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INVITED REVIEW

Curcumin and Apigenin – novel and promising therapeutics against chronic neuroinflammation in Alzheimer's disease

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder, characterized by deposition of amyloid beta, neurofibrillary tangles, astrogliosis and microgliosis, leading to neuronal dysfunction and loss in the brain. Current treatments for Alzheimer's disease primarily focus on enhancement of cholinergic transmission. However, these treatments are only symptomatic, and no disease-modifying drug is available for Alzheimer's disease patients. This review will provide an overview of the proven antioxidant, anti-inflammatory, anti-amyloidogenic, neuroprotective, and cognition-enhancing effects of curcumin and apigenin and discuss the potential of these compounds for Alzheimer's disease prevention and treatment. We suggest that these compounds might delay the onset of Alzheimer's disease or slow down its progression, and they should enter clinical trials as soon as possible.

***Key Words:** Alzheimer's disease; neuroinflammation; anti-inflammatory drugs; plant secondary metabolites; reactive oxygen species*

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Alzheimer's disease – a Global Burden

Alzheimer's disease (AD) is a complex and heterogeneous progressive disorder of the central nervous system (CNS) (Singh and Guthikonda, 1997; Fang et al., 2013). The incidence of AD is about 35 million people worldwide that accounts for 10–15% of people aged 65 or older and 35% of those 85 years and older. With increased expectation of life and aging population, it is estimated that this figure will triple in the next 40 years, resulting in increased health care costs worldwide (Massoud and Gauthier, 2010).

Low Grade, Chronic Neuroinflammation in AD

Neurofibrillary tangles (composed of hyper-phosphorylated tau) and senile plaques (composed of beta-amyloid, Aβ) combined with carbonyl and oxidant stress as well as glucose deficit are the major pathological hallmarks of the disease (Münch et al., 1998). In addition, pro-inflammatory activation of astroglia and microglia has been observed in many neurodegenerative diseases such as Parkinson's disease and AD (Wong et al., 2001a), and even autism-spectrum and obsessive-compulsive disorders (Qian et al., 2010; Kern et al., 2013). AD is also characterized by a cholinergic deficit, thus current treatments for AD primarily focus on enhancement of cholinergic transmission. However, these treatments are only symptomatic, and no disease-modifying drug is available for AD (Rosenblum, 2014). With failure of so many anti-amyloid trials (Castello et al., 2014), alternative therapeutic interventions are more and more aiming to target other features of the neurodegenerative brain. Consequently, targeting AD-associated neuroinflammation with anti-inflammatory compounds and antioxidants has been suggested as a novel, promising disease-modifying treatment for AD (Wong et al., 2001b; Holmquist et al., 2007; Latta et al., 2014).

The inflammatory response in AD is a double-edged sword. At first, it is a self-defence reaction aimed at eliminating harmful stimuli and restoring tissue integrity. However, neuroinflammation becomes harmful when it turns chronic. Analysis of the time-course of neuroinflammation in AD shows that neuroinflammation (measured as number of activated microglia) starts in patients with mild cognitive impairment peaks in moderately affected cases before it declines in the severe cases (Arends et al., 2000). Increased levels of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukine-1 beta (IL-1β) and interleukin-6 (IL-6), prostaglandins and reactive oxygen and nitrogen species are also observed in AD at all stages of the disease (Mrak and Griffin, 2005). Activated microglia can be visualized by protein markers such as ionized calcium binding adaptor molecule 1 (Iba1) and translocator protein 18 kDa (TSPO) (Martin et al., 2010). In one key study, patients with AD, patients with mild cognitive impairment and older control subjects were scanned with the TSPO ligand (11)C-PBR28 ([methyl-(11)

C]N-acetyl-N-(2-methoxybenzyl)-2-phenoxy-5-pyridinamine). Patients with AD had greater (11)C-PBR28 binding in cortical brain regions than controls, and (11)C-PBR28 binding inversely correlated with the patient's performance on a variety of neuropsychological tests (Kreisl et al., 2013).

