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Review Article

Novel Insight to Neuroprotective Potential of Curcumin: A Mechanistic Review of Possible Involvement of Mitochondrial Biogenesis and PI3/Akt/ GSK3 or PI3/Akt/CREB/BDNF Signaling Pathways

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Neurodegeneration is a gradual mechanism of neuronal loss arising from numerous cellular and molecular events such as mitochondrial dysfunction, oxidative stress, inflammation, and apoptosis, and the consequence of these processes is neuroplasticity impairment, cognitive diseases, mood-related diseases, and normal cellular activity. Over the last year, major advances have been made in the field of the introduction of herbal compounds with neuroprotective efficacy, one of which is curcumin. Curcumin (diferuloylmethane) is the most abundant turmeric component extracted from the *Curcuma longa* plant rhizomes. Accumulating evidence indicates that curcumin may induce mitochondrial biogenesis and can function as an antioxidant, anti-inflammatory, and anti-apoptotic agent, which may be used effectively to treat chronic neurodegenerative diseases and any situation in which the neurodegeneration process takes place. Curcumin has been shown to play a critical role in activating two essential signaling pathways phosphatidylinositol-3(PI3)/ protein kinase B(Akt)/ glycogen synthase kinase-3 (GSK3) and PI3/Akt/cAMP response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) and preventing the incidence of neurodegeneration via these two pathways. Curcumin's protective functions against neural cell degeneration due to mitochondrial dysfunction and consequent events such as oxidative stress, inflammation, and apoptosis in neural cells have been documented and clinical data have increased to suggest that curcumin may be a standard candidate as a neuroprotective agent. Therefore, in this review, we summarized the clinical and experimental studies and interpreted the key contributory mechanisms of neuroprotective properties of curcumin in neurodegenerative diseases and disorders. We also tried to understand the function of PI3/Akt/GSK3 and PI3/Akt/CREB/BDNF signaling pathways in the neuroprotective properties of curcumin and tried to evaluate their association with antioxidant, anti-inflammatory, anti-apoptosis and biogenesis effects of mitochondria.

Key words: Curcumin, neuroprotection, PI3/Akt/GSK3, PI3/Akt/CREB/BDNF

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Neurodegeneration is characterized by progressive neuronal loss that is correlated with multiple cellular and molecular mechanisms resulting in neuroplastic dysfunction, cognitive impairment, and mood-related behavior (1, 2). Neuroprotection concepts are complex and include preventing cell death and restoring activity to damaged neurons, as well as restoring neuronal numbers and behavioral output (3, 4). Based on biological description, neuroprotective agents must be able to restore neural regeneration and maintain normal cellular function and behavior. Previous studies suggested that the protection of neural activity and behavioral functions such as learning and memory, may be good criteria for assessing a neuroprotective agent. On the other hand, there should be a clear correlation between the ability of one neural survival induction agent, neuroplasticity, and cognitive performance to receive the title of neuroprotective (4, 5). There are four distinctive methods for conferring neuroprotection according to the basic principle of neurodegenerative treatment: (1) antagonizing cytotoxic causal events (excess intracellular Ca^{2+}, accumulation of irregular proteins, excitotoxic effects of amino acids, oxidative stress, inflammation-related processes etc.); (2) stimulating endogenous protective processes (anti-free radical or DNA repair systems, neurotrophic factor development, possible steroid cyto-protective action, etc.); (3) promoting damaged structure repair strategies (grafts) or deep brain or cortical neuro-stimulation to activate possible 'protective' cell mechanisms (beyond symptomatic actions); (4) recovery of neuropl-asticity processes by neuroprotection activation including signaling pathways and activation of neurogenesis, and regulation of neurodegenerative associated behavioral disorder such as learning and memory loss, anxiety and depression (4, 5). Under these strategies, the production of drugs to delay or prevent the progression of neurodegenerative diseases and disorder may emerge logically from an enhanced understanding of the etiology and pathogenesis of these diseases and disorders (3, 4). The drawbacks of existing neurodegenerative disease pharmacological therapies have led to comprehensive work into novel natural compounds and non-pharmacological strategies to alter the course of these disorders, while reducing the side effects of drugs (3, 6). There has definitely been considerable improvement in these fields over the past few years with the possibility of the introduction of herbal compounds with "neuroprotective" efficacy (5, 6). Curcumin is one of these herbal compounds that has a high potential as a neuroprotective agent (7). Curcumin (diferuloylmethane) (Figure-1) is the most abundant component of turmeric, extracted from the *Curcuma longa* plant rhizomes (8, 9). This non-nutritious yellow pigment is a proven nutraceutical dietary phenol, and therefore of great medicinal and pharmacological significance (9). Studies have shown that curcumin can induce cell regeneration and defense in multiple organs such as the brain, cardiovascular system, liver, gastrointestinal system, respiratory system, and improve the functionality of these systems (10-12) (Figure-2).

