
The Role of Curcumin in Post-Ischemic Brain

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Abstract: Progressive accumulation of misfolded amyloid and tau protein in intracellular and extracellular spaces is the most crucial etiopathological feature of brain ischemia, synaptic damage, or neural communication impairment. Clinical data suggest that dietary intake of curcumin enhances neurogenesis and offers neuroprotection. Curcumin is a natural polyphenolic compound with diverse and attractive biological properties. It may prevent aging-associated changes in cellular proteins, such as β -amyloid peptide and tau protein, that lead to protein insolubility and aggregation after ischemic brain damage. Therefore, curcumin seems to be a promising supplementary agent against neurodegeneration development after brain ischemia. The aim of this chapter is to highlight our current understanding of the neuroprotective role of curcumin in cerebral ischemia-reperfusion injury. The limitations and adverse events of curcumin are also presented.

Keywords: amyloid; brain ischemia; curcumin; tau protein; neuroprotection

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INTRODUCTION

In both developing and developed countries, there is a tremendous increase in the prevalence of ischemia-related brain injury (1). Current epidemiological data indicate that 17 million patients suffer from ischemic stroke per year, 1.5 times higher in men than in women, of whom 6 million die each year (2, 3). Brain ischemia elicits complications, including motor dysfunction, depression, fatigue, progressive dementia, and Alzheimer's disease (AD)-type neuropathological changes. Moreover, outcomes after stroke frequently lead to a high risk of early rehospitalization and institutionalization, with adverse consequences in terms of socioeconomic costs (3).

Recent experimental and clinical data suggest that ischemia-related brain damage causes neurodegeneration of the brain through inflammation (4–9), accumulation of the β -amyloid ($A\beta$) peptide pathway components (2, 9) outside the neurons due to cleavage of membrane-embedded proteins into neurotoxic single amyloidal units (10), and formation of neurofibrillary tangles (NFTs) (11, 12) inside the neurons due to the accumulation of paired helical filaments of hyperphosphorylated tau proteins (10). These changes damage neurons in different regions of the hippocampus, leading to brain atrophy and dysfunction (1, 13, 14).

Currently, thrombolysis is the first choice of treatment during ischemic stroke in humans; however, it has a limited therapeutic window regarding the time after the incident (15). In addition, it does not affect the progressive changes that develop slowly during, and after, recirculation (15). Moreover, there is no available treatment to prevent brain ischemia and/or delay or stop neurodegeneration progression associated with ischemia. Also, the current drugs for AD, such as acetylcholinesterase (AChE) inhibitors (galantamine and donepezil), rivastigmine (AChE and butyrylcholinesterase (BChE) inhibitor), and N-methyl-D-aspartate (NMDA) receptor antagonist memantine have not been able to significantly change the pathological process or provide improvements (16). Thus, the primary goal of drug discovery is to find or design neuroprotective molecules that are able to improve cognitive and motor functions after ischemia-related brain damage in AD. Because of the lack of effective pharmacological options, alternative therapeutics such as nutraceuticals are evaluated. Several evidences suggest a significant correlation between lifestyle factors, diet, and the onset of dementia and AD development (17). The intake of a ketogenic diet, or diets rich in probiotics, antioxidants, and ω -3 polyunsaturated fatty acids, or plant-based food may be beneficial to ameliorate the hallmarks of AD and other neurodegenerative diseases (17, 18). One of the promising dietary ingredient is curcumin, which displays a broad range of pharmacological activities, including antioxidant, anti-inflammatory (14), antibacterial, and antitumor actions (19).

Curcumin is a phytochemical extract from *Curcuma longa* rhizomes (19) of the *Zingiberaceae* (ginger) family. It is commonly used in Indian, Asian, and Middle Eastern cuisine. In Ayurvedic, traditional Persian, and Chinese medicines, it is used for its blood-purifying properties (20), treatment of skin and muscle inflammation, cough, sinusitis, allergy, bronchial dysfunctions, asthma, and hepatic disease (20). Chemically, it is known as diferuloylmethane ($C_{21}H_{20}O_6$), with a molecular mass of 368.37 g/mol. There are two aryl rings containing orthomethoxy phenolic OH-groups, symmetrically linked to a β -diketone moiety, which

have an impact on the physicochemical properties, biological functions, and antioxidant activities of curcumin (21). In addition, it shows potential as a therapeutic option for cognitive impairment and AD treatment due to the ability to lower A β levels and inhibit A β deposition and aggregation in mice (22), monkeys, bears (23), and humans (24). Moreover, it is a promising imaging agent for medical diagnostics (14).

