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NEUROPROTECTIVE EFFECTS OF CURCUMIN

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Abstract

Neurodegenerative diseases result in the loss of functional neurons and synapses. Although future stem cell therapies offer some hope, current treatments for most of these diseases are less than adequate and our best hope is to prevent these devastating diseases. Neuroprotective approaches work best prior to the initiation of damage, suggesting that some safe and effective prophylaxis would be highly desirable. Curcumin has an outstanding safety profile and a number of pleiotropic actions with potential for neuroprotective efficacy, including anti-inflammatory, antioxidant, and anti-protein-aggregate activities. These can be achieved at sub-micromolar levels. Curcumin's dose–response curves are strongly dose dependent and often biphasic so that *in vitro* data need to be cautiously interpreted; many effects might not be achievable in target tissues *in vivo* with oral dosing. However, despite concerns about poor oral bioavailability, curcumin has at least 10 known neuroprotective actions and many of these might be realized *in vivo*. Indeed, accumulating cell culture and animal model data show that dietary curcumin is a strong candidate for use in the prevention or treatment of major disabling age-related neurodegenerative diseases like Alzheimer's, Parkinson's, and stroke. Promising results have already led to ongoing pilot clinical trials.

1. INTRODUCTION

Many neurodegenerative diseases of aging involve the accumulation of protein aggregates, oxidative damage, and inflammation. Curcumin has multiple desirable characteristics for a neuroprotective drug, including anti-inflammatory, antioxidant, and anti-protein-aggregate activities that we have previously reviewed.[1,2] Because of its pluripotency, oral safety, long history of use, and inexpensive cost, curcumin has great potential for the prevention of multiple neurological conditions for which current therapeutics are less than optimal. Examples reviewed include Alzheimer's, Parkinson's, Huntingtin's, head trauma, aging, and stroke. Despite the widely held belief that curcumin's poor systemic bioavailability precludes therapeutic utility outside of the colon,[3,4] there is ample animal model evidence for very effective neuroprotection in a variety of disease models. Conversely, many of curcumin's reported toxic effects are achieved only at doses that will not be reached in systemic tissues with oral dosing. One of the key obstacles with curcumin, as with other compounds lacking adequate patent protection, is that there has been no push for development from the private sector. What is needed is preclinical and clinical development support from either government or philanthropic support. One example of this might be support from the US NIH Aging and Complementary and Alternative Medicine Institutes. In the following pages, we reviewsome of the literature supporting the neuroprotective utility for curcumin, beginning with Alzheimer's disease.

2. BIPHASIC OR DOSE-DEPENDENT RESPONSES TO CURCUMIN

As reviewed elsewhere in this volume, curcumin is both a potent antioxidant and anti-inflammatory agent and has a long history of use, both as a food preservative and in traditional Indian and Asian medicine, often as an oral or topical extract for conditions where Western medicine might employ a nonsteroidal anti-inflammatory drug and/or vitamin E. Curcumin's activity and structure–function relation as a radical scavenger, metal chelator, and antioxidant

has received considerable attention . It clearly reduces mRNA production for pro-inflammatory mediators, including cytokines, inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2.[5,6] Apparently, this is due to limiting activator protein (AP)-1 and nuclear factor (NF)-κB-mediated gene transcription[7,8]; however, the direct molecular targets at low doses are not entirely clear. Curcumin inhibition of AP-1 and NF-κB-mediated transcription occurs at relatively low (<100 nM) doses and might be due to inhibition of histone acetylase (HAT) or activation of histone deacetylase (HDAC) activity.[9] At high doses (>3 μM) that are relevant to colon cancer but unlikely achievable with oral delivery in plasma and tissues outside of the gut, curcumin can act as an alkylating agent,[10] a phase II enzyme inducer,[11] and stimulate antioxidant response element-mediated protective gene expression.[12] Some of the effects of curcumin at high *in vitro* doses are clearly toxic and undesirable beyond its use in cancer therapy. For example, inhibition of proteasomal function and potentiation of huntingtin toxicity can be achieved with dosing >3 μM *in vitro*.[13] Proteasomal inhibition would clearly be undesirable in neurodegenerative disorders, which often have protein aggregate accumulation, whereas proteasome stimulation would be protective. However, the dose dependence of curcumin's effects on the proteasome is biphasic with doses up to 1 μM (e.g., achievable *in vivo*) causing 46% increased proteasomal activity and higher doses leading to proteasome inhibition.[14] Proteasome activation would presumably be a useful response in neurodegenerative diseases with accumulating aggregates.

