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REVIEW

# Curcumin: a natural substance with potential efficacy in Alzheimer's disease

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**Abstract:** Curcumin is a component of turmeric, a spice used in many types of cooking. Epidemiological evidence suggesting that populations that eat food with a substantial amount of curcumin were at lower risk of Alzheimer's disease (AD) led to the idea that this compound might have a neuroprotective effect. Curcumin has substantial antioxidant and anti-inflammatory effects, and is being used as a potential preventative agent or treatment for many types of cancer. There is evidence to suggest that the addition of curcumin to cultured neuronal cells decreases brain inflammation and protects against β-amyloid-induced neurotoxicity. Curcumin also protects against toxicity when β-amyloid is administered to produce animal models of AD. Curcumin decreases β-amyloid formation from amyloid precursor protein, and also inhibits aggregation of β-amyloid into pleated sheets. Studies in transgenic mice with overproduction of β-amyloid demonstrate a neuroprotective effect of curcumin as well. Cognitive function was also improved in these animal models. Clinical trials of curcumin in AD have not been very promising. It is possible that this is due to poor oral bioavailability of curcumin in humans, and thus several approaches are being developed to improve delivery systems or to create analogs that will mimic the neuroprotective effects and easily reach the brain. The lack of efficacy of curcumin in humans with AD may also result from treating for too short a time or starting treatment too late in the course of the disease, where substantial neuronal death has already occurred and cannot be reversed. Curcumin may be beneficial in protecting against development or progression of AD if taken over the long term and started before symptoms of AD become apparent.

**Keywords:** curcumin, Alzheimer's disease, β-amyloid, neuroprotection

## Incidence of Alzheimer's disease (AD)

AD is characterized by profound loss of short-term memory and impaired cognition, accompanied by neurodegeneration. Pathological changes including neuritic plaques and neurofibrillary tangles are hallmarks of the disease.[1] Although the overall worldwide incidence of AD is 4.7%, it is higher in Europe and the Americas at about 6.5%. The incidence climbs from about 8% in those over age 65 years, to 45% in people older than 85 years.[2] Currently, 5.4 million Americans have AD, and it is the sixth leading cause of death.[3] The total cost of AD in the US is estimated to be about $200 billion.[3]

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## Etiology of AD

The factors that precipitate neurodegeneration in AD are currently not understood. Although many neuronal populations degenerate as the disease progresses,[4] loss of cholinergic neurons was one of the earliest neurochemical findings, suggesting a


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selective vulnerability of this population.[5] Amyloid precursor protein (APP) is a membrane glycoprotein cleaved by three secretases, α, β, and γ. Cleavage by α-secretase generates a C-terminus fragment (C83) and soluble APP (sAPP), thought to be neurotrophic and neuroprotective.[6,7] In contrast, sequential processing of APP by β-secretase (BACE-1) and γ- secretase generates β-amyloid$_{1–40}$ and β-amyloid$_{1–42}$, widely thought to be neurotoxic.[8]

One of the components of γ-secretase is presenilin-1, which may be the catalytic core of the enzyme.[9,10] Alterations in presenilin-1 are associated with some cases of early-onset familial AD.[9] Presenilin-1 is a substrate for glycogen synthase kinase-3β (GSK-3β), which can phosphorylate presenilin-1, thus modulating its activity.[11] Increased expression of GSK-3β has also been associated with AD.[12,13] Presenilin-2 mutations also increase the activity of γ-secretase.[14,15] Mice with mutations in these genes have increased levels and deposition of β-amyloid, as well as deficits in learning and memory.[16–18]

