Curcumin and Alzheimer's Disease

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Curcumin has a long history of use as a traditional remedy and food in Asia. Many studies have reported that curcumin has various beneficial properties, such as antioxidant, antiinflammatory, and antitumor. Because of the reported effects of curcumin on tumors, many clinical trials have been performed to elucidate curcumin's effects on cancers. Recent reports have suggested therapeutic potential of curcumin in the pathophysiology of Alzheimer's disease (AD). In *in vitro* studies, curcumin has been reported to inhibit amyloid- β -protein (A β) aggregation, and A β -induced inflammation, as well as the activities of β -secretase and acetylcholinesterase. In *in vivo* studies, oral administration of curcumin has resulted in the inhibition of A β deposition, A β oligomerization, and tau phosphorylation in the brains of AD animal models, and improvements in behavioral impairment in animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies. At present, four clinical trials concerning the effects of curcumin on AD has been conducted. Two of them that were performed in China and USA have been reported no significant differences in changes in cognitive function between placebo and curcumin groups, and no results have been reported from two other clinical studies. Additional trials are necessary to determine the clinical usefulness of curcumin in the prevention and treatment of AD.

Introduction

Curcuma longa is a member of the ginger family and is indigenous to South and Southeast Asia; turmeric is derived from the rhizome of this plant. Turmeric has a long history of use in traditional medicines in China and India [1], where it is also used as a curry spice in foods. Curcuminoids are the active components responsible for the majority of the medicinal properties of turmeric, and they consist of a mixture of curcumin (75–80%), demethoxycurcumin (15–20%), and bisdemethoxycurcumin (3–5%) (Figure 1) [2], which is available commercially [3] (e.g. Wako Pure Chemical Industries, Ltd, Japan). Much of evidences supporting the beneficial properties of curcumin has been reported, including antiinflammatory, antioxidant, chemopreventive, and chemotherapeutic properties [1]. Part of cur-

cumin's nonsteroidal antiinflammatory drug-like activity is based on the inhibition of nuclear factor κ B (NF κ B)-mediated transcription of inflammatory cytokines [4], inducible nitric oxide synthase [5], and cyclooxygenase 2 (Cox-2) [6]. Many studies concerning the antitumor activity of curcumin have been conducted, and the clinical benefits of curcumin against tumors are being actively investigated, although clinical trials are still in a relatively early phase [1]. Curry consumption in old age has been recently reported to be associated with better cognitive functions [7]. Furthermore, some reports have suggested possible beneficial effects of curcumin on the experimental models of Alzheimer's disease (AD) [8–13]. On the basis of these results, four clinical trials have been initiated [1,14,15].

In this review, recent studies concerning the effects of curcumin on the pathophysiology of AD are summarized

Figure 1 Chemical structures of curcumin (A), demethoxycurcumin (B), and bisdemethoxycurcumin (C).

with a focus on potential candidate compounds suitable for use in the development of preventive and therapeutic agents for AD.

Amyloid β is a Key Molecule of Alzheimer's Disease

AD is a progressive neurodegenerative disorder characterized by the deterioration of cognitive functions and behavioral changes [16]. Senile plaques, neurofibrillary tangles, and extensive neuronal loss are the main histological hallmarks observed in AD brains. Main disease mechanism-based approaches are dependent on the involvement of two proteins; amyloid- β -protein ($A\beta$) and tau. $A\beta$ is the main constituent of senile plaques and tau is the main component of neurofibrillary tangles.

High levels of fibrillary $A\beta$ are deposited in the AD brain that is associated with loss of synapses and neurons and impairment of neuronal functions [17–20]. $A\beta$ was sequenced from the meningeal vessels and senile plaques of AD patients and individuals with Down's syndrome [21–23]. Subsequent cloning of the gene encoding the β -amyloid precursor protein (APP) and its localization to chromosome 21 [24–27], coupled with the earlier recognition that trisomy 21 (Down's syndrome) invariably leads to the neuropathology of AD [28], set the stage for the proposal that $A\beta$ accumulation is the primary event in AD pathogenesis. In addition, certain mu-

tations associated with familial AD and hereditary cerebral hemorrhage with amyloidosis have been identified within or near the $A\beta$ region of the coding sequence of the APP gene [29–33], and these mutations cluster at or very near to the sites within APP that are normally cleaved by proteases called α -, β -, and γ -secretases (Figure 2) [34]. Furthermore, other genes implicated in familial AD include presenilin-1 (PS1) and presenilin-2 (PS2) [35–37], which alter APP metabolism through a direct effect on γ -secretase [38,39]. These facts support the notion that aberrant APP metabolism is a key feature of AD.