Recent research has also shown the major effects of curcumin on the control of gene expression in the central nervous system in addition to its neuroprotective effects, which may play an important role in its current therapeutic potential (7, 13, 14). Several experimental and clinical models indicate variable complex underlying mechanisms for curcumin neuroprotective effects including activation and induction of survival molecules and neurotrophic factors, modulation of inflammatory behavior, anti-apoptotic behavior, modulation of oxidative stress, and upregulation of mitochondrial function (9, 14-15). Several studies have recorded the importance of curcumin in neurogenesis, neuronal repair, and neurotoxicity (3, 16). It was proposed that curcumin may have neuropr-otective capabilities and could decrease the risk of

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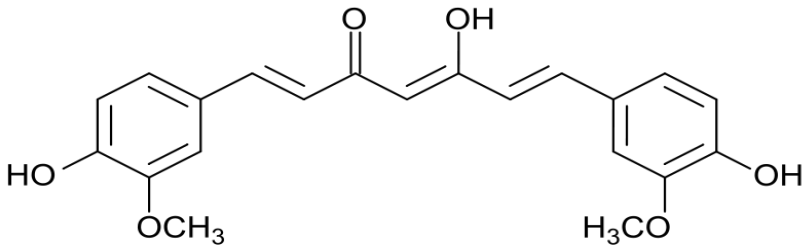

Fig. 1. Structure of curcumin.

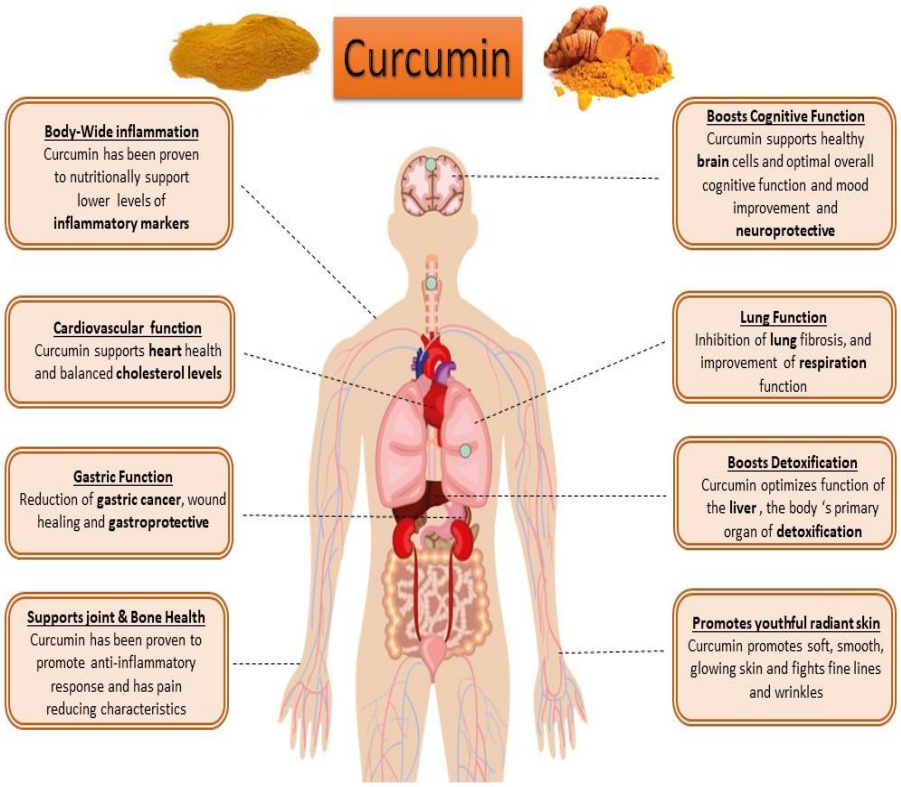

Fig. 2. Curcumin impacts on the functioning of various body systems.

developing dementia because it inhibits key enzymes and precursor protein involved in Alzheimer's pathogenesis and other associated diseases (17, 18).

Mitochondrial dysfunction has emerged over the last decades as a common pathological characteristic considered as a "convergence point" for neurodegeneration. Although the quest for cure is still a utopia in the field of neurodegenerative diseases, it is clear that the pathobiology of mitochondria is a significant contributing factor to neurodegenerative events that occur during the course of such diseases (5, 19). Recent findings have demonstrated the mechanisms underlying mitochondrial dysfunction in Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), with both bioenergetics and functional defects being transversal to all three diseases. Such neurodegenerative disorders are partially the product of a dynamic interplay involving robust changes in the transportation and turnover of mitochondria, leading to a mitoenergetic crisis, synaptic starvation, and eventually neuronal degeneration and loss (20, 21).

