu L, Liao RF, Jin Y, Wang RK (2018) Crocin, a natural product attenuates lipopolysaccharide-induced anxiety and depressive-like behaviors through suppressing NF-κB and NLRP3 signaling pathway. Brain Res Bull 142:352–359

Zhang J, Zheng Y, Luo Y, Du Y, Zhang X, Fu J (2019) Curcumin inhibits LPS-induced neuroinflammation by promoting microglial M2 polarization via TREM2/TLR4/NF-κB pathways in BV2 cells. Mol Immunol 116:29–37

Zhao G, Zang SY, Jiang ZH, Chen YY, Ji XH, Lu BF, Wu JH, Qin GW, Guo LH (2011) Postischemic administration of liposome-encapsulated luteolin prevents against ischemia-reperfusion injury in a rat middle cerebral artery occlusion model. J Nutr Biochem 22:929–936

Zhao L, Wang JL, Liu R, Li XX, Li JF, Zhang L (2013) Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer’s disease mouse model. Molecules 18:710–722

Wang J, Tong ML, Zhao B, Zhu G, Xi DH, Yang JP (2020) Parnethiol ameliorates intracerebral hemorrhage-induced brain injury in rats. Phytother Res 34:153–160

Webers A, Heneka MT, Gleeson PA (2020) The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer’s disease. Immunol Cell Biol 98:28–41

Wightman EL, Haskell CF, Forster JS, Veasey RC, Kennedy DO (2012) Epigallocatechin gallate, cerebral blood flow parameters, cognitive performance and mood in healthy humans: a double-blind, placebo-controlled, crossover investigation. Hum Psychopharmacol 27:177–186

Williams P, Sorribas A, Howes MJ (2011) Natural products as a source of Alzheimer’s drug leads. Nat Prod Rep 28:48–77

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:5892–5901
Zhou JM, Gu SS, Mei WH, Zhou J, Wang ZZ, Xiao W (2016) Gink- 
golides and bilobalide protect BV2 microglia cells against OGD/ 
reoxygenation injury by inhibiting TLR2/4 signaling pathways. 
Cell Stress Chaperones 21:1037–1053

Zhu C, Xiong Z, Chen X, Peng F, Hu X, Chen Y, Wang Q (2012) Arte- 
misinin attenuates lipopolysaccharide-stimulated proinflammatory 
responses by inhibiting NF-κB pathway in microglia cells. PLoS 
ONE 7:e35125

Ziegler J, Facchini PJ (2008) Alkaloid biosynthesis: metabolism and traf- 
ficking. Annu Rev Plant Biol 59:735–769

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