NEUROPATHOLOGY AFTER BRAIN ISCHEMIA

Ischemic stroke in humans and animals is characterized by various neurobehavioral changes such as memory deficits, with a gradual decline in intellectual and cognitive functions (1). Eventually, it leads to dementia, which is a syndrome (or group of symptoms) that causes deterioration in behavior, ability to perform everyday tasks, memory, and learning capacity (25). Generally, it is not a normal part of aging but affects older groups of people (25). After ischemic brain damage, many changes occur in the brain, including the loss of neuronal cells in the CA2, CA3, and CA4 areas of the hippocampus (1, 9, 13). In addition, acute and chronic neuronal changes are associated with a decrease in acetylcholine levels, suggesting insufficient neuronal excitable transmission (26, 27). Also, synaptophysin and 95-density postsynaptic protein levels changes were observed in the hippocampus after focal cerebral ischemia (27). Of note, transient brain ischemia leads to synaptic autophagy and neural loss (28, 29). In addition, this type of ischemia causes severe alterations in both the corpus callosum and subcortical white matter (30), and activation of glial cells in later stages (31). Brain ischemia results in increased permeability of the blood-brain barrier (BBB); thus, inflammatory cells may easily invade the brain tissue. Also, it facilitates the leakage of amyloid and tau protein from serum into the brain parenchyma (30, 32–35), which is an etiological factor for white matter damage. Inflammatory process is implied to be a significant component, which contributes to neurodegeneration progression. Inflammation was once considered a secondary process to ischemic neurodegeneration, but recent studies present that inflammatory mediators may stimulate amyloid protein precursor metabolism by upregulation of β -secretase (9).

Extensive research has revealed that brain ischemia is associated with numerous neuronal alterations, including A β peptide production and accumulation, tau protein phosphorylation, NFT formation, mitochondrial damage, synaptic disappearance, microglia, and astrocyte activation (1, 2, 7, 9, 11, 36, 37). These depositions of extracellular A β plaques and intracellular accumulation of tau protein-containing NFTs are characteristic of neurodegenerative diseases, including AD. Characteristic elements of this disease comprise extraneuronal senile plaques composed of A β peptides 1-40 (A β ₁₋₄₀) and 1-42 (A β ₁₋₄₂) together with intraneuronal NFTs generated by phosphorylation of tau protein in the brain (13). The amyloid protein precursor and amyloid peptide are found to be upregulated in neurons and in extracellular space (8). Therefore, disruptions in A β metabolism and/or A β clearance contribute to AD pathogenesis. Noteworthy, in experimental post-ischemic injury in the CA1 and CA3 areas of the hippocampus and medial temporal cortex, the expression of genes related to AD is altered, including genes of the amyloid protein precursor, α -secretase, β -secretase, presenilin 1,

presenilin 2, and tau protein (38). In addition, vascular damage and reactive gliosis are associated with deposits of amyloid in both ischemia-related brain injury and AD brain, which indicate the importance of the cerebrovasculature in further pathogenesis of AD (8).

AMYLOID AFTER BRAIN ISCHEMIA

The deposition of amyloid plaques, which are dense (39) or diffuse (40), is proposed to be a characteristic feature of the brain neurodegenerative diseases (41). These are mainly present in the hippocampus, ischemic cortex, entorhinal cortex, corpus callosum, and around the lateral ventricles (39) as well as thalamus (40). The A β peptide is generated from amyloid protein precursor (APP) via sequential proteolytic processing by β -APP-cleaving enzyme-1 (BACE1) and γ -secretase to generate multiple A β forms of varying amino acid lengths (14) that aggregate readily into oligomers and fibrils. The A β_{1-42} form is postulated to be the most neurotoxic A β species (42). They are mainly found in neurons, microglial cells (43), astrocytes (44), and oligodendrocytes (1, 45). The abnormal accumulation of A β peptide may be involved in the repair of ischemic tissue followed by astrocyte cell loss (1, 36, 44) and the development of glial scar (36, 44). Moreover, these changes are responsible for the development of leukoaraiosis after ischemic brain damage (46). Neurons affected by these deposits undergo synaptic degradation and neuronal cell death (47). Experimental data have shown that in cerebral ischemia, A β peptide is generated as a result of neuronal injury and death (48), which contributes to the development of dementia with the AD phenotype through neurotoxic effects (49, 50).