As discussed below, many protective effects, including anti-amyloid, antioxidant, and anti-inflammatory activities, can be obtained with doses at or below 1 μM. For example, low-nanomolar doses can inhibit histone acetyltransferase[15] and JNK-stimulated AP-1 activity, suggesting that these functions are likely central to many *in vivo* effects, [16,17] including central nervous system (CNS) neuroprotective activity.[18] Also as reviewed below, low-dose curcumin can limit the aggregation of multiple forms of amyloid-forming peptides that lead to intraneuronal or extracellular aggregates in a variety of neurodegenerative diseases.

3. ALZHEIMER'S DISEASE

Alzheimer's (AD) is the most prevalent form of age-related dementia, with AD risk doubling every 5 years after age 65. Thus, AD risk for persons living into their eighties rises to 20–40% depending on the population. There are millions of AD patients in the United States today and this number is expected to double and double again with the demographic shift toward a more aged population, leading to over 10 million expected cases, unless preventive measures can be achieved.[19] The classical pathology of AD involves neurodegeneration and the accumulation of protein aggregates to form two major lesions: neurofibrillary tangles (NFTs) and senile plaques. The senile plaques consist of abnormal neuronal proceses ("dystrophic neurites") and activated glial cells surrounding and penetrating a more central proteinaceous deposit of amyloid fibrils made up of β-amyloid (Aβ) peptide. The Aβ peptide is typically 40–42 amino acids in length and is derived from a larger single membrane spanning "amyloid precursor protein" (APP) by endoproteolytic cleavage. The N-terminus is exoplasmic and cut by a rate-limiting β-secretase enzyme (BACE 1). The final secreted amyloid peptide product is amphipathic with the 12–14-amino-acid C-terminal hydrophobic amino acid tail cut from within the membrane by a "γ-secretase" enzyme complex. Aβ peptide is, thus, normally rapidly produced and equally rapidly degraded. However, at elevated concentrations, it has a strong tendency to self-aggregate to form poorly degradable, β-pleated sheet-rich oligomers, protofilaments, and, finally, filaments that have the histochemical staining properties of amyloid. These Aβ filaments deposited in plaques can be visualized with the amyloid dyes thioflavin S and Congo red. The 2-amino-acid longer Aβ1–42, typically a minor species, forms aggregates more than a thousand times faster than Aβ1–40. A large number of different autosomal-dominant AD mutations have been found in APP and the "presenilin" component of the γ-secretase complex and all of these cause more Aβ1–42 to be made, resulting in early-

onset AD. Thus, the genetics of AD clearly implicate an etiopathogenic role for increased Aβ1–42. Further, because mutations in Aβ itself can also increase the aggregation rate and cause AD, most researchers are convinced that Aβ aggregates initiate pathogenesis.[20,21] Transgenic mouse models that overexpress human mutant APP develop neuritic amyloid plaques that closely resemble the senile plaques in AD patients,[22,23] but although they show hyperphosphorylated tau, they do not develop neurofibrillary tangles. More recently, tangle pathology has been achieved by expressing high levels of mutant human tau or wild-type human tau on a mouse tau knockout background, but curcumin effects have not been reported on in these models.