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In this context, in the last decade mitochondria has emerged as an appealing therapeutic target for tackling such neurodegenerative diseases in a timely manner. Natural and mitochondrial based antioxidants such as curcumin have been widely used to mitigate AD, PD, and HD-related symptomatic and neuropathological features (22, 23). Curcumin has been shown to have important neuro- and mitochondria-protective properties against a broad-spectrum of neurotoxic compounds and neurodegenerative diseases/ injury-associated diseases (23, 24). Several exogenous and endogenous causes, such as age, nuclear and mt-DNA mutations, medications, neurotoxic agents, and misfolded/ aggregated proteins, have been shown to induce mitochondrial dysfunction, which is closely related to the initiation and pathogenesis of neurodegenerative disease (24, 25). Based on *in vitro* and *in vivo* data, curcumin has an excellent ability to protect CNS cells against mitochondrial pathology in a wide range of neurodegenerative events and against multiple stimulating factors (e.g., ischemia and substance abuse mediated neurodegeneration by mitochondrial dysfunction), neurotoxic compounds (e.g., methamphetamine, alcohol aluminum, manganese, D-galactose), and adverse effects of certain existing medications on neurodegeneration (e.g., oxaliplatin) as well as misfolded-/aggregated-/mutant protein pathologies (e.g., amyloid β, amyloid precursor protein, and α-synuclein) (24-26). In addition, curcumin performs its mitochondrial defensive properties by: (a) retaining mitochondrial ΔΨm/ increasing mitochondrial fusion activity, mitochondrial biogenesis and synaptic proteins; (b) reducing fission machinery, mitochondrial swelling, lipid peroxidation, protein carbonylation;(c) modulating/ targeting the signaling of phosphor- cyclic AMP response element binding protein (CREB)- brain-derived neurotrophic factor (BDNF) and serine/threonine kinase 1 (AKT)/ glycogen synthase kinase-3 (GSK3); (d) restoring glutathione (GSH) and superoxide dismutase (SOD) levels; and(e) reducing tumor necrosis factor-α (TNF-α) and interleukin (IL-1β) and decreasing certain inflammatory biomarkers (7, 14, 19, 26-31).

The results showed that ongoing curcumin therapy was correlated with reduced dementia levels in brain cognition centers (30, 32, 33). It has been shown that chronic use of curcumin in patients with neurodegenerative disorder can cause gray matter volume increase (33, 34). The amount of hippocampal cells increases following chronic curcumin therapy, possibly because of the neurotrophic effects of curcumin (35, 36).

Curcumin has been shown to robustly upregulate neuroprotective protein concentrations of B-cell lymphoma 2 (Bcl-2) in areas of the rodent brains and human neuronal cells (37, 38). Recent studies have shown that chronic curcumin treatment offers robust defense against glutamate and N-methyl- d-aspartate (NMDA) -induced cell death of cultured central nervous system (CNS) neurons, including cerebellar granule cells, hippocampal neurons, and cortical neurons (39, 40). Numerous animal models stated that the neuroprotection against excitotoxicity caused by curcumin consists of multiple mechanisms (40, 41). Those mechanisms include NNMDA receptor inhibition, gamma aminobutyric acid (GABA) activation, changes in cellular Ca^{2+} concentration, changes in gene expressions such as upregulation of *Bcl-2*, downregulation of *p53* and *Bax*, activation of *Akt* and CREB cell survival factors, as well as modulation of c-Jun N-terminal Kinases (*JNK*), *p38* and mitogen activated protein kinase (*MAPKs*) (40-46). Through all these pathways, it has been shown that curcumin has antioxidant, anti-inflammatory, anti-apoptotic, immunomodulatory and cell-protective properties as a general mechanism (40-46). Curcumin is reported to be neuroprotective in adult brain ischemic models, and may reduce brain injury by inhibiting neuronal apoptosis (47-49). Curcumin was suggested as a putative agent in the

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treatment of some cell degenerative disorders, and may induce organ function modulation in certain multiple disorders. Also, several studies have pointed out that apoptosis can be prevented to some degree by the protective qualities of curcumin (50, 51). Moreover, the synergistic effects of curcumin on the activation of antioxidant enzymes and mitochondrial biogenesis, and also its properties in inhibiting oxidative stress was documented (52, 53). Studies have also shown that curcumin has antioxidant and anti-inflammatory properties that inhibit large cytokines that cause inflammation (Figure-3) (54, 55).

