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Curcumin and neurodegenerative diseases

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Abstract

Over the last ten years curcumin has been reported to be effective against a wide variety of diseases and is characterized as having anti-carcinogenic, hepatoprotective, thrombosuppressive, cardioprotective, anti-arthritic, and anti-infectious properties. Recent studies performed in both vertebrate and invertebrate models have been conducted to determine whether curcumin was also neuroprotective. The efficacy of curcumin in several pre-clinical trials for neurodegenerative diseases has created considerable excitement mainly due to its lack of toxicity and low cost. This suggests that curcumin could be a worthy candidate for nutraceutical intervention. Since aging is a common risk factor for neurodegenerative diseases, it is possible that some compounds that target aging mechanisms could also prevent these kinds of diseases. One potential mechanism to explain several of the general health benefits associated with curcumin is that it may prevent aging-associated changes in cellular proteins that lead to protein insolubility and aggregation. This loss in protein homeostasis is associated with several age-related diseases. Recently, curcumin has been found to help maintain protein homeostasis and extend lifespan in the model invertebrate *Caenorhabditis elegans*. Here, we review the evidence from several animal models that curcumin improves healthspan by preventing or delaying the onset of various neurodegenerative diseases.

Keywords

Curcumin; Model organisms; Mammals; Neurodegenerative diseases

1. Introduction

Curcumin ((1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the main component of *Curcuma longa* (*C. longa*), generically known as turmeric, a perennial plant of the family Zingiberaceae that grows naturally in Southeast Asia. Turmeric is a spice present in Indian curries and many dishes in South Asia. It has also been used for thousands of years in Indian and Chinese medicine (1). The main components of turmeric extracts (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) are commonly known as curcuminoids. Multiple beneficial effects of curcumin, which could be linked to its ability to act as a strong anti-oxidant and anti-inflammatory, have been reported during the last ten years. In studies performed on cell cultures and in different animal models, curcumin has been reported to provide a number of beneficial effects. These studies have led to the identification of several pharmacological targets of curcumin and have shed some light on the molecular mechanisms activated by this compound. Interestingly, and maybe due to its lack of toxicity and inexpensive cost, some clinical trials have also been conducted with this compound. Curcumin has been reported to be effective against a wide variety of diseases

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like cancer (2, 3), cardiovascular disease (4), obesity (5, 6), liver disease (7, 8), inflammatory disease (9–11) and even aging (12–14).

In addition to the age-related pathologies noted above, curcumin may have beneficial effects on specific kinds of diseases characterized by the formation of aggregated fibrillar proteins deposits. Collectively known as conformational diseases (15, 16), they are responsible for tremendous social and economic burden. Especially under neurodegenerative conditions, the aggregation of aberrant forms of specific proteins such as α-synuclein (Parkinson's disease, PD) (17), β-amyloid (Alzheimer's disease, AD) (18) and huntingtin (Huntington's disease, HD) (19) may contribute to the onset and/or progression of the disease. Initially, the protein aggregates themselves were considered to be the toxic insult leading to cell death. However, more recent studies suggest that soluble aggregate precursors such as soluble oligomers or fibrils, may initiate pathology by influencing neuronal function (15). Although a detailed characterization of how these insoluble intra-and extracellular deposits develop is still unclear, multiple factors such as pH, metal ions, protein concentration, and oxidative stress have been reported to play a role in their formation.

It has been estimated that AD and PD are the two neurodegenerative diseases with the greatest incidence in the United States of America and that AD accounts for 60% to 80% of all dementia diagnosed (20). The costs associated with treating these diseases and paying caregivers, as well as the loss of productivity of those afflicted, has been estimated to be approximately 800 billion Euros (21). These statistics strongly suggest that developing therapies aimed to reduce or delay neurodegenerative disease should be a priority for the biomedical community.