The "amyloid cascade hypothesis," in which mutations in APP, presenilin-1, or presenilin-2 genes lead to increased production of β-amyloid, is now widely considered to contribute to the neurodegeneration seen in AD.[19] Mutations in these genes are linked to some forms of AD[20] and although generally responsible for early-onset disease, they have also been reported in some patients with late-onset disease.[21] Nevertheless, only about 5% of AD cases are caused by these mutations, and so it seems that there must be other factors that lead to an overproduction and deposition of β-amyloid. β-amyloid deposition leads to many toxic sequelae, including activation of microglia and astrocytes, oxidative stress, and possibly production of neurofibrillary tangles.[22–25] The neurofibrillary tangles contain hyperphosphorylated tau,[26,27] which, unlike normal tau protein, cannot stabilize microtubules. Thus, the microtubules become destabilized, affecting axonal function and transport.[27,28] β-amyloid also interferes with many neuronal processes, in particular those associated with signal transduction.[29–31]

Oxidative stress and inflammation have also been suggested to play a role in the neurodegeneration seen in AD.[32–35] Oxidative stress is thought to be an early, precipitating factor,[36] and may contribute to generation of β-amyloid, either on its own,[37,38] or in conjunction with inflammation.[39–41] This has led to the suggestion that treatment with anti-inflammatory agents or drugs that reduce oxidative stress could be useful in the prevention or treatment of AD.[42,43] Another contributor to the generation of β-amyloid is iron, which is found in higher than normal amounts in the brain of AD patients, and appears to accelerate translation of APP messenger ribonucleic acid and increase β-amyloid by stimulating an iron responsive element.[44,45]

## Current treatments

The finding of massive degeneration of cholinergic neurons in AD led to the development of treatments targeted towards increasing cholinergic activity.[46] Thus far, the most successful drugs have been cholinesterase inhibitors, which increase the amount of acetylcholine in the synaptic cleft, enhancing the function of the remaining cholinergic neurons. The cholinesterase inhibitors donepezil, galantamine, and rivastigmine are the current standard of treatment.[47–50] The problem with cholinesterase inhibitors is that their effectiveness will decline as cholinergic neurons continue to degenerate. For this reason, a number of selective cholinergic agonists are currently in development.[51] The other currently approved treatment for AD is the N-methyl-D-aspartic acid receptor antagonist memantine.[48,52–54] There has been some evidence that both cholinesterase inhibitors and memantine may act to slow the course of AD progression by decreasing β-amyloid deposition or neurotoxicity,[46,55–58] although this has been debated.[58–62]

Treatments directed at inflammation have been tested in patients with AD. The observation that people with rheumatoid arthritis treated chronically with nonsteroidal

**Table 1** The effects of curcumin on mechanisms involved in the degeneration in Alzheimer's disease

| Mechanisms involved in degeneration in Alzheimer's disease | Effects of curcumin |
|---|---|
| **β-amyloid** | |
| • Increased production | • Decrease in β-amyloid[117] |
| • β-sheet formation | • Inhibition of sheet formation[115,116] |
| • Neurotoxicity | • Decrease neuronal toxicity[107] |
| • NF-κB activation | • Decrease NF-κB activation[30] |
| • ERK1/2 | • Decrease ERK-1/2 expression[109] |
| • γ-secretase activity | • Inhibit γ-secretase[119] |
| • Presenilin-1 mutation | • Modulate presenilin-1[119] |
| **Oxidative stress** | |
| • IL-1β | • Decrease IL-1β[123] |
| • GSK-3β | • Decrease GSK-3β[112] |
| • Caspase-3 | • Prevent β-amyloid induced increase[110] |
| • Akt | • Activate neuroprotective pathway[110] |
| | • Iron chelation[120] |
| | • Decrease phosphorylation |
| **Other** | |
| • Iron | |
| • Tau | |

**Abbreviations:** ERK-1/2, extracellular signal-regulated kinase-1/2; GSK-3β, glycogen synthase kinase-3β; IL-1β, interleukin-1β; NF-κB, nuclear factor-κB.

anti-inflammatory drugs appeared to have a lower incidence of AD provided the groundwork for this hypothesis.[63,64] This was supported by animal and cell culture studies indicating that treatment with nonsteroidal anti-inflammatory drugs could decrease levels of β-amyloid and tau, possibly by the inhibition of γ-secretase.[65–67] Unfortunately, in spite of multiple trials, there has been little success with this treatment in older patients with AD, and in fact the ADAPT trial (AD Anti-inflammatory Prevention Trial) was stopped early due to the incidence of cardiovascular complications.[68–71] However, there is evidence that treatment with nonsteroidal anti-inflammatory drugs may benefit some people, especially if they begin treatment when they are young.[69,72,73] It is likely that anti-inflammatory treatments would be more useful if they were started before symptoms of the disease become apparent, as by that time the brain damage is substantial, and it may not be possible to reverse it.