Several studies indicated that curcumin-based Bcl-2 development facilitates the regeneration of severed axons in mammals (45, 56, 57). An investigation was conducted to determine whether curcumin in rodent hippocampus increases the Bcl-2 levels (45, 58, 59). Such results, offer a clear justification for investigating curcumin as a possible treatment for neurodegenerative diseases (13, 60). Regulation of signal transduction by curcumin within critical brain regions affects the role of multiple neurotransmitter systems, and may thus explain the efficacy of curcumin in protecting neurons. In this article, we reviewed the key components of the main mechanism and signal transduction pathways and targets for the behavior of curcumin, and sought to combine these mechanisms with data emphasizing curcumin's neuroprotective impact.

To find the available evidence and information in the literature on the role of curcumin's neuroprotective properties in preventing or treating

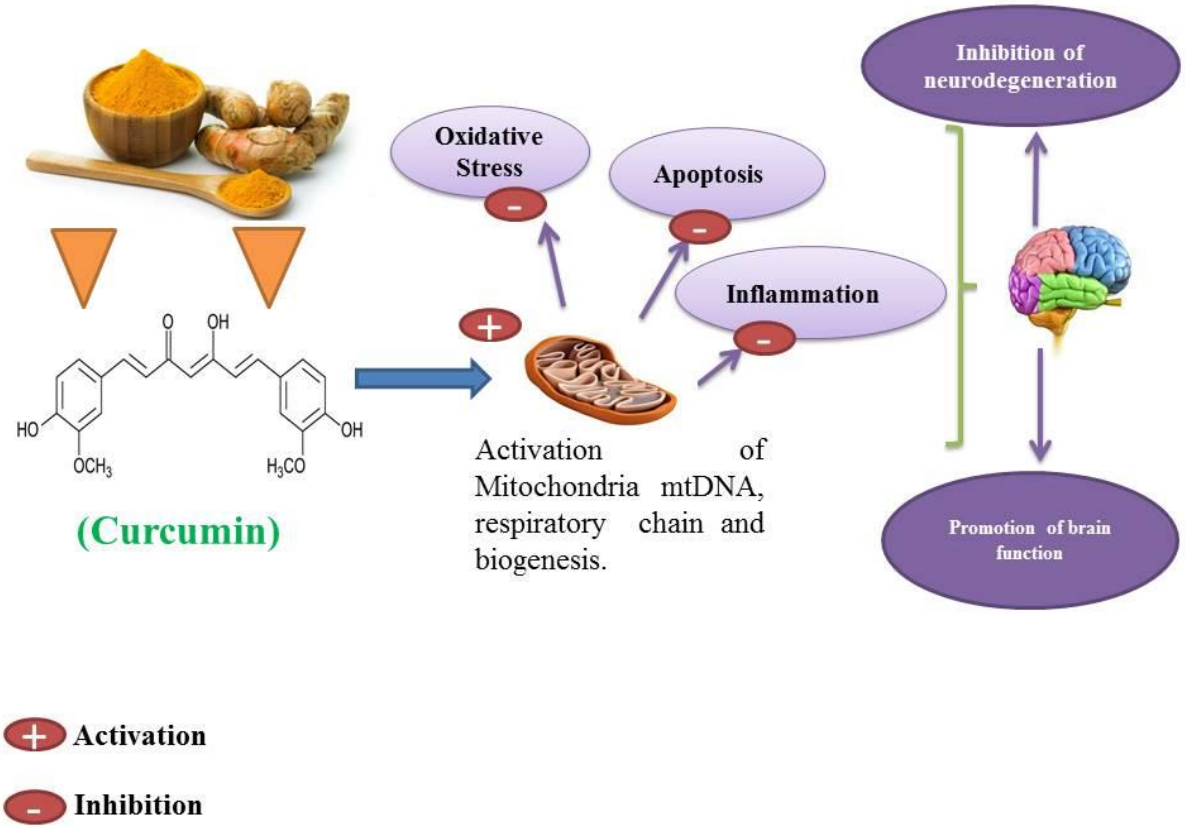

Fig. 2. The protective effect of curcumin in multiple body organs is mediated through mitochondrial biogenesis which ultimately inhibits oxidative stress, inflammation, and apoptosis leading to increased function of body organs.

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neurodegenerative disorder and diseases with focus on occurrence of oxidative stress, inflammation, and apoptosis/cell death sequels, searches were performed in many databases such as Web of Science, PubMed, Elsevier Science Direct, Google Scholar, Core Collection, Cochrane, through papers corresponding to the years 1990-2019. It should be noted that "curcumin," "neuroprotection," "neurodegenerative disease," "signaling pathways," "oxidative stress," "apoptosis", and "inflammation" were the search terms and key words for analyzing all published papers in this manner. We have used the MESH term "OR" operator between synonyms keywords and "AND" operator between individual keywords to find articles and documents, as well as articles with the greatest consistency with our objective. For the review of papers, we had included papers which considered both animal and human studies, highlighted the effects of curcumin neuroprotection in neurodegenerative diseases and/or disorders, pinpointed three distinct and distinguishing main mechanisms e.g. antioxidant, anti-inflammatory and anti-apoptosis, and referred to 200 papers. Only two main PI3/Akt/GSK3 and PI3/Akt/CREB/BDNF signaling pathways were selected from all the signaling pathways involved in neuroprotection, and therefore selected and reviewed 20 papers. Also, due to the prevalence of curcumin-related studies and word counting limitations, we avoided evaluating other signaling pathways and focused on PI3/Akt /GSK3 and PI3/Akt / CREB / BDNF.