PD is named after James Parkinson who described "shaking palsy" in 1817. This disease is characterized by several symptoms such as bradykinesia, tremors, rigidity, dementia and depression. At the molecular level, this motor dysfunction has been associated with pathological spherical inclusions in neurons of the substantia nigra, known as Lewy bodies, and with a loss of nigrostriatal dopamine (DA) neurons. Despite great effort, the etiology of this disease is still undetermined. However, it does seem clear that a cumulative loss of dopaminergic neurons during aging could contribute to the onset/progression of the disease. This pathology can be accelerated by exposure to environmental toxins, excitotoxicity, oxidative stress, or mutations in the α-synuclein gene, which encodes a protein found in Lewy bodies in idiopathic PD lesions. Due to the loss of dopaminergic neurons in the substantia nigra, striatal cholinergic neurons are disinhibited, leading to an imbalance of dopaminergic/cholinergic neurotransmission (22). Since DA does not cross the blood brain barrier, pharmacological approaches to treat PD have focused on developing drugs able to increase DA or reduce acetylcholine (ACh) activity in the brain. The primary approaches include the use of levodopa, a DA precursor and indirect agonist of G protein-coupled D2 receptors which increase DA production; direct stimulation of D2 receptors with selective agonists such as bromocriptine, ropinirole, pramipexole or rotigotine; or preventing DA enzymatic catabolism by enzymes like monoamine oxidase type B (e.g., selegiline and rasagiline) or Catechol-O-Methyltransferase (e.g., Entacapone and tocalpone). These compounds are often administered with anti-muscarinics, such as benztropine or trihexyphenidyl in order to decrease striatal cholinergic excitability (23).

AD is a neurodegenerative illness characterized by early onset of short-term memory loss and cognitive decline that eventually leads to dementia. This disease is associated with a particular brain pathology that includes neurofibrillar tangles and senile plaques (β-amyloid, Aβ). Aggregated Aβ in senile plaques have a β sheet secondary structure and are arranged in fibrils (24). A significant amount of neuronal loss has been reported during AD progression (e. g., basal forebrain, hippocampus and associative cerebral cortex). At molecular level, this

neuronal loss seems to be associated with a reduction of choline acetyltransferase activity and, as a consequence, with a marked diminution in ACh levels. No drugs are currently available to prevent this neuronal degeneration. To date, the potential anti-amyloid therapeutic approaches to treat AD focus on the amyloid cascade theory, such as the Aβ vaccine or treatment with metal-complexing agents (25, 26). However, several drugs that prevent ACh degradation have also been used to improve cognition during AD (e.g., tacrine or donepezil).

HD is a neurodegenerative disorder caused by the autosomal dominant mutation of the huntingtin gene. Altered protein aggregates affect muscle coordination and lead to abnormal involuntary movements, known as chorea, as well as cognitive and psychiatric problems. Tetrabenazine, an inhibitor of the vesicular monoamine transporter 2 (VMT2) that promotes dopamine degradation, is used to treat Huntington's chorea, but not to treat HD itself (27).

Unfortunately, current treatments in PD, AD and HD, beyond symptomatic improvement, do not have neuroprotective properties or the potential to modify the course of the disease, and even symptomatic relief is temporary. Additionally, all these compounds are highly toxic and can cause severe side-effects (nauseas, stomach cramps, dizziness, drowsiness, insomnia, headache, diarrhea, dry mouth, mydriasis and even delirium, depression or hallucinations).

2. An important role for Curcumin

With all this in mind, it is easy to understand the excitement generated by a compound like curcumin. If curcumin could be shown to have strong efficacy, it has the potential to become a candidate for nutraceutical intervention in neurodegenerative disease. It is interesting to note that, because of its strong affinity for fibrillar amyloid proteins, curcumin is already used to stain *in vitro* tissue sections from affected individuals (28). The search for curcumin derivatives with higher specificities for Aβ fibrils and adequate lipophilic properties for crossing the blood-brain barrier is a subject of current research (29, 30). Further fueling these efforts is research showing that curcumin is able to prevent aggregation of Aβ *in vitro* and in cell cultures (31, 32), suggesting that curcumin could alter the effects of protein aggregation in animal models and potentially in humans.