Mutations in the gene encoding the tau protein cause frontotemporal dementia with parkinsonism, which is characterized by severe tau deposition in neurofibrillary tangles in the brain, but no $A\beta$ deposition [40, 41]. Thus, genetic and pathological evidence strongly supports the notion that the $A\beta$ accumulation in the brain is the first pathological event leading to AD (amyloid cascade hypothesis; Figure 3), and neurofibrillary tangles observed in AD brains are likely to have been deposited after changes in $A\beta$ metabolism and initial plaque formation [42].

$A\beta$ deposited in the brain consists of two major species, $A\beta_{40}$ and $A\beta_{42}$, which differ depending on whether the C terminus of $A\beta$ ends at the 40th or 42nd amino acid, respectively (Figure 2) [43–45]. In the brains of AD patients, $A\beta_{42}$ is the predominant species deposited in the brain parenchyma [46]. In contrast, $A\beta_{40}$ appears to be

Figure 2 Diagram of APP and of its principal metabolic derivative, amyloid β ($A\beta$). $A\beta$ is generated from APP by two proteases (β -secretase and γ -secretase), whereas a third protease, α -secretase, competes with β -secretase for the APP substrate.

Figure 3 The amyloid cascade hypothesis. This hypothesis proposes a series of pathogenic events leading to AD. Cerebral amyloid β ($A\beta$) accumulation is the primary factor in AD, and the rest of the disease process results from an imbalance between $A\beta$ production, accumulation, and $A\beta$ clearance.

the predominant species deposited in the cerebral vasculature (cerebral amyloid angiopathy; CAA) [43]. There is a strong correlation between $A\beta$ 40 and mature senile plaques [43]. In the brains of Down's syndrome patients, $A\beta$ 42 can form numerous diffuse plaques as early as at the age of 12 years, whereas $A\beta$ 40 is first detected in plaques almost 20 years later [47]. Further experimental studies indicate that $A\beta$ 42 aggregates more easily than $A\beta$ 40 [48], and $A\beta$ 42 is essential for amyloid deposition in the parenchyma and vasculature [49].

In Vitro Studies with Curcumin

Anti- $A\beta$ Aggregation Effect

Inhibition of $A\beta$ aggregation, especially $A\beta$ 42, in the brain (anti-amyloidogenic therapy) is the primary strategy for the development of AD therapies and is currently the most active area of investigation. Furthermore, it has been reported that $A\beta$ fibrils are not the only toxic form of $A\beta$ implicated in the development of AD. Smaller species of aggregated $A\beta$, known as $A\beta$ oligomers, may

1) Nucleation foramtion phase

2) Extension phase (first order kinetic model)

Figure 4 A nucleation-dependent polymerization model [54,55]. This model consists of two phases; (1) nucleation phase and (2) extension phase. Nucleus formation requires a series of association steps of monomers representing the rate-limiting step in amyloid fibril formation. Once the nucleus has been formed, further addition of monomers becomes thermodynamically favorable, resulting in rapid extension of amyloid fibrils *in vitro*.

represent the primary toxic species in AD [34,50–53]. Some studies have been reported about the anti-Aβ aggregation effect of curcumin *in vitro*.