3.1. Amyloid Reduction

We initially tested curcumin in a mutant APP transgenic plaque-forming animal model and found that it not only reduced indices of oxidative damage and inflammation, but it also reduced amyloid plaques and accumulated Aβ.[24] We also found that curcmin reduced oxidative damage, inflammation, and cognitive deficits in rats receiving CNS infusions of toxic Aβ.[25] Tests on cultured HEK or 293 cells transfected with human APP and producing measurable Aβ failed to show any evidence of secretase inhibition and reduced Aβ production. However, because curcumin structurally resembles the amyloid-binding dye Congo red, we tested the ability of curcumin to bind amyloid and inhibit Aβ aggregation and found that it dose-dependently blocked Aβ aggregation at submicromolar concentrations.[1] A more extensive report on these observations showed that curcumin not only stained plaques and inhibited Aβ aggregation and fibril formation *in vitro*; but curcumin also inhibited the formation of Aβ oligomers and their toxicity and readily entered the brain to label plaques *in vivo*.[26] More significantly, we found that curcumin appeared to reduce preformed amyloid *in vitro* and to markedly suppress Aβ accumulation and plaques *in vivo* even when the drug treatment was begun when the mice were old enough to already have well-established amyloid burdens at levels similar to AD patients. This efficacy in late stages of amyloid deposition is in marked contrast to other antioxidants and other treatments that fail to reduce amyloid in the same Tg2576 model mice when treatments are begun late.[27,28] Curcumin's *in vivo* capacity to reduce β-amyloid accumulation might derive from multiple activities beyond this first mechanism: (1) direct binding inhibition of Aβ aggregate formation. Amyloid formation has been shown to be limited by five additional mechanisms: (2) metal chelation,[29] (3) the antioxidant vitamin E,[28] (4) lowering cholesterol[30,31] and reducing expression of the β-secretase enzyme BACE1 by reducing its induction by both (5) pro-inflammatory cytokines [interleukin (IL)-1β and tumor necrosis factor (TNF)-α)[32] and (6) the lipid peroxidation product 4 hydroxynonenal acting on JNK-mediated transcription.[33] Curcumin might work to limit amyloid production by direct inhibition of aggregates and control of all five of these pathways, including chelating metals,[34] limiting oxidative damage better than vitamin E,[35,36] lowering cholesterol,[37,38] reducing pro-inflammatory cytokines,[24,38,39] lipid peroxidation,[25]and protein oxidation[24] and JNK-mediated transcription[39] to control BACE1 expression. For example, treatment with curcumin reduced BACE1 mRNA in cultured primary rat neurons and in aging Tg2576 (Morihara, Ma, and Cole, unpublished data). Iron chelation is another activity that also has *in vivo* support.[40] Further, although it is not clear whether it can do so *in vivo* because the dosing seems to require >3 μM,[11] curcumin can induce phase II enzymes in astrocytes and heme oxygenase-1 in neurons *in vitro*.[41] Two additional mechanisms might contribute to amyloid reduction: (7) Amyloid aggregates can be cleared via phagocytosis by brain macrophages, curcumin at dosing as low as the 100–500-nM range can stimulate microglial phagocytosis, and clearance of amyloid *in vitro* and curcumin appears to promote phagocytosis *in vivo* (Yang, et al., unpublished data). (8) Finally, one of the major defenses against intraneuronal protein aggregate formation is the induction of heat shock proteins (HSPs) that function as molecular chaperones to block protein aggregate formation.[42] Increased HSP expression from transgenes clearly protects from neurotoxicity arising from

intraneuronal protein aggregates.[43] Like several other nonsteroidal anti-inflammatory drugs (NSAIDs), curcumin can potentiate the production of HSPs in response to cellular stress *in vitro* and *in vivo*[44]. Curcumin potentiates the *in vitro* and *in vivo* HSP response to infused (*in vivo*) or applied solubleAβ aggregates on neurons in culture (Frautschy et al., unpublished results). Thus, there are eight known ways for curcumin to limit β-amyloid accumulation and protect against amyloid peptide-mediated toxicity.

A very recent report using direct *in vivo* multiphoton microscopy to repeatedly observe the same amyloid plaques in AD model mice showed the ability of curcumin to enter the brain, bind plaques, and reduce amyloid plaque size by 30%, and to significantly reduce soluble Aβ *in vivo*.[45] These data encourage the continued development of curcumin as an anti-amyloid agent and efforts to understand its mechanisms of action.

3.2. Inhibition of Amyloid Toxicity

The mechanisms by which β-amyloid peptide aggregates act to cause AD remain unclear, but they appear to include induction of oxidative damage[46,47] as well as inflammation[4,49] and neurotoxicity, the latter mediated through JNK activation.[50,51] Thus, curcumin might act not only by limiting amyloid aggregates but also by suppressing their pro-oxidant, pro-inflammatory, and JNK-mediated toxic amyloid aggregate effects. Further, high doses of curcumin can also inhibit amyloid toxicity *in vitro* and neurotoxic p75 neurotrophin receptor signaling.[52] AD pathogenesis also involves the accumulation of other protein aggregates, including intraneuronal tau amyloid as NFTs and α-synuclein aggregates (discussed below), which curcumin could potentially suppress. Tau dimerization is initiated by oxidative damage[53] and at least some tau kinases, notably mitogen-activated protein kinase (MAPK), are activated by oxidative damage.[54] Further, tau pathology appears to induce oxidative stress and mitochondrial dysfunction, suggesting antioxidants might protect.[55] Finally, like all amyloids, tau aggregates contain a core β-sheet domain that plays a central role in aggregation and might be blocked by natural and synthetic amyloid-binding dyes, potentially including curcumin.