However, as alluded earlier, one of the principal limitations for the use of curcumin in nutraceutical interventions is its limited bioavailability, which is mainly due to its poor absorption and fast metabolism. Although curcumin is very stable in acidic media, at physiological pH it is easily degraded to ferulic acid and feruloylmethane (33). Whether these metabolites could have similar properties to those reported for curcumin is still an active field of research. In parallel, efforts to increase its bioavailability in mammals, particularly in humans (34–37), by conjugating it to a stable carrier or by co-administering it with inhibitors of curcumin metabolism have rendered some interesting results.

Despite what are apparent pharmacokinetic limitations, curcumin has been reported to have multiple pharmacological activities and to be effective against a wide variety of diseases due to its anti-carcinogenic (38, 7, 39, 40, 2, 3, 37), hepatoprotective (8, 41–44), thrombosuppressive (45, 46), cardioprotective (47–49), anti-arthritic (9–11), and anti-infectious properties (50–54).

Everything considered, the demographic shift toward an older population makes compounds with this broad spectrum of potential clinical applications particularly interesting. The remainder of this review will summarize the effects curcumin in diverse experimental models of neurodegenerative diseases and speculate on the directions the field is headed in

the immediate future. We particularly emphasize studies of curcumin in invertebrate models, mice and clinical trials in humans.

3. Effect of curcumin in cell cultures

In addition to the reported benefits of curcumin in traditional Chinese and Indian medicine, the beneficial effects of curcumin have been demonstrated in a wide variety of cells, including neurons (55), astrocytes (56) and microglia (57). Effects have also been tested in primary cell cultures from different regions of the central nervous system, including cortical (58), mesencephalic (59), hippocampal (55) and spinal cord (60). Curcumin is known to possess neuroprotective properties (61), and its anti-inflammatory (62), anti-oxidant (63) and insulin-sensitizing effects (64) have been described using neuronal/glial primary and immortalized cells though its interaction with different molecular targets including metals, pro-inflammatory cytokines, protein kinases and other enzymes (65).

Aβ aggregation is a feature of AD and curcumin has been shown to be able to inhibit the formation of the Aβ fibrils *in vitro* (66). In fact, in a classic experiment where 214 antioxidant compounds were tested, curcumin proved the strongest inhibitor effect on the formation of Aβ fibrils (67). Furthermore, curcumin demonstrates a dose-dependent effect on the inhibition of $A\beta_{1\text{-}40/1\text{-}42}$ fibrils and even destabilizes preformed fibrils *in vitro* (66). Several studies have also demonstrated the ability of some curcuminoids compounds, including turmeric extract, to suppress Aβ aggregation and oligomerization (68–70). Yang and colleagues documented the ability of curcumin to inhibit Aβ aggregation and protect against Aβ-induced cell death (31). In addition, Zhang et al. showed that curcumin decreased both Aβ levels and Amyloid precursor protein (APP) maturation in mouse primary cortical neurons (71). Curcumin-mediated cell survival in Aβ as well as APP-challenged cell systems is due to attenuation of apoptosis and oxidative injury. Curcumin treatment of human neuroblastoma SK-M-NC cells prevents cell death elicited by the Aβ peptide through the inhibition of NFκB activation (72). Similarly, PC12 rat pheochromocytoma cells are protected from Aβ insult through an anti-oxidant pathway (73). Interestingly, curcumin is also able to prevent the fibrillation pattern of α-synuclein, the main protein involved in PD, in vitro (74).

Neuroinflammation plays a key role in the onset and progression of neurodegenerative diseases. In line with this idea, curcumin reduces the expression of IL-1α, IL-6 and TNF-α in LPS-stimulated BV2 microglia in a dose dependent manner (75). It is known that amyloid aggregates can be cleared via phagocytosis by brain macrophages and that patients with AD show signs of defective phagocytosis that results in an ineffective clearance of Aβ plaques. Interestingly, curcumin can stimulate microglial phagocytosis and clearance of Aβ *in vitro* as well as increase the induction of heat-shock proteins in response to the addition of soluble Aβ aggregates to neuronal cultures (76).