Over the past decade, various compounds have been demonstrated to interfere with Aβ aggregation in an *in vitro* model, a nucleation-dependent polymerization model (Figure 4), which is thought to represent the mechanism of Aβ aggregation that leads to the formation of Aβ fibrils [54,55]. The formation of Aβ oligomers would also be consistent with this model [56,57]. We used this system to investigate anti-Aβ aggregation effects [12,58,59]. In our study, curcumin dose-dependently inhibited the formation of Aβ fibrils from Aβ40 and Aβ42 and their extensions, as well as destabilized preformed Aβ fibrils ($EC_{50} = 0.19\text{--}0.63\ \mu\text{M}$) (Figures 5 and 6) [12]. Similarly, the other group reported that curcumin inhibited Aβ40 aggregation, disaggregated fibrillar Aβ40, and prevented Aβ42 oligomer formation and toxicity at concentrations between 0.1 and 1.0 μM [13]. Furthermore, in the other group, curcumin had the strongest inhibitory effect on Aβ fibril formation of 214 compounds tested in an *in vitro* assay ($IC_{50} = 0.25\ \mu\text{g/mL} = 0.679\ \mu\text{M}$) among 214 tested compounds [60]. However, the other group reported that curcumin inhibited Aβ oligomerization ($IC_{50} = 361.11 \pm 38.91\ \mu\text{M}$) but did not inhibit fibrilization *in vitro* at concentrations between 30 and 300 μM [61]. One possible explanation for the discrepancy between these results may be attributed to the differences of

curcumin concentration, because small molecules might have concentration-dependent multiphasic behavior on modulating protein aggregation [61]. Additional studies are required to investigate the precise activity of curcumin on Aβ aggregation.

Antioxidative Effect

The evidences to support a role of oxidative stress in AD with increased levels of lipid peroxidation, DNA and protein oxidation products (4-hydroxy-2-nonenal, 8-HO-guanidine, and protein carbonyls, respectively) are increasing [62]. Aβ can efficiently generate reactive oxygen species in the presence of the transition metals copper and iron, and will form stable dityrosine cross-linked dimers, which are generated from free radical attack under oxidative condition [62]. Alanine-2 carbonyl is an oxygen ligand in Cu^{2+} coordination of Aβ, which may explain the presence of N-terminally truncated Aβ3-40/42 and the cyclized pyroglutamate Aβ3-40/42 species in both diffuse and cored AD plaques [63]. Because Aβ-induced oxidative stress in neuronal cells may be a cause of AD pathology, one of the pharmacological approaches for AD is antioxidant therapy [64–66]. Therefore, the natural oxidant curcumin has been investigated as a potential compound for the prevention and cure of AD. Curcumin has been reported to protect PC12 (ED_{50} values = $7.1\ \mu\text{g/mL} = 19.3\ \mu\text{M}$) and human umbilical vein endothelial cells (ED_{50} values = $6.8\ \mu\text{g/mL} = 18.5\ \mu\text{M}$) from Aβ42 insult because of its strong antioxidant properties, as measured by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide reduction assay [10]. Furthermore, pretreatment of PC12 cells with 10 $\mu\text{g/mL}$ ($= 27.5\ \mu\text{M}$) curcumin reduced Aβ(25–35) induced increases in the level of antioxidant enzyme, DNA damage and attenuated the elevation of intracellular calcium levels and tau hyperphosphorylation induced by Aβ(25–35) [67].

Inhibition of β-secretase

One of the key steps in Aβ generation is cleavage of APP by β-secretase, β-site APP-cleaving enzyme 1 (BACE-1). In a neuronal cell culture study, 3–30 μM of curcumin suppressed Aβ-induced BACE-1 upregulation [68]. Furthermore, 1–30 μM curcumin attenuated the production of Aβ-induced radical oxygen species, and 20 μM curcumin prevented structural changes in Aβ toward β-sheet-rich secondary structures [68]. In another study, 20 μM curcumin almost completely suppressed the up-expression of APP and BACE-1 mRNA levels, which was increased by copper or manganese ions

Figure 5 Effects of curcumin on the kinetics of amyloid β (A β) fibril formation from fresh A β 40 (A) and A β 42 (B), of the extension of A β 40 fibrils (C) and A β 42 fibrils (D), and of the destabilization of A β 40 fibrils (E) and A β 42 fibrils (F) [12]. Reaction mixtures containing 50 μ M A β 40 (A), 25 μ M A β 42 (B), 2.3 μ M sonicated A β 40 fibrils and 50 μ M A β 40 (C), 2.3 μ M sonicated A β 42 fibrils and 50 μ M A β 42 (D), 25 μ M A β 40 fibrils (E), or 25 μ M A β 42 fibrils (F), 50 mM phosphate buffer (pH 7.5), 100 mM NaCl, and 0 (filled circles), 10 (open circles), or 50 μ M (open squares) curcumin were incubated at 37 $^{\circ}$ C for the indicated time. Curcumin dose-dependently inhibited the formation of A β fibrils from A β 40 and A β 42 and their extensions, as well as destabilized preformed A β fibrils.