It has been observed that the incidence of AD is quite low in India.[74–76] This could be a result of genetics, as the incidence of the apolipoprotein-E4 (ApoE4) allele is also low in India. In one meta-analysis it was reported to be 34% ApoE ε4/– and 4% ApoE ε4/4 versus 56% and 11% in the US.[77] Another study reported a frequency of 0.073 in a rural community in India versus 0.11 in a small Pennsylvania town.[78] Although not completely correlated with the incidence of AD, presence of the ApoE4 allele is considered a risk factor.[77,79–81]

In spite of the genetic differences, there is also a difference in the pathology of AD in India, with a decrease in β-amyloid$_{1–42}$ in both normal controls and those patients who do develop AD, as well as a decrease in hyperphosphorylated tau.[82,83] It has been postulated that the reduced incidence or severity of AD in India might, beyond genetics, reflect differences in diet or environment.[74] Indeed, people in India consume large amounts of curcumin, about 80–200 mg/day,[84] which has long been known to have anti-inflammatory and antioxidant effects.[85–88] Thus, it was suggested that curcumin might have a neuroprotective effect and be useful in the treatment or prevention of AD.[89–91]

## Pharmacology of curcumin

Curcumin (diferuloylmethane), a component of turmeric, comes from the herb *Curcuma longa*. It has been used for centuries as a spice in many foods, especially in Southeast Asia, and also as a coloring agent in condiments such as mustard. Toxicity studies have indicated that it is quite safe even in high doses (up to 12 g in humans).[92,93] Its oral bioavailability, however, is poor,[89,94,95] with low blood levels following oral administration and the majority of metabolites found in the feces.[96] This could limit its usefulness as an oral therapeutic agent. Numerous studies are under way to develop delivery systems that will increase blood levels following administration of curcumin.[97]

Curcumin has been used in Ayurvedic medicine for numerous purposes, and there has recently been a lot of interest in its potential to treat many diseases.[98] Its antibacterial effects were first described in 1949.[99] In the last 10 years, interest in this compound for many uses has surged. Antifungal and antiviral properties have been described.[100–102] Curcumin has antioxidant properties[87,103,104] and anti-inflammatory properties.[87,88,105] It is being proposed as a treatment or sensitizing agent for different types of cancer or to protect the body from the toxicity of certain agents used in cancer chemotherapy.[98,106] It is thought to lower cholesterol and may regulate glucose and insulin levels, with potential for treatment of type II diabetes.[98]

The pharmacological effects of curcumin are mediated via actions on multiple sites, including transcription factors, enzymes, growth factors, neurotransmitter receptors, growth factor receptors, cytokine receptors, inflammatory mediators, and numerous protein kinases.[98] In terms of potential effects in AD, the ability to inhibit acetylcholinesterase, protect against β-amyloid toxicity and/or decrease its production, reduce the effects of oxidative stress, and decrease inflammation may be useful.

## Curcumin for AD

Given the importance of β-amyloid accumulation in the pathogenesis of AD, numerous in vitro and in vivo studies have examined the interaction of curcumin with β-amyloid. Several studies have investigated the dose-related neuroprotective effect of curcumin against β-amyloid-induced toxicity in cultured neuronal cells.[107] Several mechanisms for this protective effect have been proposed. In both human neuroblastoma cells, blocking nuclear factor-κB with curcumin was shown to prevent β-amyloid-induced cell death.[30] Curcumin also reduced hypoxia-induced cell death in mouse hippocampal cells by inhibiting nuclear factor-κB-induced repression of peroxiredoxin-6.[108] In a Human acute monocytic leukemia cell line (Sigma-Aldrich), curcumin was shown to reduce the β-amyloid-induced expression of the cytokines tumor necrosis factor-α and interleukin-1β, as well as activation of mitogen-activated protein kinase and phosphorylation of extracellular signal-regulated kinase-1/2.[109] In rat prefrontal cortex neurons, the β-amyloid-mediated increase in capsase-3 was inhibited, and the neuroprotective pathway involving Akt was activated, by addition of curcumin.[110] Again in rat cortical