A link between iron metabolism and AD pathogenesis is suggested by the presence of an iron-responsive element (IRE) in the 5′ UTR of the APP mRNA (77). Additionally, high amounts of iron and copper in amyloid plaques could be responsible for stimulating free radical generation and thus increasing protein and DNA oxidation, lipid peroxidation, advanced glycation end products, carbonyls, malondialdehyde, peroxynitrite, and heme oxygenase-1 (OH-1) while decreasing levels of cytochrome c oxidase (78). In this context, the anti-oxidant properties of curcumin might also be linked to its capacity to complex with redox-active metals since curcumin can bind iron or copper ions in *in vitro* experiments (79) and because copper-curcumin complexes show radical scavenger and superoxide dismutase-like properties (80).

PD has been modeled *in vitro* through the specific neurotoxic effect of the 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (81) on dopaminergic neurons. Neurotoxicity triggered by 6-OHDA is attenuated by curcumin treatment in both SH-SY5Y and MES23.5 cells through the inhibition of reactive oxygen species (ROS), mitochondrial protection and anti-apoptotic mechanisms (82, 83). Curcumin also confers protection against MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and MPP^+ (1-methyl-4-phenylpyridinium) induced apoptosis in PC12 cells through the Bcl-2-mitochondria-ROS-iNOS pathway (84), and by the inhibition of the JNK pathway, which contributes to preventing dopaminergic neuronal death in SH-SY5Y cells (85).

Taken together these results suggest that curcumin could also have beneficial effects in whole organisms. In the next section we will analyze the current state of research involving curcumin and invertebrate models of aging and neurodegenerative disease.

4. Effect of curcumin in invertebrates models of aging and neurodegeneration

C. elegans has been used to identify molecules with a broad range of activities like anti-helminthics, antifungals, and compounds with neuronal activity (86–91). Additionally, a number of pharmacological interventions on the aging process have been demonstrated in this system (92–105). Many of the *C. elegans* small molecule studies to date have focused on the effects of natural products like extracts from *Ginkgo biloba* (106), blueberry phenols (107), or resveratrol (108). Interestingly, curcumin is also able to increase lifespan through a mechanism that involves the regulation of protein homeostasis (104). However, curcumin seems to have no effect on mouse lifespan (109) although it is possible that this compound could affect other aspects of aging including neurodegenerative diseases or that it could extend lifespan when administered differently.

In addition to the multiple benefits and resources for exploitation of the worm system as a platform for drug discovery, worms have also been genetically engineered to express human disease-associated proteins. For example, a robust model of protein aggregation in which human Aβ $peptide_{3\text{-}42}$ is expressed under the control of the *unc-54* myosin promoter in muscle tissue has been developed in *C. elegans* (110). Models expressing tau protein in neurons (111, 112), α-synuclein in different tissues (113–116) and mouse prion protein (117) have also been generated in this model system. There are also transgenic worms expressing chains of polyQ of different lengths, characteristic of the huntingin protein, tagged to YFP driven by the unc-54 promoter. As observed in humans, they demonstrate an aggregation rate that is dependent on the polyQ repeat length which culminates in a paralysis phenotype (118, 119). Several compounds that increase lifespan have been reported to prevent protein aggregation in these models (120). Recently, we exploited some of these worm models of neurodegenerative diseases to test several compounds that we identified as having pro-longevity properties (104). We found that these compounds significantly decreased the paralysis phenotype associated with Aβ $peptide_{3\text{-}42}$, PolyQ, myosin and perlecans aggregation through a mechanism that requires components of the protein homeostasis network. In particular, we found that curcumin supplementation increases worm lifespan by a mechanism that depends on both the Heat Shock Factor 1 (HSF-1), a transcription factor that has long been associated with the control of stress resistance, as well as a dietary restriction (DR)-like mechanism (121). These results were later confirmed by another laboratory that found that curcumin's anti-oxidant properties are also required for the lifespan increase induced by this compound (13).

Curcumin also increases lifespan, enhances stress resistance and improves spontaneous locomotion in two different strains of *D. melanogaster* (12). Similar to the case in worms, *Drosophila* has been genetically engineered to produce models of neurodegenerative disease including AD, PD, tauopathies, several polyglutamine disorders, amyotrophic lateral sclerosis and Prion disease (122). Unfortunately, just a few interventions in neurodegenerative diseases are found in the literature. Recently, Ceasar and colleagues showed that curcumin (1–100 μg/g yeast paste) is able to increase lifespan and improve locomotion in 5 different genetic models of AD in *Drosophila* (123). After curcumin treatment, they found no changes in number or size of Aβ deposits but instead observed a tendency to favor amyloid fibril formation over the soluble oligomeric Aβ species.