Amyloid plaques have been identified as a major source of neuroinflammation in AD. In familial (early-onset) cases of AD, plaque formation is linked to mutations in the amyloid precursor protein (APP) or presenilin (PS1 and PS2) genes, which leads to altered proteolysis of APP producing increased higher levels of longer forms of β-amyloid peptide (Aβ) such as $A\beta_{42}$ (Gotz et al., 2011). In sporadic AD, plaque formation is rather caused by impaired clearance than increased production of Aβ. Clearance of Aβ is suggested to be mediated by its transport across the blood-brain barrier by the receptor for advanced glycation end products and efflux *via* the multi-ligand lipoprotein receptor LRP-1 and it is suggested that this process is impaired in sporadic AD patients (Bates et al., 2009; Srikanth et al., 2011). In cerebral interstitial fluid, Aβ aggregates to form oligomers and senile plaques, accelerated by crosslinking through advanced glycationend products (AGEs) (Loske et al., 2000). Plaques are associated with microglial activation and reactive astrocytosis and the release of free radicals and cytokines (Eikelenboom and Veerhuis, 1996; Wong et al., 2001a). Their release could cause multifaceted biochemical and structural changes in surrounding axons, dendrites and neuronal cell bodies. Also, the excessive generation of free radicals can cause oxidative damage to proteins and other macromolecules (Retz et al., 1998). Neuroinflammation also leads to hyperphosphorylation of tau by increased kinase or decreased phosphatase activity and might contribute to the formation of neurofibrillary tangles (Lee et al., 2010).

Genetic and pharmaco-epidemiological studies also suggest the importance of inflammation in AD pathogenesis. Genome-wide association studies have identified three immune-relevant genes that are associated with an increased risk of developing AD, clusterin (CLU), complement receptor 1 (CR1) and triggering receptor expressed on myeloid cells 2 (TREM2) (Patel et al., 2014). Furthermore, though non-steroidal anti-inflammatory drugs (NSAIDs) have an adverse effect in later stages of AD pathogenesis, long-term and pre-symptomatic use of NSAIDs such as naproxen was shown to reduce AD incidence but only after 2 to 3 years (Breitner et al., 2011).

Neuroinflammation as a Therapeutic Target in AD

In recent years, studies have focused on different nutritional approaches to benefit AD patients. More specifically, foods rich in ω-3 fatty acids like docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (found abundantly in marine fish), vitamins, and diverse groups of secondary, polyphenolic plant metabolites have been shown to be effective against several AD pathologies (Stevenson and Hurst, 2007; Kamphuis and Scheltens, 2010; Kim et al., 2010; Willis et al., 2010). In the following sections, we will focus on the progress made with some of the most promising plant secondary metabolites such as curcumin and apigenin.

Curcumin

Source

Curcumin, a diarylheptanoid polyphenol isolated from the rhizomes of *Curcuma longa* L. (Zingiberaceae, common name: turmeric) is a food additive in Indian cuisine and is used in Ayurvedic medicine (Ringman et al., 2005).

Pharmacokinetics

Curcumin penetrates into the CNS and exerts a broad range of anti-inflammatory effects. Considering the low bioavailability of curcumin, various physically redesigned curcumin preparations using nanoparticles, liposomes or inclusion complexes are available in the market (Prasad and Bondy, 2014). Highly bioavailable curcumin preparations, such as "Longvida" (VS Corp) can achieve μM concentrations in the brain (Dadhaniya et al., 2011).

Safety

Curcumin administered as standardized powder extract containing a minimum 95% concentrations of three curcuminoids (curcumin, bisdemethoxycurcumin and demethoxycurcumin) has an excellent safety profile with no toxicity being observed in single doses of up to 12 g per day (Lao et al., 2006).