Curcumin

The most significant bioactive chemical constituent of turmeric (golden spice) (61, 62) (Figure-1) is curcumin (a hydrophobic polyphenol). This compound was extracted from *Curcuma longa* rhizome which belongs to the family of Zingiberaceae (9, 62). It has a wide variety of medicinal and pharmacological properties (9, 63, 64).

Molecular mechanisms involved in neuroprotective effects of curcumin

Anti-apoptotic activity

Apoptosis and programmed cell death play a crucial role in the organism's growth, and since the early stage of CNS formation (65, 66). The outer and intracellular signals are thought to cause apoptotic cell death (65, 67). *In vitro* and *in vivo* studies have shown neuroprotective activities of curcumin (57, 68). Evidence relating in particular to the neuroprotective and anti-apoptotic action of curcumin has been documented recently (69, 70). Experimental studies have shown that curcumin prevents cell death through both intrinsic and extrinsic apoptotic pathways (Figure-4) (71, 72). There is some evidence that chronic curcumin therapy, also at low doses, exhibits neuroprotection in transient focal cerebral ischemia (48, 49, 68, 71).

Anti-apoptotic pathways are involved in the neuroprotective effects caused by curcumin (48, 49, 68, 71). In particular, recent biochemical and immunohistochemistry studies have revealed an enhanced expression and activation of intracellular proteases, in particular caspase-3, which act as initiators and performers of the apoptotic process (1, 73, 74). The role of caspases in apoptotic processes after a neurodegenerative cycle is confirmed by the finding that treatment with caspase inhibitors decreases brain damage caused by neurodegenerative diseases (1, 2, 73-75). Chronic curcumin therapy upregulates *Bcl-2* which encodes an anti-apoptotic protein both *in vitro* and *in vivo*, and decreases the levels of pro-apoptotic proteins p53 and Bax (44-46). These data support the assumption that curcumin-mediated protection against neurodegenerative disease and cerebral ischemia involves anti-apoptotic mechanisms (48, 49, 68, 71). Curcumin has recently been shown to inhibit GSK-3, an enzyme involved in pro-apoptotic signalization (76-78). Hence curcumin's neuroprotective activities may be due in part to GSK-3 inhibition (79, 80). According to a new study, the neuroprotective effects of curcumin were

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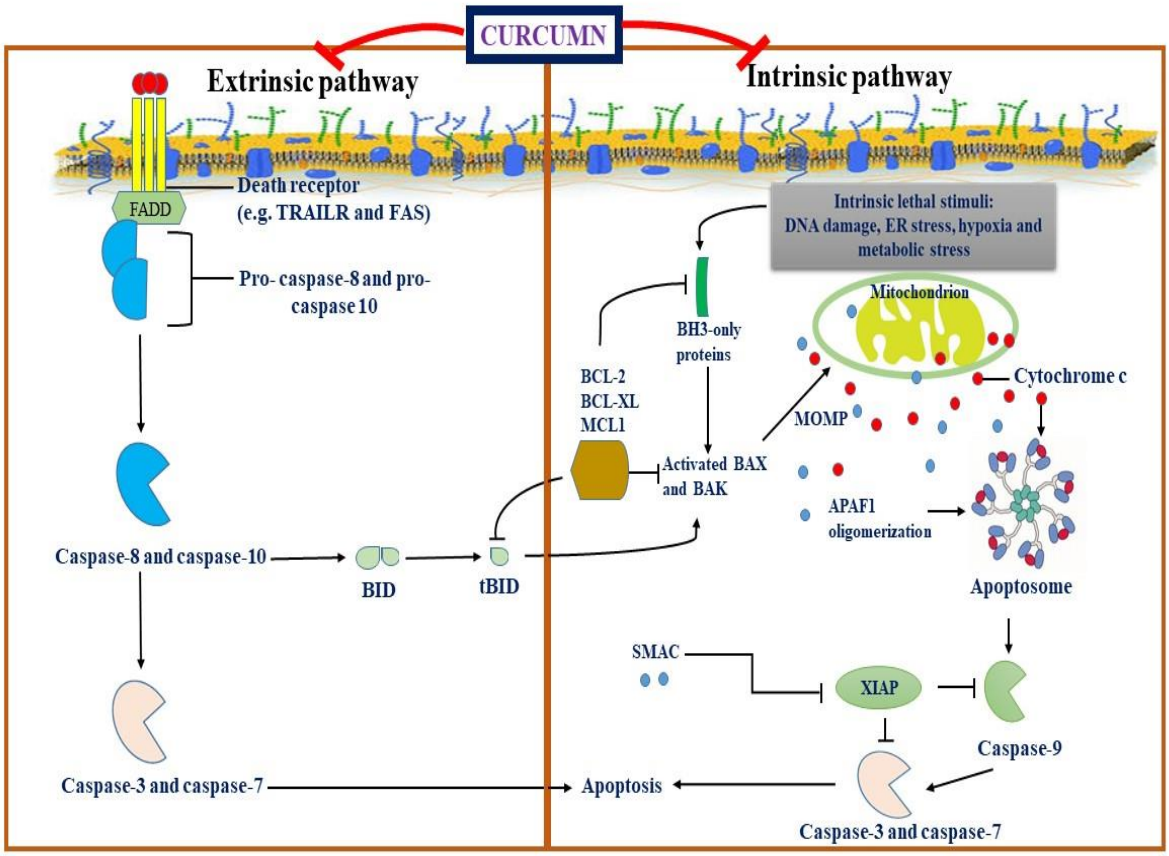