TAU PROTEIN AFTER BRAIN ISCHEMIA

The major component of NFT is hyperphosphorylated tau protein, which may have a critical role in the progression of AD (42). It is observed in neurons, astrocytes, microglial cells, and oligodendrocytes after ischemia in both the hippocampus and cortex (51–54). Hyperphosphorylated tau protein is deposited as paired helical filaments in brain tissue (55), leading to neuronal apoptosis (56), followed by memory dysfunction (55). Interestingly, the concentration of tau protein is detectable in plasma after complete brain ischemia in humans within 96 h; thus, it is a valuable biomarker of the progression of the neuronal changes during recirculation (35). Of note, the tau protein level can be useful as an indicator of neurological outcome after ischemia-reperfusion (35).

RATIONALE FOR USING CURCUMIN AFTER BRAIN ISCHEMIA

Curcumin is a neuroprotective molecule with potent antioxidant and anti-inflammatory properties (57). These pleiotropic properties also reveal anti-amyloid, anti-tau protein hyperphosphorylation, and anti-apoptotic action, as

well as increasing neuronal lifespan and promoting neurogenesis (Figure 1). Experimental data show that curcumin may be one of the most interesting and promising natural pleiotropic molecules for the treatment of ischemic stroke and various brain diseases. Moreover, its physical and chemical properties, such as being hydrophobic and lipophilic, are beneficial (58). These properties affect the absorption, bioavailability, and half-life profiles of curcumin in the brain tissue (59). Moreover, this substance is safe, inexpensive, and easily accessible (1, 60).

Studies carried out in an animal model of AD (22, 61), and humans (62–65) have shown that A β metabolism is altered by curcumin. Also, curcumin may influence brain function and the development of dementia because of its antioxidant and anti-inflammatory properties, as well as its ability to influence A β metabolism (14) and the accumulation of misfolded amyloid peptides (2, 11, 13).