Mechanistic pathways and cellular studies

Curcumin is known to exhibit various pleiotropic properties, including antioxidant, anti-inflammatory, anti-amyloidogenic, lipophilic and cognition/memory enhancing actions, which suggests a potential neuroprotective nature of this compound (Cole et al., 2007; Mishra and Palanivelu, 2008). Furthermore, curcumin has a broad cytokine-suppressive anti-inflammatory action, it down-regulates the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, IL-1, -2, -6, -8, and -12 (Abe et al., 1999). Curcumin inhibits IL-6 mediated signalling *via* inhibition of IL-6 induced signal transducer and activator of transcription 3 (STAT3) phosphorylation and consequent STAT3 nuclear translocation (Bharti et al., 2003), and interferes with the first signalling steps downstream of the IL-6 receptor in microglial activation (Ray and Lahiri, 2009). It also inhibits lipoxygenase (LOX), COX-2 and iNOS expression leading to decreased levels of prostaglandin E2 (PGE2) and nitric oxide (NO) (Lev-Ari et al., 2006; Menon and Sudheer, 2007). It has an inhibitory effect on TNF-α-induced IL-1, and IL-6 that is most likely mediated through inhibition of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) pathways (Shi et al., 2015). Curcumin also reduces levels of the astrocyte marker glial fibrillary acidic protein (GFAP) in the brain, as well as protein oxidation and reversed increases in blood monocyte chemoattractant protein 1 (MCP-1) (Giri et al., 2003). Also, curcumin has well-established anti-inflammatory effects in various pathologic conditions in humans including

rheumatoid arthritis, gastrointestinal conditions and several forms of cancer (Jurenka, 2009). At last, but not least, curcumin inhibits $A\beta_{40}$ aggregation and prevents $A\beta_{42}$ oligomer formation and toxicity (Yang et al., 2005).

Animal studies

In a study by Lim et al. (2001), curcumin was tested for its ability to inhibit the combined inflammatory and oxidative damage in Tg2576 transgenic mice. In this study, Tg2576 mice aged 10 months old were fed a curcumin diet (160 ppm) for 6 months. Their results showed that the curcumin diet significantly lowered the levels of oxidised proteins, IL-1β, GFAP (a marker of activated astroglia), soluble and insoluble Aβ, and also plaque burden. Following this work, Yang et al. (2005) evaluated the effect of feeding a curcumin diet (500 ppm) in 17-month-old Tg2576 mice for 6 months. When fed to the aged Tg2576 mice with advanced amyloid accumulation, curcumin resulted in reduced soluble amyloid levels and plaque burden. Yang et al. (2005) also demonstrated that when curcumin was injected peripherally (*via* the carotid artery), it could enter the brain and bind amyloid plaques. The ability of curcumin to bind amyloid is thought to be due to its structural similarity to the water-soluble dye Congo red, which is able to stain amyloid plaques. In addition, curcumin has been shown to inhibit $A\beta_{42}$ oligomer formation as well as, or better than Congo red, without any toxic effects (Yang et al., 2005). These data raise the possibility that dietary supplementation with curcumin may provide a potential preventative treatment for AD, by decreasing Aβ levels and plaque load *via* inhibition of Aβ oligomer formation and fibrilisation, along with decreasing oxidative stress and inflammation.

Human studies

In humans, "Longvida" curcumin (400 mg) has been shown to significantly improve working memory and mood after 4 weeks of treatment in a randomized, double-blind, placebo-controlled human trial (Cox et al., 2014).

Apigenin

Source

Apigenin (4′,5,7-trihydroxyflavone) is a flavonoid particularly abundant in the ligulate flowers of the chamomile plant (68% apigenin of total flavanoids) (McKay and Blumberg, 2006) and found in lesser concentrations in other sources such as celery, parsley, grapefruit (Shukla and Gupta, 2010).

Pharmacokinetics

Apigenin crosses the brain-blood-barrier, and concentrations in rats reached 1.2 μM after daily intraperitoneal administration of 20 mg/kg of apigenin potassium salt (which was solubilized in water and stored frozen until use) for 1 week (Popovic et al., 2014).