In summary, curcumin's known activities target at least eight anti-amyloid mechanisms relevant to AD pathogenesis, suggesting that it might be useful in preventing or treating AD. Although there is no epidemiology isolating curcumin intake as a variable, age-adjusted AD prevalence and incidence in an area with high curcumin intake (rural India) was surprisingly low compared to the United States and other Western countries.[56] Collectively, available evidence warrants the exploration of curcumin in clinical trials for AD treatment and prevention; a pilot trial in early AD evaluating dosing and efficacy with clinical end points and biomarkers is currently underway at UCLA's Alzheimer's Disease Center.[2]

4. PARKINSON'S DISEASE

Another prevalent, age-related neurodegenerative condition, the movement disorder Parkinson's disease (PD), involves relatively selective vulnerability to the neuromelanin-bearing dopaminergic neurons of the pars compacta region of the substantia nigra and their terminals in the striatum. In Western populations, significant age-related loss of pigmented neuromelanin-bearing neurons commonly occurs in the this region, but symptoms of PD do not manifest until 60–80% neuron loss.

4.1. Oxidative Damage and Inflammation

Of the age-related neurodegenerative conditions, PD has long had the strongest associations with elevated oxidative damage, including that associated with auto-oxidative dopamine breakdown and related semiquinone metabolism to superoxide, as well as monoamine oxidase

production of hydrogen peroxide.[57] Low doses of curcumin can inhibit dopamine toxicity *in vivo*.[18] More recently, mitochondrial electron transport defects at complex I and increased free-radical production have been identified in PD brain and peripheral sites, whereas oxidative damage to vulnerable dopaminergic neurons and a PD syndrome can be produced in human and animal models by the MPTP toxin (reviewed in [Ref. 58]). MPTP toxicity is mediated by MPP+, and curcumin can directly inhibit MPP+ toxicity to the PC12 neuronal cell line.[16]

Further, support for a free-radical role in PD comes from evidence that selective neuron loss, aggregation of α-synuclein, and clinical symptoms resembling PD can be produced by the pesticide toxin rotenone that targets mitochondrial electron transport and causes increased free-radical production.[59] Although not as closely associated with inflammation as AD, recent studies have shown chronic microglial activation in PD and that a single pro-inflammatory stimulus results in sustained microglial activation around dopaminergic neurons that can contribute to their loss in animal models.[60] These data provide some rationale for protection from PD with the polyphenolic antioxidant/ NSAID curcumin.

4.2. Synuclein Aggregation

Although rare, some genetic cases of PD are linked to mutations in a synaptic protein called α-synuclein that was originally identified from smaller peptides isolated in amyloid-containing fractions of AD brains.[61] The α-synuclein protein is another aggregating, fibril-forming protein that is a major component of the Lewy body lesions characteristic of PD as well as certain cases of AD and several other neurodegenerative conditions. Synuclein aggregates show evidence of nitration-based oxidative damage[62] that might play a critical role in aggregate formation.[63] Recent studies have shown that curcumin can reduce the aggregation of α-synuclein,[64] and administration to cultured cells with α-synuclein aggregate formation results in fewer aggregates.[65]

5. OTHER NEURODEGENERATIVE DISEASES WITH PROTEIN MISFOLDING

5.1. Mad Cow Disease

"Mad cow" involves the aggregation of infectious prion proteins that form protease-resistant toxic species with a β-sheet core. Low doses (IC_{50} ~ 10 nM) of curcumin effectively inhibited protease-resistant prion protein aggregation and accumulation in neuroblastoma cells *in vitro*, but an initial trial to delay scrapie pathogenesis *in vivo* was unsuccessful.[66] The reasons for the failure in the animal model remain unclear and should be further explored, but one likely explanation would be the failure to obtain adequate curcumin blood levels with oral administration.

5.2. Huntington's Disease and Other CAG Repeat Diseases

These diseases have extended C-terminal CAG repeats coding for polyglutamine, which causes protein aggregates to form at a rate determined by the repeat length. Because curcumin resembles Congo red and its chrysamine G homologue Congo red, its anti-amyloid-binding protein properties are generic and should extend to other protein-misfolding diseases with a β-pleated sheet, including the polyglutamine dieases like Huntington's disease (HD).[67] Evidence for a protective effect in an HD transgenic model has been recently obtained by a UCLA investigator,[68] leading to a pilot curcumin clinical trial with HD patients at UCLA. Marie-Charcot Tooth disorder is another example of a similar protein-misfolding neuropathy and curcumin protects against this disorder *in vitro*[69] (and *in vivo* in a transgenic model (Lupski, personal communication).