(50–100 μ M) in a time- and concentration-dependent pattern [69].

Inhibition of Acetylcholinesterase Activity

Although various new therapeutic approaches for AD have been reported, acetylcholinesterase (AChE) inhibitors remain the major class of drugs approved for AD, providing symptomatic relief [70]. Curcumin inhibited AChE in the *in vitro* assay, with an IC₅₀ value of

67.69 μ M, but curcumin had no significant effect in the *ex vivo* AChE assay [71].

Inhibition of A β -induced Inflammation

Some studies have shown that inflammation plays a role in AD pathogenesis [72,73], and therapy with anti-inflammatory drugs, such as nonsteroidal antiinflammatory drugs, reduces the incidence and progression of AD [74]. A study using PBM and THP-1 cells reported that curcumin (12.5–25 μ M) suppressed early growth

Figure 6 Electron micrographs of extended (A, B, C) and destabilized (D, E, F) A β (1–40) fibrils [12]. Reaction mixtures containing 10 mg/mL (2.3 μ M) A β (1–40) fibrils, 50 μ M A β (1–40), 50 mM Phosphate buffer, pH 7.5, 100 mM NaCl, and 0 (B) or 50 μ M curcumin (A, C), were incubated at 37°C for 0 (A), or 6 h (B, C), and 25 μ M A β (1–40) fibrils, 50 mM phosphate buffer, pH 7.5, 100 mM NaCl, and 50 μ M curcumin was incubated at 37 °C for 0 (D), 1 (E), or 4 h (F). Scale bars = 250 nm.

response-1 (Egr-1) activation, which increased the expression of cytokines (TNF- α and IL-1 β) and chemokines (MIP-1 β , MCP-1, and IL-8) in monocytes by the interaction of A β 1-40 or fibrillar A β 1-42 [75] and reduced the expression of these cytokines and chemokines [75]. The inhibition of Egr-1 by curcumin may represent a potential therapeutic approach for AD.

In a majority of AD patients, macrophages do not transport A β into endosomes and lysosomes, and AD monocytes do not effectively clear A β from the sections of the AD brain, although they do phagocytize bacteria [76]. Defective phagocytosis of A β may be related to the down-regulation of β -1,4-mannosyl-glycoprotein 4- β -N-acetylglucosaminyltransferase (MGAT3), as suggested by the inhibition of phagocytosis by MGAT3 siRNA and correlation analysis [76]. Transcription of Toll-like receptor (TLR)-3, bditTLR4, TLR5, bditTLR7, TLR8, TLR9, and TLR10 is severely depressed in mononuclear cells of AD patients on A β stimulation in comparison with those of control subjects [76]. The curcuminoid compound bisdemethoxycurcumin may enhance defective phagocytosis of A β , the transcription of MGAT3 and TLRs, and the

translation of TLR2-4 [76]. These results suggest that bisdemethoxycurcumin may correct immune defects in AD patients and provide an immunotherapeutic approach for AD [76].

***In Vivo* Studies with Curcumin**

Curcumin has been remarkably well investigated, but its bioavailability is poor. In rats, only negligible amounts were detected in the blood and urine after oral administration (1 g/kg [2.7 mmol/kg] body weight), and 75% of the amount detected was recovered in the feces [77]. High doses of curcumin (400 mg [1.09 mmol], or 3.6 mmol/kg body weight) are required to obtain detectable tissue levels in rats [77]. This is attributed to extensive metabolism of the compound in the gastrointestinal wall, glucuronidation in the liver, and enterohepatic circulation [77]. In a study using liquid chromatography technique coupled with tandem mass spectrometry, the maximum concentration ($C_{\max}$) and the time to reach maximum concentration ($T_{\max}$) of plasma curcumin in

rat were $0.06 \pm 0.01 \mu\text{g/mL}$ ($0.16 \pm 0.03 \mu\text{M}$) and 41.7 ± 5.4 min after curcumin (500 mg/kg) administration orally [78]. The elimination half-life ($t_{1/2,\beta}$) were 28.1 ± 5.6 and 44.5 ± 7.5 min for curcumin administration orally (500 mg/kg [1.36 mmol/kg]) and intravenously (10 mg/kg [0.03 mmol/kg]) [78]. There are few reports on central nervous system penetration of curcumin [77]; however, it has been reported that curcumin crosses the blood–brain barrier and labels senile plaques and CAA in AD model mice using *in vivo* multiphoton microscopy [9].