These studies demonstrate that a process long associated with age-related neurodegenerative disease is also a general feature of aging, suggesting that the loss of protein homeostasis could be a common mechanism of aging and disease. It follows that pharmacologically targeting the age-related decline of protein homeostasis could reduce and/or postpone neurodegenerative disease and extend lifespan.

There are, of course, many limitations to using these simple animal models and we should not underestimate the complexity of human disease by comparing to the events modeled in worms and flies. Indeed most of the enzymatic machinery that processes neurotoxic proteins is not present in these invertebrates and in most cases they lack critical modulators of disease progress such as complex inflammatory responses.

Nevertheless, these results suggest that edible compounds like curcumin could be used to suppress age-related disease pathologies and underline some important concepts for a novel approach to the discovery of new drugs with the potential to improve the conditions of neurodegenerative diseases. It is also important to consider that compounds that affect the dynamics and patterns of protein aggregation could also generate some soluble oligomeric species potentially toxic to the cell. Additionally, at the concentration required to affect protein aggregation, some compounds could have off-target effects that act in parallel to produce deleterious effects on cell physiology. Therefore, caution ought to be taken when considering compounds identified through this experimental approach for use as potential therapeutic drugs.

5. Effect of curcumin in mammals

A small number of compounds have been tested for their ability to increase lifespan and improve healthspan in mammals. Among others, nordihydroguaiaretic acid and aspirin (2-acetoxybenzoic acid) increase the lifespan of male, but not female mice (124), probably due to sex-specific pharmacokinetics of these drugs. Interestingly, the immunosuppressant rapamycin that inhibits mTOR signaling, is able to increase lifespan in both male and female mice when administered late in life (125, 126). Therefore, it is reasonable to assume that compounds that positively affect lifespan could also produce beneficial effects on degenerative diseases and hence, the effect of these compounds on healthspan is an active field of research.

Despite there being no evidence that curcumin affects lifespan in either male or female mice when administered beginning at 4months of age (109), several interesting studies in rodents have examined the ability of curcumin to provide neuroprotection from neurodegenerative disorders, especially AD and PD. For a review of the effect of curcumin in aging, please see Dr. Lai's chapter in this issue. In a pioneering study, Frautschy and colleagues (127) showed that a curcumin nutraceutical intervention attenuated oxidative injury, microgliosis, synaptophysin loss, spatial memory deficits, postsynaptic loss, and Aβ deposits produced by intracerebroventricular infusion of Aβ amyloid in rats.

The Aβ-overexpressing Tg2576 APPSw transgenic mouse, a popular mouse model for AD, has also been used as a pre-clinical tool to evaluate the neuroprotective potential of curcuminoids on this disease. Lim and coworkers (128) evaluated the effect on Tg2576 mice fed for 6 months with high doses (5,000 ppm) or low doses (160 ppm) of curcumin and found that both doses significantly decrease two biochemical conditions which normally are found elevated in the brains of these mice; protein oxidation and the levels of the proinflammatory cytokine interleukin-1β. In their experiment, low doses of curcumin attenuated Aβ overexpression, decreased oxidative damage, and also reduced levels of glial fibrillary acidic protein, which is involved in brain injury and inflammation. In a subsequent study in Tg2576 mice, dietary administration of curcumin reduced amyloid plaque formation, attenuated both ROS and reactive nitrogen species (NOS) formation as well as decreased cell death (129). Interestingly, in a study where curcumin was intravenously administered in Aβ overexpressing mice (PS1dE9), beneficial effects including plaque disruption and attenuation of distorted neuritis were also observed (28). Besides its anti-amyloid, anti-oxidant, anti-inflammatory and cholesterol-lowing properties, curcumin can also attenuate memory deficits in $AlCl_3$ and D-galactose-challenged Kunming mice (130).