5.3. Tauopathies

Aggregates of the microtubule-associated protein tau are present in neurofibrillary tangles in AD and tau mutations have been genetically linked to neurodegeneration in some forms of frontotemporal dementia (FTD), which can be modeled in FTD mutant tau transgenic mice.[70] There is currently intense interest in the neurotoxicity of soluble tau aggregates because of a recent report using a doxycycline-regulated tau transgenic that showed that turning off tau transgene expression in older tangle-bearing mice fails to reduce tangles, but markedly protects against neurodegeneration.[71] Curcumin might protect against the formation of these soluble tau aggregates because the initial tau dimerization step can be driven by oxidative damage, notably lipid peroxidation[53] or redox-regulated disulfides.[72] Further, as discussed earlier, the induction of HSPs should also protect against aggregates. Although an abstract report claimed that curcumin can reduce tau pathology in one of the tau transgenic models, as far as we are aware there are no peer-reviewed publications on this topic. Nevertheless, in a model of CNS Aβ infusion into genomic wild-type tau transgenic mice, dietary curcumin appeared to limit Aβ infusion and tau transgene-related cognitive deficits (Frautschy et al., unpublished data). Based on this suggestive data, ongoing studies are further examining the impact of curcumin on tau pathology.

6. CEREBROVASCULAR DISEASE AND STROKE

Cerebrovascular and cardiovascular disease risk factors overlap AD risk factors and many dementia cases are mixed. Therefore, if confirmed in larger trials, curcumin's reported ability to lower total cholesterol and raise high-density lipoprotein (HDL) cholesterol in humans should be relevant to dementia prevention.[73] To provide another example, homocysteinuria appears to be an important risk factor for both AD and cardiovascular disease.[74] Curcumin effectively protects against homocysteine-induced endothelial damage.[75] Free-raical damage and inflammation contribute to ischemic damage after a stroke. Prior and even delayed curcumin treatment reduces this damage. For example, curcumin injections i.p. reduced damage to vulnerable hippocampal CA1 and preserved antioxidant enzymes and glutathione, even when initiated 3 and 24 h after ischemia[76] Further, curcumin has been shown to protect in a standard middle cerebral artery occlusion rat model for stroke.[77].

7. HEAD TRAUMA

Head trauma is a stringent test of neuroprotective activity and a validated environmental risk factor for AD.[78,79] ;epeated head trauma is also the cause of boxer's dementia (dementia pugilistica), which involves both tangles[80] and Aβ42 deposition.[81] ApoE4, the major genetic risk factor for AD and brain trauma, synergistically increases the risk of AD and Aβ deposition.[82] Further, in an APP transgenic animal model for AD, brain trauma and the APP transgene act synergistically to increase both cognitive deficits and neurodegeneration.[83] Thus, protection against head trauma by curcumin, as shown in an animal model,[84] is another mechanism for potential AD prevention by curcumin.

8. ALCOHOL-INDUCED NEUROTOXICITY

Ethanol-induced toxicity involves lipid peroxidation, inflammation, and other well-established curcumin targets. Not surprisingly, curcumin can effectively protect against ethanol-induced oxidative damage, inflammation, and resulting liver damage[6] and ethanol-induced CNS neurodegeneration *in vivo*.[85] These reports show that despite claims of poor bioavailability, properly delivered , curcumin or its metabolites are effective in protecting tissues from oxidative damage outside of the gastrointestinal tract.

9. THE AGING BRAIN

Curcumin is one of the few drugs likely to slow aging rates, as evidenced by the ability of its major metabolite, tetrahydrocurcumin, to increase the life span in middle-aged mice.[86] Evidence for an impact on aging brain has been recently produced in aging rats, where chronic curcumin treatment was shown to result in reduced lipid peroxidation and accumulation of the age-pigment lipofuscin and to increase the antioxidant defense enzymes glutathione peroxidase and superoxide dismutase as well as sodium potassium ATPase, which normally declines.[87] Curcumin resembles another biphenolic antioxidant, resveratrol, that is believed to have antiaging activity via induction of sirtuins and HDAC activtion, so curcumin's ability to limit HAT and promote neurogenesis[15] might also impact longevity, promoting a sirtuin-like effect on HAT-regulated transcription. These results are intriguing, consistent with other measures of normal brain aging, including protection against CNS oxidative damage, and support the hypothesis that curcumin might slow normal aging of the brain and presumably other tissues in which age-related oxidative damage is an issue.