In Tg2576 AD model mice, which express a 695-aa residue splice form of human APP modified by the Swedish FAD double mutation K670N-M671L [79], curcumin has been shown to suppress indices of inflammation and oxidative damage in the brain, and a low dose (160 ppm [0.43 $\mu\text{mol/g}$]) of curcumin orally administered for 6 months decreased the levels of insoluble and soluble A β and plaque burden in many affected brain regions; however, a high dose (5000 ppm [13.6 $\mu\text{mol/g}$]) did not change A β levels [11]. Lim *et al.* speculated that mechanisms underlying inhibition of A β deposition are mainly based on the inflammation-related targets such as inhibition of NF κ B-induced inducible nitric oxide synthase, Cox-2, and inflammatory cytokine production [11]. In a study that used Sprague-Dawley rats which infused both A β 40 and A β 42 to induce neurodegeneration and A β deposits, dietary curcumin (2000 ppm [5.43 $\mu\text{mol/g}$]) suppressed A β -induced oxidative damage and synaptophysin loss, but increased microglial labeling within and adjacent to A β deposits [80]. Low doses of dietary curcumin (500 ppm [1.36 $\mu\text{mol/g}$]) prevented A β -infusion-induced spatial memory deficits in the Morris water maze and loss of postsynaptic density-95 (PSD-95) and reduced A β deposits [80]. PSD-95 is a post-synaptic marker that plays a key role in synaptic transmission by anchoring NMDA receptors, and a PSD-95 loss could be related to spatial memory deficits because mice lacking PSD-95 have severe spatial memory deficits [81]. Another study conducted in Tg2576 mice showed that curcumin inhibits the formation of A β oligomers and fibrils, binds to plaque, and reduces plaque burden [13]. In a study using *in vivo* multiphoton microscopy [9], curcumin (7.5 mg/kg/day [0.02 mmol/kg/day]) administered for 7 days intravenously in a tail vein crossed the blood–brain barrier and labeled senile plaques and CAA and cleared and reduced existing plaques in APP-swe/PS1dE9 mice, which generated with mutant transgenes for APP (APP^{swe}: KM594/5NL) and PS1 (dE9: deletion of exon 9) [82]. In another study conducted in Tg2576 mice, 500 ppm (1.36 $\mu\text{mol/g}$) curcumin administered orally for 4 months reduced amyloid plaque burden and insoluble A β [8].

In our recent study using Tg2576 mice [83], oral administration of 5000 ppm (13.6 $\mu\text{mol/g}$) curcumin did not reduce A β deposition in the brain, as reported in a previous study [11]. However, the level of TBS-soluble A β monomers in the brain increased ($P < 0.01$), whereas that of oligomers, as probed with the A11 antibody, which recognizes a significant and important class of oligomers associated with AD pathogenesis, decreased ($P < 0.001$) [83]. One possible explanation is that curcumin inhibits the pathway from A β monomers to A β oligomers, but accelerates the pathway from A β oligomers to A β deposition; this explanation is supported by other *in vitro* findings, which report that curcumin inhibits oligomerization and not fibrillization [61].

Concerning tau pathology, oral administration of 500 ppm (1.36 $\mu\text{mol/g}$) curcumin reduced phosphorylated tau in the detergent lysis buffer-extracted hippocampal membrane pellet fractions [84] using 3xTg-AD transgenic mice which harbored PS1^{M146V}, APP^{Swe}, and tau_{P301} transgenes [85]. Furthermore, curcumin also reduced phosphorylated c-Jun N-terminal kinase (JNK) and insulin receptor substrate-1 (IRS-1), which are phosphorylated in the animal model of AD brain [84]. This was accompanied by an improvement of behavioral deficits in Y-maze performance [84]. These data indicated the potential use of curcumin for the treatment of tau pathology in AD patients.