cells, curcumin maintained cell viability after exposure to β-amyloid and decreased markers of oxidative stress and levels of reactive oxygen species.[111] Curcumin also appeared to reduce β-amyloid toxicity by decreasing the activity of GSK-3β and stimulating the protective Wnt/β-catenin pathway in APPswe-transfected SY5Y cells.[112] Thus, curcumin appears to act at many levels to ameliorate the neuronal damage that can be caused by inflammation, oxidative stress, or exposure to β-amyloid.

Curcumin may also affect the production and deposition of β-amyloid, long thought to be one of the triggers for neurodegeneration in AD. In both rat cortical neurons and in solution, curcumin produced a dose-dependent decrease in formation of fibrillary β-amyloid$_{1–40}$ and β-amyloid$_{1–42}$ and also destabilized fibrils that had already formed, thus breaking up the β-sheet conformation seen in AD plaques.[111,113–115] The mechanism for this effect is not known, but may involve binding to β-amyloid and preventing aggregation.[113,114] Analogs of curcumin that maximize the inhibition of β-amyloid aggregation are being developed.[116]

Other lines of evidence suggest that curcumin exerts a benefit by decreasing levels of β-amyloid. Curcumin inhibited production of β-amyloid$_{1–42}$ in cultured cells, and also decreased the level of the APP protein.[117] It did not appear that processing of APP by BACE-1, an enzyme involved in production of β-amyloid, was involved as neither BACE-1 protein nor messenger ribonucleic acid levels were affected by curcumin; it was concluded that the effect must involve posttranslational processing of APP.[117] Indeed, a subsequent study found that curcumin did not alter levels of mature APP, but did decrease immature and total APP.[118] These authors suggested that inhibition of the APP maturation process could account for the observed decrease of both β-amyloid$_{1–40}$ and β-amyloid$_{1–42}$ by interrupting the pathway that leads to their production.[118] Curcumin does appear to affect the activity of γ-secretase, by decreasing the expression of the catalytic component of the enzyme presenilin-1.[119] This may result from inhibition of GSK-3β, which normally phosphorylates presenilin-1 to stimulate γ-secretase.[112,119] In addition to increasing levels of β-amyloid, activation of GSK-3β may also phosphorylate tau, allowing it to produce paired helical filaments.[27] Another mechanism by which curcumin may decrease formation of β-amyloid would be through its ability to chelate iron,[120] as increases in iron may facilitate production of β-amyloid.[44] Curcumin decreases iron-induced neurotoxicity in primary cultures,[121] and it has been proposed that the beneficial effect of curcumin in transgenic mice animal models of AD may be due, in part, to its effects on iron.[122] Thus, curcumin may decrease production and deposition of β-amyloid through many different mechanisms, including alterations in the activity of γ-secretase and maturation of APP, inhibiting the activity of GSK-3β and tau production, and chelating iron. These actions are summarized in Table 1.