Taken together, these studies illustrate the potential of curcumin to reverse neurodegeneration and improve the cognitive impairments associated with AD. There are also data suggesting that curcumin could have a protective effect against neurodegeneration in PD. As found for Aβ, curcumin can also inhibit the aggregation of α-synuclein (131), and several studies performed in rodents have examined the neuroprotective potential of curcuminoids against both MPTP- and 6-OHDA-induced dopaminergic degeneration. In these studies, orally and intravenously administered curcumin modulates dopaminergic damage in 6-OHDA-treated rodents by suppressing apoptosis and inducing microglial activation with a consequent improvement in locomotion (132, 133). Dietary, intravenous and intraperitoneal curcumin administration reversed the dopaminergic neurotoxicity in MPTP-treated rodents. In these experiments curcumin was able to decrease the oxidative stress, inhibit the activity of monoamine oxidase B, suppress apoptosis, inhibit protein nitration, increase levels of glutathione and decrease the activity of mitochondrial complex I induced by MPTP treatment (134–137). Unfortunately, there are limited data on the potential beneficial role of curcumin in other neurodegenerative diseases. This could be the result of the low incidence of these diseases. Recently, it has been shown that dietary curcumin in a doses of 555 ppm causes a decrease in huntingtin protein aggregation, improved rearing deficits but impairing climbing behavior in the CAG140 mice, an animal model of HD (138). These *in vivo* pre-clinical studies exhibit the potential of curcumin as a neuroprotector and suggest a role for this compound in the prevention and reversal of degenerative diseases such as AD or PD (Table 1).

6. Curcumin in clinical trials

As described above, therapeutic options for the treatment of neurodegenerative diseases offer limited benefits and multiple side effects, indicating the need to develop safe and effective pharmacological agents for the prevention and treatment of these kinds of diseases. Due to its anti-oxidant and anti-inflammatory effects, as well as its ability to inhibit protein aggregation, curcumin represents one of the most promising compounds with therapeutic potential. Epidemiologic evidence of curcumin action is illustrated in a recent large population-based study of 1010 elderly non-demented Asians. Subjects in this study that consumed curry occasionally, often or very often scored significantly better on the Mini-Mental State Examination (MMSE), an established measure of cognitive function, than did those who never or rarely consumed curry (139). The therapeutic use of curcumin has been tested in two independent clinical trials. The first one was a 6-month randomized, placebo-controlled, double-blind, clinical pilot study of curcumin conducted in patients with AD in

Hong Kong, China. In this study, thirty four subjects started the trial and 27 completed; 8 subjects on 0 g, 9 on 1 g, and 11 on 4 g curcumin per day. No difference was observed between the 1 and 4 g groups. On this study, curcumin serum levels reached a maximum of 250 nM at 1.5 h when given with food and 270 nM at 4 h when given with water. The inability to detect any relative protective effect of curcumin could be due to the lack of cognitive decline in the placebo group. However, when compared with the placebo control group, curcumin showed increased plasma levels of Vitamin E and increased serum $A\beta_{40,}$ suggesting that curcumin could disaggregate Aβ-deposits in the brain and release Aβ for circulation and disposal (140). The second clinical trial was a phase II double-blind study on mild to moderate AD, performed in California, USA with patients that receive 2–10 mg of curcumin for 6 months. Unfortunately, no significant improvement in cognitive function or changes in the levels of Aβ, total tau and phosphorylated tau in plasma and CSF were found (141) (Table 1). To date, two other studies are still active. One is a phase II study in India using 2 g/day of curcumin. The second is an early intervention conducted in the USA with a combination of 5.4 g of curcumin and bioperine, another natural product derived from black pepper that has been claimed to increase the bioavailability of several nutritional compounds. These studies are directed to evaluate the efficacy, safety and tolerability of curcumin in moderate AD.

Despite the somewhat disappointing results of the clinical trials available to date, it is premature to conclude a total lack of effect of curcumin on AD or PD. Additional studies with larger numbers of patients and longer period of treatment could be required to improve the clinical conditions, delay the onset or ameliorate the progression of these diseases.