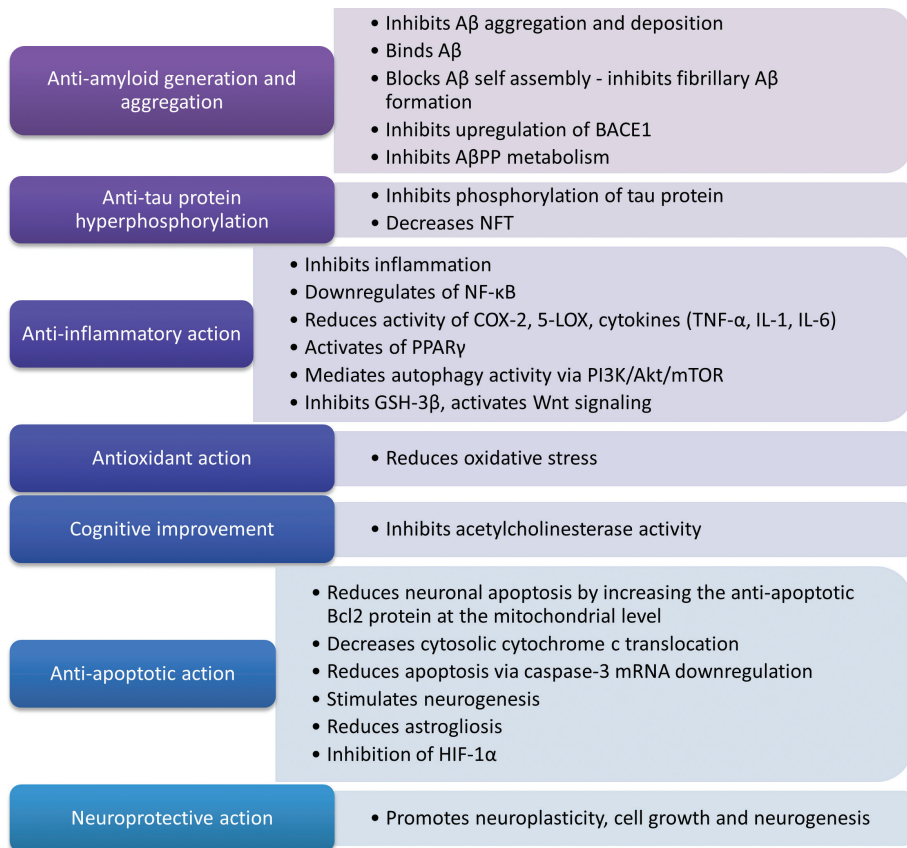


Figure 1. Potential mechanism of action of curcumin. Based on (14). 5-LOX, 5-lipoxygenase; AD, Alzheimer's disease; A β , β amyloid; BACE1, β -APP-cleaving enzyme-1; COX-2, cyclooxygenase-2; HIF-1 α , hypoxia-inducible factor 1-alpha; IL-1, interleukin-1; IL-6, interleukin-6; NFT, neurofibrillary tangles; NF- κ B, nuclear factor kappa B; PPAR γ , peroxisome proliferator-activated receptor-gamma; TNF- α , tumor necrosis factor- α .

Moreover, it inhibits phosphorylation of tau protein, thus decreasing NFT (66, 67). The basic strategy for developing treatment of post-ischemic neurodegeneration is to target all these pathways involved in its pathogenesis (68). Effective penetration of the BBB and neuronal membranes is necessary. Curcumin easily crosses the BBB (68, 69). Also, it binds and disaggregates oligomers and fibrils of amyloid peptides (70) and increases the clearance of amyloid (14).

Anti-amyloid properties

The A β peptide is a product of amyloid protein precursor (APP). The generation of a β -amyloid peptide is catalyzed by enzymes such as β -secretase and γ -secretase. Of note, these enzymes are attractive targets for curcumin after cerebral ischemia. Curcumin inhibits β -secretase activity; thus, it has the potential to decrease A β peptide levels (57, 70). Moreover, it inhibits the maturation of the APP and the amyloidogenic pathway, which contributes to a reduced A β peptide concentration (71). Therefore, the modulation of APP by curcumin reduces amyloid levels due to the increased retention of the immature APP in the endoplasmic reticulum and interference with APP endocytosis (71). In addition, curcumin inhibits amyloid aggregation (72, 73), modulates the formation of nontoxic aggregates, reduces the toxicity of many amyloid conformers (e.g., monomeric, oligomeric, prefibrillar, and fibrillar amyloid), and decreases the permeability of the cell membrane induced by amyloid aggregates (74). Curcumin, as well as pyrazoles and isoxazoles (derived from curcumin) are able to destabilize A β_{1-40} and A β_{1-42} and inhibit the metabolism of A β PP (75). Of note, the inhibition of A β_{1-40} and A β_{1-42} formation by curcumin is dose-dependent, where the most effective activity was observed with an EC₅₀ of 0.09–0.63 μ M (70, 76). Also, the high lipid content of brain tissue allows lipophilic curcumin to cross the BBB and inhibit the aggregation of amyloid proteins (58).

Brahmkhatri et al. found that polymeric nanoparticle-encapsulated curcumin conjugates with gold nanoparticles inhibited aggregation of the N-terminal area of amyloid and were able to dissolve aggregates (77). Also, Mithu et al. revealed that the A β_{1-42} fibrils were disrupted by curcumin, which induced significant structural changes in the Asp-23-Lys-28 salt bridge region and near the C terminus (78). Moreover, Garcia-Alloza et al. demonstrated that systemic treatment with curcumin for 7 days cleared and reduced existing amyloid plaques in APP^{swe}/PS1^{dE9} mice but also reversed structural changes in dystrophic dendrites, including abnormal curvature and dystrophy size (22). In addition, disruption of clearance is associated with the rise of A β peptide in brain tissue. One way includes the transport of A β peptide via LRP1 across the BBB to the blood, followed by enzymes that degrade A β peptide (79). Curcumin may bind to the A β peptide and promote receptor-mediated efflux of A β peptides (70). In addition, it suppresses the RAGE-mediated influx of A β peptides across the BBB from blood. Moreover, curcumin may stimulate phagocytosis by activating microglial cells and increase the presence of phagocytic cells around A β peptide deposits (68). The presence of two phenolic (OH) groups and one active methylene (CH₂) group in curcumin makes it an excellent ligand for metal chelation, and may remove metal from amyloid (80).