The studies described above were all done in vitro in either cultured cell lines or primary neuronal cell cultures. In vivo studies have also shown protective effects of curcumin in animal models of AD. The initial study was in the transgenic Tg2576 APPSw mouse model of AD, which contains a human mutation for AD and develops age-related pathology and behavioral changes similar to those in AD.[16] Expression of interleukin-1, measures of oxidative damage, levels of β-amyloid, and plaque burden were all decreased following treatment of these animals with both high and low oral doses of curcumin for 6 months.[123] The decreases were substantial at low doses (about 40%), and similar to those which had been seen previously following treatment with the anti-inflammatory drug ibuprofen.[124] These results were confirmed in a subsequent study, which also showed levels of curcumin in the brain following chronic oral treatment.[125] Another model which has been studied involves the administration of ibotenic acid and β-amyloid$_{1–40}$ into rat brains to produce neurodegeneration and β-amyloid deposition, as well as memory loss.[126] In this model, curcumin treatment for 20 days after the lesion, was found to improve performance in the Morris water maze, a test of short-term memory.[126]A subsequent study indicated decreases in measures of inflammation and apoptosis, again supporting the neuroprotective effect of curcumin.[127] Combining curcumin with omega-3 fatty acids increased its effectiveness at preventing tau phosphorylation and reducing memory impairment in 3xTg-AD transgenic mice.[128]

The promising results of these in vitro and in vivo animal studies have prompted tests of curcumin in humans (http://www.clinicaltrials.gov). In one, curcumin (1 g/day or 4 g/day) was combined with gingko for 6 months. Serum β-amyloid levels increased in the curcumin-treated group, suggesting loss from the brain, but there was no difference in mental status at the end of the trial.[129] Curcumin could be detected in the blood 2 hours after treatment, suggesting that it had been absorbed, but levels were low.[129] In a 24-week trial of patients with mild to moderate AD, no improvement was seen in the curcumin-treated (2 g/day and 4 g/day doses) groups.[130,131] The main side effect was gastrointestinal symptoms, but again the blood levels were low, suggesting that bioavailability was problematic. Other trials currently in progress include one combining a larger dose of curcumin with BioPerine® (Sabinsa Corporation,

NJ, USA; an ingredient of black pepper thought to improve absorption of curcumin) and another using Longvida®, (Verdure Sciences, IN, USA) a curcumin formulation thought to have better bioavailability.[132,133] There have been no reports as yet from these studies.

## Future directions

One of the reasons suggested for the lack of beneficial results of curcumin in AD clinical trials has been the inability to produce sufficient brain levels following oral absorption.[134] It has been repeatedly shown that curcumin has poor water solubility and poor oral bioavailability, and that much of an administered dose is excreted in the feces.[91,95,135,136] For this reason, there are a number of new formulations being developed which are hoped will improve the bioavailability and delivery of curcumin.[137] These include curcumin analogs that mimic the active site of the compound,[138] as well as analogs that mimic the curcumin anti-amyloid effect combined with an anticholinesterase effect.[139] Solid lipid particle complexes and carrier systems[140–146] and nanoparticle preparations[137,147–151] are also being developed, as well as water soluble conjugates.[153] A nanoparticle preparation has been shown to provide higher blood levels and was effective in Tg2576 transgenic mice.[154] Much of this research has been spurred on by the potential for curcumin as an anticancer drug, but the benefits of finding better drug delivery systems will also be useful in potential treatment of AD.

Another possible reason that the clinical trials with curcumin have not shown any striking benefit is that they have been too short. When curcumin is administered to a transgenic mouse or a rat with toxin-induced neuronal damage, it may lead to disruption of β-amyloid deposition and even reverse some of the behavioral effects. However, in humans, AD progresses over a period of many years, and by the time symptoms are seen, there is extensive neuronal damage.[155,156] Similar results have occurred with the β-amyloid vaccine, β-amyloid antibody treatment, and γ-secretase inhibitors, which were effective in transgenic mice, but did not improve cognitive function in patients who were already symptomatic for AD.[157–164] For this reason, a treatment that may be neuroprotective should be initiated early to slow and prevent the damage from occurring, or if it has begun, to prevent it from progressing as rapidly.[157] Thus, curcumin may have a role as a protective agent rather than a reversal agent, and it may benefit from being combined with other compounds, such as resveratrol, piperine, or epigallocatechin gallate from green tea, that have been shown to exert neuroprotective effects or that may enhance the effectiveness of curcumin.[90,165,166]

## Disclosure

The author reports no conflicts of interest in this work.

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