7. Conclusions and future directions

While identifying compounds that improve the healthspan of mammals is undoubtedly more relevant for human drug development, the prohibitive cost of mouse studies makes it extremely unlikely that large scale chemical screens will be carried out in mice. Basic research in more cost-effective model systems is therefore a critical starting point for identifying such compounds and elucidating their mechanism(s) of action. Cell culture and invertebrate model organisms provide opportunities to assay promising compounds, like curcumin, in an efficient manner. Moreover, once candidate compounds are identified, model systems allow for rapid elucidation of the genetic pathways being targeted by these compounds. Furthermore, some pathological features of certain diseases are now being seen as a more general feature of aging. Perhaps the clearest example of this is the failure of protein homeostasis associated with age-related neurological disease, which leads to the formation of intra- or extracellular protein aggregates. This is consistent with a mechanistic relationship between aging and disease.

The disappointing outcomes of dozens of phase III clinical trials in AD, PD and others suggests that preclinical studies in animal models are less relevant than we would hope. Since aging is a major risk factor for many human diseases, compounds that slow aging are highly sought after due to their potential for treating age-related diseases. Here, we argue that the recent growth of a new subfield, the chemical biology of aging, will lead to the identification of candidate compounds and mechanistic insights that will ultimately propel forward treatments of age-related diseases. Curcumin is a great example of this general idea due to the multiple beneficial effects reported for curcumin *in vitro*. Curcumin has been reported to increase lifespan in *C. elegans* and *Drosophila* but does not seem to increase lifespan in mice. Nevertheless, there is enough evidence to suggest that curcumin could be of help in the treatment of several neurodegenerative diseases and other age-associated diseases to significantly improve healthspan. This could be due to its well-known anti-oxidant and anti-inflammatory properties, but could be also the result of a modulation of

protein aggregation through the regulation of protein homeostasis or a dietary restriction-like mechanism as recent studies in worms suggest (Figure 1). Since most of the drug therapies for neurodegenerative diseases (like AD and PD) currently available have shown little efficacy and produce multiple side-effects, a nutraceutical intervention with an innocuous and cheap compound like curcumin could represent a major avenue for the treatment of these diseases. One of the main limitations for a nutraceutical intervention with curcumin on neurodegenerative diseases is its limited bioavailability. This could be addressed by chemical modifications of curcumin, through its conjugation with lipophilic compounds or by co-administration of curcumin with compounds that facilitate its absorption. Despite that, clinical trials available to date do not provide conclusive evidence of the efficacy of curcumin for preventing or treating neurodegenerative diseases. There are, however, some encouraging results suggesting that curcumin could be of therapeutic relevance in these kinds of diseases. Of course, more studies are needed to explore the effects of this compound in long-term nutraceutical interventions and the fact that curcumin seems to be innocuous in humans could prompt additional studies on the effect of curcumin in the onset and progression of several neurodegenerative diseases.