Fig. 4. Anti apoptotic effect of curcumin. Curcumin prevents cell death by reducing both intrinsic and extrinsic apoptotic pathways. In the extrinsic pathway of apoptosis, death ligands such as TRAIL and FAS cause death receptors activation, which leads to the activation of pro-caspase and caspase 8 and 10, which consequently activate caspase 3 and 7 and lead to apoptosis. In the intrinsic pathway of apoptosis caused by any damage, such as DNA damage, hypoxia, etc., cytochrome C is released and results in the production of apoptosome, and therefore to the activation of caspasce-9, caspase 3 and 7, and finally apoptosis. Some proteins such as BCL-2, BCL-XL inhibit BAX, which leads to stability of the MOMP protein causing mitochondrial survival and inhibiting the apoptosis process. On the other hand, SMAC protein is an inhibitor of XIAP. XIAP is a caspase 3 and 7 inhibitor. Curcumin may inhibit both intrinsic and extrinsic apoptosis, and therefore inhibit the occurrence of cell death. FADD: Fas-associated protein with death domain; TRAIL: tumor necrosis factor related apoptosis-inducing ligand; BID: BH3 interacting-domain death agonist; Bcl-2: B-cell lymphoma 2; MOMP: mitochondrial outer membrane permeabilization; SMAC: second mitochondria-derived activator of caspases;XIAP: X-linked inhibitor of apoptosis protein.

associated with the reduction of apoptotic events in the brain cortex, hippocampus, amygdala and other strategic brain regions (81-83). All of these studies have shown that the anti-apoptotic activity of curcumin in brain areas such as hippocampus and amygdala is responsible for its neuroprotective effects in neurodegeneration cognitive enhancement (16, 84). Many previous studies have shown that in neurodegenerative disorders such as PD, AD and HD and other related conditions, curcumin induces enhancement in cognitive function such as learning and memory (85, 86). Many studies have also shown that curcumin can prevent substance abuse (such as nicotine, alcohol and methamphetamine) mediated hippocampal neurodegeneration, and can improve learning and memory in the subject (44, 46). As mentioned above, improved learning and memory, as well as regulation of mood-related behavior can be a criterion for being a neuroprotective agent, and as revealed by previous studies, some parts of curcumin neuroprotective properties were mediated by inhibition of apoptosis in hippocampus and amygdala, leading to increased cognition in subjects suffering from neurodeg-eneration (16, 87, 88). Chronic curcumin therapy inhibits activated caspase-3 expression and reduces brain DNA fragmentation during neurodegeneration or after transient focal cerebral ischemia (83, 89).

