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EDITORIAL

The Current Evidence for the Therapeutic Role of Curcumin in Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder, accounting for approximately 60-80% of all dementia cases, with an estimated 24 million patients worldwide [1]. The disease affects cognitive function, resulting in memory, language, and behavioral deficits and an inability to perform basic daily activities [1]. Although the exact mechanism surrounding the development of AD is not well understood, one major hypothesis is that neuronal loss is subsequent to neuroinflammation, following deposition of amyloid-β (Aβ) plaques and the generation of neurofibrillary tangles (which is a result of abnormal tau protein phosphorylation) [2]. Aβ plaques are created following the cleavage of amyloid precursor protein (APP) by β- and γ-secretases into insoluble Aβ peptides. The aggregates of Aβ have multiple neurotoxic mechanisms including binding to Ca^{2+} channels (which increases intracellular Ca^{2+} levels and induces excitotoxicity apoptosis), producing oxidative stress (*via* increasing levels of reactive oxygen species) and initiating the formation of neurofibrillary tangles (which produce neuronal death due to a communication disruption between neurons) [3]. Currently, the only approved drugs for the treatment of AD are used for symptomatic relief and do not prevent disease progression [4]. These drugs mainly inhibit the acetylcholinesterase enzyme, preventing the breakdown of acetylcholine at the synapse, and allowing more cholinergic neurotransmission. Another drug target is the NMDA receptor, which when antagonised, results in a decrease in the Ca^{2+} influx, thereby reducing excitotoxicity [4]. As the available drugs only aid in reducing the symptoms of the disease, treatments targeting the pathogenesis, and hence, preventing the progression of the disease, need to be explored. One route of investigation has focused on antibody treatments aimed at degrading Aβ plaques [5]. Another strategy involves the screening of known bioactive compounds in models of AD.

Curcumin is a bioactive phytochemical from turmeric and is thought to hold pleiotropic activities such as anti-inflammatory, anti-apoptotic and anti-oxidant effects [6-8]. It is currently being examined for the treatment of several diseases, including AD [9]. Curcumin has been reported to reduce neuroinflammation, oxidative stress and Aβ aggregation, preventing neurotoxicity in models of AD [9]. Of the mechanisms explored, the prevention of Aβ plaques is promising due to this being the major hypothesis in the development and progression of AD. Yang *et al*. (2005) reported that Tg2576 mice (a highly relevant mouse model with age-related cognitive deficits), aged 17 months, treated with 500 ppm of curcumin for 5 months had significant 32.5% and 85% reductions in the plaque burden and insoluble Aβ levels, respectively, compared to control mice [10]. It is thought that this effect is due to an inhibition of the β-amyloid precursor protein cleaving enzyme (BACE-1), which is the first enzyme involved in the cleavage of APP to Aβ. Using a *Drosophila melanogaster* model (which overexpressed BACE-1), Wang *et al*. (2014) demonstrated that demethoxycurcumin had a strong inhibition on BACE-1 with an IC_{50} of 17 μM [11]. Further analysis into this mechanism revealed that curcumin activates the Wnt/β catenin pathway, which inhibits the transcription of BACE-1 *via* T-cell factor-4 [12]. Curcumin has also been shown to reduce oxidative stress in preclinical models of AD. Rats with streptozotocin-induced dementia and orally treated with curcumin (10, 20 or 50 mg/kg) for 21 days had a dose-dependent reduction in the

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levels of MDA (a marker of oxidative stress), which also correlated to a dose-dependent increase in GSH (free radical scavenger) within the brain [13]. Therefore, there is a large amount of preclinical evidence suggesting that curcumin may aid in preventing disease progression in AD.

Curcumin for use in AD has also been examined in clinical trials. However, results to date have been mixed. Cox *et al*. (2015) reported that a lipid formulation containing 80 mg of curcumin had a significant positive effect on memory and sustained attention in healthy adults aged 65-80 years [14]. Conflicting data were published by Baum *et al*. (2008), who found that both 1 and 2 g of curcumin, administered for 6 months, did not affect mini-mental state examination scores in adults aged over 50 with AD and cognitive decline. However, although not significant curcumin increased the serum Aβ levels, indicating that curcumin may prevent Aβ aggregation [15]. Small *et al*. (2018) also reported a significant reduction in amyloid and tau accumulation in the amygdala, with significant improvements in memory and attention being observed in healthy adults (aged between 51 and 84 years) with curcumin treatment (90 mg, twice daily for 18 months) [16]. Curcumin has also been shown to enhance Aβ clearance by macrophages in AD patients [17, 18]. Zhang L. *et al*. (2006) isolated macrophages from AD patients and reported that macrophages following curcumin treatment resulted in a significantly greater Aβ uptake and co-localisation of Aβ with the intracellular component, phalloidin, when compared to control macrophages [17]. The authors also demonstrated that macrophages isolated from AD patients had a significantly lower uptake of Aβ compared to macrophages isolated from healthy patients [14]. This effect was confirmed by Masoumi *et al*. (2009), who reported that curcuminoids provided additivity with 1α,25-dihydroxyvitamin D_3 and provided greater Aβ phagocytosis and clearance with macrophages from AD patients [18]. Although the clinical trial data is conflicting on if curcumin significantly improves cognitive decline, there is evidence that it can prevent Aβ aggregation and increase uptake and clearance. If curcumin can provide these effects in AD patients, this drug could prevent disease progression, something that is currently lacking with our current therapeutics. More clinical trials comparing early and late-stage AD patients are needed to confirm this effect and determine the therapeutic value of curcumin in AD. Finally, it remains to be clarified if any pharmacological effect of curcumin in improving cognitive deficits in AD could be augmented by utilising novel drug delivery systems, which have been recently shown to enhance the oral bioavailability of curcumin in humans.

CONFLICT OF INTEREST

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