10. STEM CELL NEURODIFFERENTIATION AND ADULT NEUROGENESIS

Although still controversial, adult neurogenesis appears to be both modulatable and therapeutically significant.[88] It would be of obvious utility to functionally replace lost neurons in neurodegenerative diseases. Curcumin has been reported to stimulate neuronal differentiation of stem cells *in vitro* and adult neurogenesis *in vivo*, notably in the striatum.[15] Although this is a single report that needs confirmation and extension, it shows additional potential for curcumin in conditions with CNS injury and neurodegeneration.

11. OBSTACLES FACING THE CLINICAL DEVELOPMENT OF CURCUMIN

As summarized in Table 1, curcumin has at least ten neuroprotective effects and it can apparently act at nanomolar or even picomolar doses. For example, curcumin's ki for amyloid binding is 200 picomolar.[89]

Curcumin is neuroprotective in multiple animal models and has great potential for the prevention or treatment of age-related dementia arising from AD or cardiovascular disease, Parkinson's disease, other diseases of aging, and aspects of aging itself. Like any drug, it needs preclinical development to establish dosing, formulation, pharmacokinetics, therapeutic windows, and potential toxicity. Normally, these issues are the concern of drug companies, but in the absence of patent protection, this is unlikely to occur. Further, large clinical trials will be required to establish efficacy for any of curcumin's many disease indications. Primary prevention of age-related neurodegeneration would be the eventual goal, but this is even less likely to ever be tested in clinical trials. Government or philanthropic support will likely be required to realize curcumin's potential for ameliorating age-related neurodegeneration and other debilitating conditions with enormous personal and economic costs.

12. CONCLUSION: RATIONALE FOR MULTITARGET APPROACH TO AGE-RELATED DISEASE

Most chronic age-related conditions are not caused by foreign pathogens, but the failure to repair or resist chronic age-related lesions arising from naturally occurring damage or imbalances. They involve prolonged multistep cascades that induce slow degeneration that would best be dealt with by long-term prevention with very inexpensive and safe interventions rather than new drugs with unknown or unacceptable costs and side-effect profiles. This is a huge issue because in the absence of a foreign pathogen, most of the targets will involve essential physiological pathways, where major inhibition will predictably lead to sideeffects.

With modest efficacy from multiple beneficial activities, a pleiotropic drug like curcumin can be efficacious without side effects. Further, the original cause might be superseded by subsequent steps in the cascade and no single pathway might be responsible for ongoing degeneration. For example, most of these diseases involve inflammation and oxidative damage, which are known curcumin targets. Atherosclerosis and stroke, colon cancer, and Alzheimer's are prime examples. Furthermore, Alzheimer's and other neurodegenerative diseases of aging typically involve amyloidogenic protein misfolding and aggregation that can be directly combated by curcumin's anti-amyloid activity and possibly by potentiating HSP synthesis. Curcumin's favorable effects on cholesterol metabolism are also likely to reduce vascular disease and mixed dementia that cause dementia and frequently overlap AD. There are other likely beneficial effects. Finally, stimulation of neurogenesis might facilitate functional replacement of lost neurons, and curcumin has been reported to stimulate adult neurogenesis. With so much potential, the argument for curcumin's further development for neurodegenerative and other diseases of aging is compelling.

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Table 1

Ten neuroprotective effects of curcumin.

LIMITS	MECHANISM
Pro-inflammatory cytokine induction	Inhibition of AP-1, NF-κB, HAT, HDAC stimulation?
Reactive oxygen species (ROS)	Scavenger, metal/Fe chelator, induces AO defense enzymes
Aβ production	Suppresses cholesterol, BACE1 induction
Amyloid aggregates	Congo red mimetic/aggregate inhibitor
Misfolded protein accumulation	Potentiates HSPS
Neurotoxicity	JNK pathway
Excitotoxicity	COX-2 induction via AP-1, NF-κB
Toxicity	Phase II inducer, HO-1
Particulate toxins	Increases phagocyte clearance
Neuron loss	Stimulates neurogenesis

Note: References are reviewed in the text.