Anti-tau properties

Hyperphosphorylated tau protein as paired helical filaments is a component of NFT in brain ischemia (81). They change the cytoarchitecture of brain tissue, increase oxidative stress, cause mitochondrial dysfunction, and promote neurodegeneration (82). Therefore, the phosphorylation of tau protein may be a link between oxidative stress and cognitive decline. The tau protein hyperphosphorylation is modulated by several kinases, including glycogen synthase kinase-3 β (GSK-3 β) and mitogen-activated protein kinase (MAPK) (82), cyclin-dependent kinase 5, S6 kinase, protein kinase A, calcium/calmodulin-dependent protein kinase II, SAD kinase, extracellular signal-regulated kinase 2, microtubule affinity-regulating kinase, and Src family kinases (Fyn and c-Abl). Therefore, a combined therapy involving these checkpoints could become a viable therapeutic option for ischemia-related brain damage and/or AD treatment (83). Curcumin has been found to inhibit tau protein aggregation, and disintegrate preformed tau protein oligomers and the formation of tau protein fibril (84). Moreover, it inhibits GSK-3 β activity, diminishing tau protein dimer formation and hyperphosphorylated tau protein oligomerization in aged human tau protein transgenic mice (66).

Anti-inflammatory action

Another reason for using curcumin in therapy for neurological diseases is its ability to reduce neuroinflammation. It is a potential anti-inflammatory agent, which can downregulate many neuroinflammatory marker proteins, such as nuclear factor kappa B (NF- κ B) (85). Curcumin is able to diminish the activity of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), the enzymes involved in the arachidonic acid metabolism (86). Moreover, it reduces the levels of several cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (87). It can activate the peroxisome proliferator-activated receptor-gamma (PPAR γ) (88). Besides reducing neuroinflammation, Wang et al. have shown that curcumin significantly decreased the expression of phosphatidylinositol 3-kinase (PI3K), phosphorylated Akt, and mTOR at protein levels (89). Curcumin mediates autophagy via PI3K/Akt/mTOR (90), which further suggests its neuroprotective effect (89). Of note, the important feature of curcumin is the ability to change the composition of bacterial populations and reduce intestinal inflammation (91). It has been proved that any changes in gut microbiota are associated with different pathologies, even with neurological diseases such as AD, schizophrenia, brain ischemia, and depressive disorders (92). Curcumin is a modulating factor of inflammation; thus, it impacts the gut-brain axis (91).

Antioxidant action

Curcumin acts as a powerful antioxidant in post-ischemic brain. High metabolic rate of the central nervous system, its increased demand for O₂, and large quantities of membrane phospholipids and polyunsaturated fatty acids significantly

contribute to an increase of reactive oxygen species, which may be present in chronic progressive neurological diseases (93). Curcumin is able to scavenge superoxide anions (O_2^-) and hydroxyl radicals (OH^\cdot), and increase antioxidant levels, such as glutathione (94). In addition, it protects cells from lipid peroxidation, DNA damage, and protein oxidation or protein carbonylation (95).

Antiapoptotic action

Curcumin diminished neuronal apoptosis by increasing the antiapoptotic Bcl2 protein at the mitochondrial level, and decreasing cytosolic cytochrome c translocation (96). In addition, it reduced apoptosis (97) via caspase-3 mRNA down-regulation (90), decreased mitochondrial membrane potential (97), stimulated neurogenesis (98), and reduced astrogliosis (99). In a recent study, curcumin protected ischemic neurons from apoptosis through the neuroprotective effect associated with both autophagy and hypoxia-inducible factor 1-alpha (HIF-1 α) inhibition (100). In addition, curcumin can inhibit the PP1 and Akt/p70S6K pathways to activate extracellular signal-regulated kinases (ERK1/2) and subsequent autophagy (101).