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Curcumin has been found to block important pro-apoptotic molecules (GSK-3, caspase cascades), and enhance survival pathways through extracellular signal-regulated kinase (ERK1/2) and Bax proteins (29, 71). A group of studies suggested that curcumin effectively suppressed apoptosis caused by f high Ca^{2+} concentration decline during brain cell toxicity (45, 90, 91). The extra- and intracellular concentration of Ca^{2+} plays a significant role in controlling the switching between pro-survival and pro-apoptotic pathways within the cell (91, 92). Because of changes in Ca^{2+} concentration, curcumin inhibits programmed cell death by either regulating the cell membrane in noradrenergic and dopaminergic neurons, or excessive blockage of apoptosis-associated Ca^{2+}, or inactivation of cytotoxicity based on NMDA (93, 94). Curcumin also inhibits de-phosphorylation-induced apoptosis of protein kinase B and ceramide C2 (N-acetylsphingosine)-induced suppression of GSK-3 and protein phosphate (PP2A) (79, 95). Using mouse glial cells, it was shown that curcumin can block the executor stage of apoptosis by activating phospholipase C and 3-phosphoinositol kinase (PI-3K) (79, 96). Evidence suggested that curcumin increases the mechanism of apoptosis in cancer cells, and induces synergistic effects of the chemotherapeutic agent in killing the same cells (97, 98). Curcumin activates neurogenesis in brain cells due to blockage of the apoptosis or autophagia associated signaling pathway (16, 99). Curcumin regulates also many factors involved in cell survival pathways including CREB, BDNF, anti-apoptotic protein (Bcl-2), and extracellular signal-regulated protein (ERK)/ mitogen - activated protein (MAP) kinases (28, 100-103). It may upregulate neurogenesis, progenitor cell formation, maturation and survival (86, 104). It has been reported that therapy of subjects with neurodegenerative disease or abused substance mediated neurodegeneration with curcumin exerts regenerative neuro-structural (increased brain cell volume) and neurochemical effects (increased protein level – neural viability and function marker) (105, 106). Data indicate that curcumin can become an effective alternative in neurodegenerative diseases [e.g. AD, HD, PD, and amyotrophic lateral sclerosis], and depressive disorders due to the anti-apoptotic effects, as well as the suppression of pro-apoptotic receptors and the enhancement of pro-survival signals (13, 14). As non-differentiated precursor cells in the CNS, neural progenitor cells (NPCs) supply new neurons and glial cells to repair damage in the adult brain (107-109). Recently, NPCs have been found to undergo apoptosis. Treatment of NPCs with curcumin significantly inhibited apoptosis. Curcumin could support the survival of NPCs, leading to an increase in neurogenesis (109, 110). Recent results have suggested that curcumin therapy shows heterogeneity in the clinical response to neurodegenerative disorder due to changes in the balance of pro-and anti-apoptotic gene expression (111, 112). Another research investigated the impact of chronic curcumin treatment on the hippocampus, as measured by changes in the subcellular level of apoptosis-regulatory proteins caused by neurotoxin, alcohol and nicotine (113, 114). Robust protective effects against various apoptotic insults caused by b-amyloid have been demonstrated (7, 115). Nearly all data indicate that curcumin blocks the pro-apoptotic signal transmission cascade in neurons; however, a recent study found that this agent can also induce apoptosis in cancer (97, 116). Past research found that curcumin administration had a major effect on neural necrosis caused by abused drugs and neurodegenerative events (44- 46, 77). All of these properties may contribute to curcumin's potential therapeutic efficacy in neurodegenerative disorders, but the exact mechanism remains unclear. Summary of multiple studies result about curcumin anti-apoptotic effects on various animal models and cell lines is indicated in Table 1.

Modulation of inflammation

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Table.1. Summary of multiple studies result about curcumin anti-apoptotic effects on various animal models and cell lines.