Safety

Apigenin is considered very safe and even at high doses no toxicity was observed. However, apigenin may induce muscle relaxation and sedation at high doses (Viola et al., 1995; Ross and Kasum, 2002).

Mechanistic pathways and cellular studies

Extensive studies have shown that apigenin has potent antioxidant, anti-inflammatory, and anti-carcinogenic properties (Panes et al., 1996; Gupta et al., 2001). Apigenin has been shown to have inhibitory effects *in vitro* on the release of several pro-inflammatory mediators in lipopolysaccharide (LPS)-induced settings of murine cell lines. Apigenin strongly inhibited levels of IL-6 in mouse macrophages (Smolinski and Pestka, 2003) and suppressed CD40, TFN-α and IL-6 production *via* inhibition of interferon gamma (IFN-γ)-induced phosphorylation of STAT1 in murine microglia (Rezai-Zadeh et al., 2008). Evidence of its anti-inflammatory properties is also exemplified in studies that show dose-dependent suppression of the inflammatory mediators NO and prostaglandin, through inhibition of iNOS and COX-2 in both microglial and macrophage mouse cells (Liang et al., 1999). Furthermore, apigenin conferred protection against $A\beta_{25–35}$-induced toxicity in rat cerebral microvascular endothelial cells (Zhao et al., 2011). In human monocytes and mouse macrophages, apigenin has been shown to attenuate the release of inflammatory cytokines by inactivation of NF-κB, mediated by suppression of LPS-induced phosphorylation of the p65 subunit (Nicholas et al., 2007). Other effects reported for apigenin include decreasing expression of adhesion molecules (Panes et al., 1996) and its well-known defensive properties against oxidative stress, such as free radical scavenging and increasing intracellular glutathione concentrations (Myhrstad et al., 2002; Shukla and Gupta, 2010). Apigenin is reported to exert many of its effects through interactions with the signaling molecules in the 3 major MAPK pathways (extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK) and p38) in both murine and human cell culture models (Yin et al., 1999; Ha et al., 2008).

Animal studies

There are very few studies on apigenin in AD animal models. One recent study by Zhao et al. (2013) tested the neuroprotective effects of apigenin in the APP/PS1 double transgenic AD mouse model. Four month-old mice were orally treated with apigenin (40 mg/kg) for 3 months. Their results showed that apigenin-treated mice displayed improvements in memory and learning deficits, and a reduction of fibrillar amyloid deposits with lowered insoluble Aβ concentrations, mediated by a decrease in β-C-terminal fragment (β-CTF) and β-site AβPP-cleaving enzyme 1 (BACE1). Additionally, the apigenin-treated mice showed restoration of the cortical ERK/cAMP response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) pathway involved in learning and memory typically affected in AD pathology. Enhanced activities of superoxide dismutase and glutathione peroxidase were also observed and increased superoxide anion scavenging (Zhao et al., 2013). Similarly, in another study, $A\beta_{25–35}$-induced amnesia mouse models were treated

with apigenin (20 mg/kg), resulting in improvements in spatial learning and memory, in addition to neurovascular protective effects (Liu et al., 2011). Other *in vivo* studies with non-AD-related animal models report significant reductions in LPS-induced IL-6 and TFN-α production in apigenin pre-treated mice (50 mg/kg) (Smolinski and Pestka, 2003). Another study indicated neuroprotective effects in apigenin pre-treated mice (10–20 mg/kg) subjected to contusive spinal cord injury, including reduction in IL-1β, TFN-α, intercellular cell adhesion molecule-1 (ICAM-1) and caspase-3, with an increase in Bcl-2/Bax ratio (Zhang et al., 2014).

Human studies

Based on the published literature, no studies in humans have been conducted with apigenin with respect to inflammation or cognitive performance.

Conclusion

Based on the results emerging from cell culture, animal and human studies, we conclude that both curcumin and apigenin are exceptional candidates for an anti-inflammatory therapy against AD and other related degenerative disorders, ready to enter clinical trials within a short time frame.

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