Neuroprotective activity and neurogenesis

Curcumin stimulates brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and platelet-derived growth factor (PDGF) (102), which may enhance neurogenesis, synaptogenesis and improve cognition in rats (103). Besides, levels of synaptophysin and PSD95 can be restored in animal models of neurodegenerative diseases (104). Experimental studies show that curcumin reduced the volume of brain infarction and brain edema (99,105). Curcumin improved motor and sensory activity; however, improvements in neurobehavioral and neurological deficits were minimal (24, 99). Another feature of curcumin is neuroprotection against local cerebral ischemia/reperfusion injury via the activation of Notch signaling pathway (98). It stimulated neurogenesis and decreased apoptotic index within three days of reperfusion (98). Moreover, curcumin played a role in neuroprotection through preventing lipid peroxidation and decreasing peroxynitrite, while increasing endogenous antioxidant enzymes in a cerebral ischemia model of rats (106). In addition, curcumin has been recognized to improve neurological function scores, maintain the integrity of the BBB, and reduce the infarct volume of the cerebral cortex (1, 107, 108). Moreover, curcumin attenuated glutamate neurotoxicity in the hippocampus (107).

Influence on microcirculation

Another role of curcumin includes its impact on cerebral circulation, which can be improved by reduced adhesion of platelets in brain microvascular endothelial cells (BMECs) and inhibition of inflammation of blood vessels (109). However, curcumin may exhibit angiostatic abilities by controlling the expression of genes of metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF),

which are recognized as suppressors of extracellular matrix organization and initiating angiogenesis (110). Also, it enhanced the generation of granulation tissue, including rapid re-epithelialization and neo-vascularization in wound healing through modulation of the expression of TGF- β 1, its receptors, and nitric oxide synthase (111).

Regulatory role on epigenetics

Curcumin plays significant regulatory roles in modulating the methylation, acetylation, ubiquitination, and phosphorylation status of histone and other DNA-binding proteins (112), mainly by inhibiting histone acetyltransferases (HATs) activity and activating histone deacetylases (HDAC) in AD (112). Curcumin has been considered a selective inhibitor of the p300/CREB binding protein HAT activity (113). Therefore, curcumin can diminish the catalytic activity of HATs and inhibit nuclear histone acetylation that reduces the inflammation via the NF- κ B pathway in some brain diseases (85).

LIMITATIONS OF CURCUMIN TREATMENT AND SIDE EFFECTS

Toxicological assessments have revealed that curcumin is a pharmacologically safe substance. The intake of 8 g daily in the short-term has been shown to exert no significant side effects (64). Similar effects were observed in a phase I study, with 8 g of curcumin daily for three months (80). To date, clinical studies of curcumin have revealed limited effects, most likely because of curcumin's relatively low solubility and bioavailability. Curcumin has poor water solubility, and it is unstable in most body fluids (68). In addition, the selection of cohorts with ischemia-related brain damage or diagnosed AD has an impact on the effectiveness of this treatment because of pre-existing major neuropathologies. However, curcumin may have potential in targeting early brain ischemia or AD pathology (by treating healthy, pre-clinical, and mild cognitive impairment-stage cohorts). New curcumin formulations that increase bioavailability are renewing optimism concerning curcumin-based therapy (14). Several studies have shown that high doses of curcumin can cause adverse side effects, including headache, nausea, diarrhea, abdominal pain, yellow stool, skin rash, swelling of the skin, and dermatitis (64). Moreover, since curcumin may interact with some drugs, it is not recommended for people taking blood thinners, reserpine, or nonsteroid anti-inflammatory drugs (57).

CONCLUSION

Ischemia-reperfusion leads to neuronal damage and death, with misfolded protein deposits. In addition, it results in cognitive deficits and/or impairment of motor coordination with probable development of dementia of AD phenotype (28). Due to the pleiotropic influence of curcumin on the brain, including anti-amyloid, anti-tau protein, antioxidant, anti-inflammatory, and neuroprotective properties,

curcumin is a promising candidate for the treatment of post-ischemic neurodegeneration with misfolded proteins (1). Therefore, this multi-functional therapeutic compound may have a potential clinical utility in the treatment of neurodegenerative disorders. Currently, the existing data of using curcumin as a therapeutic option in the ischemic-related brain diseases seems interesting. However, there are limited number of studies performed in humans. Further, it requires extensive, multi-center research efforts.

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