The summary of these *in vivo* studies of curcumin for AD showed in Table 1.

Human Studies with Curcumin

Safety Studies

In patients with cancer or pre-cancerous lesions, some safety and pharmacokinetic studies of curcumin have been reported. A prospective phase I trial of curcumin in patients with high risk or premalignant lesions was performed in Taiwan [86]. A total of 25 patients were enrolled, and curcumin was taken orally at dosages ranging from 500 to 8000 mg/day (1.36–21.7 mmol/day) for 3 months [86], and no toxicity was observed at any dose [86]. Serum concentrations of curcumin usually peaked 1–2 h after the oral intake of curcumin and gradually declined within 12 h, and average peak serum concentrations ranged from $0.51 \pm 0.11 \mu\text{M}$ at 4000 mg/day (10.9 mmol/day) to $1.77 \pm 1.87 \mu\text{M}$ at 8000 mg/day (21.7 mmol/day) [86]. A dose-escalation study in healthy subjects was conducted in the United States [87]. Twenty-four healthy volunteers were administered a single dose of curcumin ranging from 500 to 12,000 mg (1.36–32.6 mmol) [87]. Seven of the 24 subjects (30%) experienced only minimal toxicity

Table 1 Summary of the *in vivo* studies of curcumin for Alzheimer's disease

Author	Model animal	Dose and duration of curcumin	Neuropathological and biochemical investigation	Behavioral investigation
Lim et al. [11]	Tg2576	160 ppm (0.43 μ mol/g) administered orally for 6 months	Insoluble A β , soluble A β and A β plaque burden were significantly decreased. Oxidized proteins and proinflammatory cytokine (IL-1 β) in the brain were lowered.	N.D.
		5000 ppm (13.6 μ mol/g) administered orally for 6 months	Insoluble A β , soluble A β and A β plaque burden were unchanged. Oxidized proteins and proinflammatory cytokine (IL-1 β) in the brain were lowered.	N.D.
Frautschy et al. [80]	Sprague-Dawley rats	500 ppm (1.36 μ mol/g) administered orally for 2 months	A β deposition were reduced and loss of PSD-95 were prevented.	A β -infusion induced spatial memory deficits in the Morris Water Maze were prevented
		2000 ppm (5.43 μ mol/g) administered orally for 3 months	Oxidative damage and synaptophysin loss were significantly suppressed.	N.D.
Yang et al. [13]	Tg2576	500 ppm (1.36 μ mol/g) administered orally for 5 months	Reduced amyloid levels and A β plaque burden	N.D.
Garcia-Alloza et al. [9]	APPswe/PS1dE9	7.5 mg/kg/day (0.02 mmol/kg/day) administered for 7 days intravenously in a tail vein	Crossed the blood–brain barrier and labeled senile plaques and cerebral amyloid angiopathy and cleared and reduced existing plaques	N.D.
Begum et al. [8]	Tg2576	500 ppm (1.36 μ mol/g) curcumin administered orally for 4 months	Reduced amyloid plaque burden and insoluble A β	N.D.
Ma et al. [84]	3xTg-AD	500 ppm (1.36 μ mol/g) curcumin administered orally for 4 months	Reduced phosphorylated tau in the detergent lysis buffer-extracted hippocampal membrane pellet fractions	Improvement in Y-maze performance.
Ours [83]	Tg2576	5000 ppm (13.6 μ mol/g) administered orally for 10 months	A β deposition in the brain were not reduced, TBS-soluble A β monomers in the brain were increased, and A11-positive oligomers were decreased	N.D.

N.D., not described.

(diarrhoea, headache, rash, and yellow stool), which was not dose-related [87]. Low levels of curcumin (29.7–57.6 ng/mL [0.0806–0.156 μ M]) were detected only in two subjects administered 10,000 or 12,000 mg (27.1 or 32.6 mmol) over 1–4 h after administration [87]. These studies showed that curcumin can be administered safely to patients at a single dose of 12,000 mg (32.6 mmol) and at dosages of up to 8000 mg/day (21.7 mmol/day) for 3 months [87].