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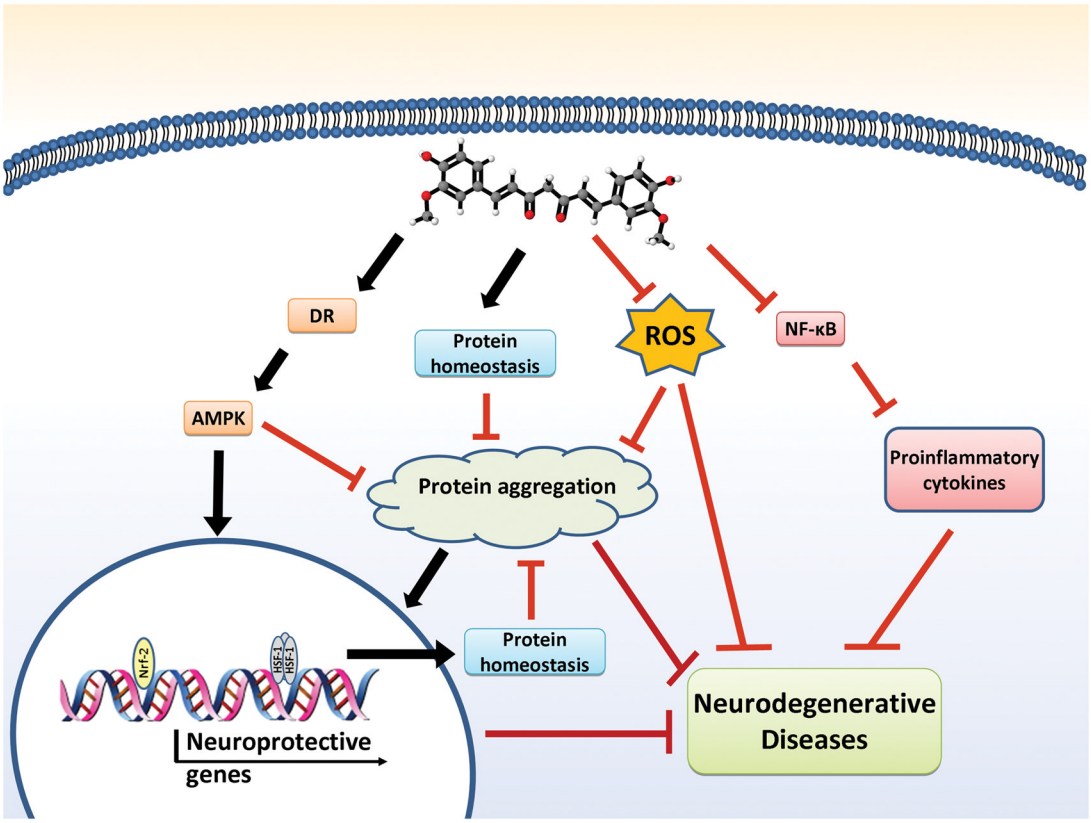

Figure 1. Model depicting the proposed mechanism of curcumin to provide neuroprotection

By it chemical structure, curcumin may act as a natural free radical (ROS) scavenger. Acting through the Neurotrophic factor κB (NF- κB) curcumin can decrease the release of different interleukins. Curcumin could act as a stress response mimetic that induces some components of the protein homeostasis network or as it is known to bind amyloid, directly acts in the misfolded cascade. This induction requires the transcription factors HSF-1 and Nrf2 (SKN-1 in *C. elegans*). Additionally, curcumin could act as a DR mimetic to activate these transcription factors through the AMPK pathway (Black arrows = induction, red symbol = inhibition).

Table 1

Preclinical and clinical studies described in this paper

Animal Model	Dose	Disease	Effects	Reference
Sprague-Dawley rats	Diet, 500 and 2000 ppm, 2 months	AD (Aβ ICV infusion)	↓Spatial memory deficits, oxidative damage, microgliosis, synaptophysin	127
Tg2576 APPSw mice	Diet, 160 and 5000 ppm, 6 months	AD (Aβ overexpression)	↓IL-1β, oxidative damage, GFAP, Aβ	128
Tg2576 APPSw mice	Diet, 500 ppm, 4 months	AD (Aβ overexpression)	↓cell death, iNOS, IL-1β	129
PS1dE9 mice	IV, 7.5 mg/kg/day, 7 days	AD (Aβ overexpression)	↑restoration of distorted neuritis, plaque disruption	28
Kunming mice	PO, 200 mg/kg, 45 days	AD($AlCl_3$, D-galactose)	↓Spatial memory deficits	130
Sprague-Dawley rats	PO, 50 mg/kg, 4 days	PD (6-OHDA)	TH^+ cells protection	132
ICR mice	IP, 50mg/kg, 3 times	PD (MPTP)	↓oxidative damage, ↑dopaminergic neurons	134
Swiss albino mice	IP, 80 mg/kg, 7 days	PD (MPTP)	↓MAO-B	136
CAG140	Diet, 555 ppm	HD	↓protein aggregation, ↑rearing, ↓climbing	138
Humans	Curry consumption	AD	Improve in cognitive function	139
Humans	1–4 g	AD	No changes in cognitive function	140
Humans	2–10 mg	AD	No changes in cognitive function or Aβ serum levels	141

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