Many clinical trials to study the effects of curcumin on cancer have been performed and few adverse ef-

fects have been reported [1]. However, some studies reported that curcumin might exhibit carcinogenic potential through oxidative DNA damage *in vitro* [88–90] and *in vivo* [91–94], and this adverse effect needs to be carefully monitored in future studies.

Clinical Trials with Curcumin for AD

Currently, 4 clinical trials concerning the effects of curcumin on AD has been conducted (<http://clinicaltrials.gov/ct2/results?term=alzheimer+and+curcumin>), and 2

Table 2 Current status of the clinical studies of curcumin for AD

Title	Study design	Place	Dose of curcumin	Other drugs	Duration of the experiment	Patients	Current status
A pilot study of curcumin and ginkgo for treating AD [14].	Treatment, randomized, double-blind, placebo control	Hong Kong, China	1 g/day, 4 g/day	All patients also received 120 mg/day standardized ginkgo leaf extract	6 months	Possible or probable AD	Completed
A Phase II, double-blind, placebo-controlled study of the safety and tolerability of two doses of curcumin C3 complex versus placebo in patients with mild to moderate AD [15].	Treatment, randomized, double-blind, placebo control	California, USA	2 g/day, 4 g/day	No	24 weeks	Probable AD	Completed
Phase II study of curcumin formulation (Longvida) or Placebo on Plasma Biomarkers and Mental State in moderate to severe AD or Normal cognition	Treatment, randomized, double-blind, placebo control	Maharashtra, India	2 g/day, 3 g/day	No	60 days	Probable AD	Recruiting
Early intervention in mild cognitive impairment (MCI) with curcumin + bioperine	Diagnostic, Open label	Louisiana, USA	5.4 g of curcumin + bioperine/day		24 months	MCI	Active, not recruiting

of them have been completed and another 2 studies are still active (Table 2). A study of the results of these studies has been published [14], and one study has been reported in the abstract of the conference [15]. In a clinical trial in China, 34 patients with probable or possible AD randomized to 4 (10.9 mmol), 1 (2.7 mmol) (plus 3 g placebo), or 0 g curcumin (plus 4 g placebo) once daily showed no significant differences in changes in Mini-Mental State Examination scores or plasma A β 40 levels between 0 and 6 months [14]. Curcumin appeared to cause no side effects in AD patients in this study [14]. It is necessary to observe these patients for a longer duration. A 24-week, randomized, double-blinded, placebo-controlled study on the effects of two dosages of curcumin (2000 and 4000 mg/day [5.43 and 10.9 mmol/day]) in patients with mild-to-moderate AD was performed in the United States [15,77]. Cognitive examinations are being performed and plasma and cerebrospinal fluid (CSF) samples are being collected at baseline and at 24 week [15]. A β 40 and A β 42 are being measured in plasma and CSF, and total tau and p-tau 181 are being measured in CSF

[15]. Till July 2008, 11 subjects who received placebo, 9 who received 2 gm (5.43 mmol/day), and 10 who received 4 gm (10.9 mmol/day) of curcumin completed the study [15]; no significant differences in cognitive function or in plasma or CSF biomarkers were observed between placebo and curcumin groups, and no adverse events were reported [15]. It is premature to give the conclusion of the effect of the curcumin for AD in these clinical studies, and additional analyses using data from a larger number of patients and that obtained after a long duration of treatment are needed.

Conclusion

Curcumin has been shown to have the following properties: anti-A β aggregation, antioxidative, and inhibition of β -secretase, AChE, and A β -induced inflammation *in vitro*. Oral administration of curcumin inhibits A β oligomerization and tau phosphorylation in the brain *in vivo*. Furthermore, 160–500 ppm (0.43–1.36 μ mol/g) of orally administered curcumin inhibits A β deposition in

the brains of AD model mice. These findings suggest that curcumin may be one of the most promising compounds for the development of AD therapies. However, there have never been any reports about beneficial effects in human AD. A clinical trial with curcumin for AD that has been reported is not enough number of patients and duration of observation to judge the effect of curcumin for AD. Further clinical trials are required in AD patients.

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Conflict of Interest

The authors have no conflict of interest.

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