Cell line/Animal model	Dose and period of treatment	Major outcomes	Ref.
Animal model for excitotoxicity (rat)	Doses of 0, 1,26, 2,6, 6 and 10μM curcumin for 24 hours on cortical neurons	Curcumin inhibits apoptosis in glutamate-induced cell death and increases BDNF and TrkB expression	58
Animal model of transient focal cerebral ischemia (rat)	Doses of 100 and 300 mg /kg i.p. 60 minutes after occlusion of the cerebral artery	Curcumin significantly decreased the protein expression of caspase-3. Modulates TUNEL-positive cells and inhibits cell death.	69
Animal model traumatic brain injury (TBI)(rat)	Doses of 50 mg /kg administered intraperitoneally 15 min after TBI induction.	Increased expression and nuclear translocation of Nrf2 and enhanced expression of antioxidant enzymes in the TBI model.	71
Animal model of focal cerebral ischemia-reperfusion(rat)	Doses of 100 mg/kg and 300 mg/kg.	Curcumin improves the symptoms of nerve damage and volume of infarction, reduces the water content of the brain and relieves neuronal apoptosis (Bax level) and also increases the expression of p-MEK, p-ERK, p-CREB, Bcl-2.	72 and 50
Animal model of cerebral ischemia (rat)	1 and 2 mg / kg, i.p. 30 min after focal cerebral ischemia / reperfusion	Decreased Nitrites/nitrates contents and TNF(alpha) level	49
Animal models of nicotine morphine and alcohol induced neurotoxicity	Doses of 10, 20, 40 and 60 mg / kg curcumin for 21 days i.p.in nicotine or alcohol-dependent rat	Decreased nicotine and/or induced apoptosis, oxidative stress and inflammation and increased levels of P-CREB and BDNF.	45,46 and 47
N2a / WT cell line and APP / PS1 transgenic mice animal model for Alzheimer pathophysiology detection	Single doses of 1 and 0.16 mg / kg for animals and 5 μM for cell line.	Decreases in Caveolin-1, inactivation of GSK-3 and inhibition of abnormal excessive Tau phosphorylation, inhibition of Bax and increase in Bcl-2	81
Animal model of cerebral ischemia (rat)	100 and 300 mg/kg of curcumin following ischemia	Reduced TUNEL-positive cells and biomarkers of apoptosis in cortex	80
Hypoxia-hypercapnia rat model	Curcumin at doses of 20, 40, 60 and 80 mg / kg following hypoxia-hypercapnia	Decreases of hypoxia-hypercapnia-induced brain damage and oedema, lowering expression levels of aquaporin (AQP)-4 protein and apoptotic biomarker.	83
H2O2-induced neurotoxicity of the PC12 cell line	Doses of 12.5–200 μM of curcumin	Attenuation of caspase activation, DNA damage and accumulation of reactive oxygen species (ROS), increase of MAPK and AKT pathways.	84
Animal model of aged rat	Curcumin was added to feed at 480 mg /kg and the animal was treated for 6 and 12 weeks.	Curcumin enhanced neurogenesis related genes and cognition activity and inhibited apoptotic protein caspase 3.	17
D-galactose-induced neurodegeneration	Curcumin was administered 50 and 100 mg /kg orally for 63 days.	Reduction of caspase-3, malondialdehyde, enhanced mitochondrial enzymes and glutathione levels and improved cognition	85
Rat model of Alzheimer disease cognitive defect by of streptozotocin,	Curcumin treatments were 5,15, 25, 50, 100 and 200 mg / kg; gavage was performed for 30-60 days.	Increases in neurogenesis and memory recognition and decreases in neuro-inflammation, oxidative stress and apoptosis. Increases in activation capability	87,88 ,89 and 104

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homocysteine and heavy iron injection		Nrf2. Increase in CREB, BDNF and ERK.	
Human retinal pigment epithelium cells SH-SY5Y neuronal cells with H2O2 induced neurotoxicity DBTRG glioblastoma cells Rat Retinal culture. Hippocampus cell culture	Curcumin incubation at 10, 20 and 40 µM	Decrease in Caspase-3 and-9 activity, increase in endothelial vascular growth factor (VEGF) levels, regulatory effects on oxidative stress, intracellular Ca2+ levels, VEGF levels, PARP expression levels, and caspase-3 and-9 values. Modulation of the activities of CaMKII and/or ser/ thr phosphatases.	91 ,92,93 and 94
Rat model of chronic stress and depression	Curcumin administered as 2.5,5,10,20 and 40 mg/ kg, p.o.	Increased neurogenesis of the hippocampus. Up-regulation of 5-HT(1A) and CREB and BDNF receptors and extracellular signal-regulated kinase (ERK) and reduction of apoptosis-related proteins.	100 ,101 and 103
Streptozotocine induced diabetic rats	Curcumin administered as a single dose of 60 mg/ kg as ip	Curcumin reduces diabetes caused by changes in dopamine D1, D2 receptors, CREB transcription factor and phospholipase C and decreased apoptosis of cortex and cerebellum biomarkers.	102
Mouse multi-potent neural progenitor cells (NPCs)	Cells were treated with different curcumin concentrations (0.1, 0.5, 1, 10, 20, and 50 M)	Stimulate and develop adult hippocampal neurogenesis, inhibition of apoptosis-related proteins such as caspase-3.	108 ,109, and 111
Spinal cord neural progenitor cells	Lower dosage of 0.1, 0.5, 1 µM curcumin for 24-48 hours	Activation of mitogen-activated protein kinase (MAPK), inhibition of apoptosis-related proteins such as caspase-3. P38, c-Jun NH2-terminal kinases (JNK).	110
Cell culture of Hippocampus that is exposed to glutamate for induction of neurotoxicity	Curcumin (0.1, 1.0 and 10 µM) for 24 hours.	Curcumin caused inhibition of ER stress-associated TXNIP / NLRP3 inflammasome and cell death activation	114
Status epilepticus animal model	Curcumin at a dosage of 200 mg/kg/day or 300 mg /kg/day via gavage for 2 weeks.	Inhibition of apoptosis and necrosis-related proteins.	115

A significant body of evidence has emerged in recent years indicating that inflammation plays a role in the pathological processes that underlie neurodegenerative disorders and diseases (117, 118). Curcumin has been shown to affect inflammatory mediator levels such as those involved in cyclooxygenase−prostaglandins and nitric oxide synthase−nitric oxide (NOS-NO) pathways, TNF-α, IL-1β, and other cytokines (119-122). Experimental studies have shown that arachidonic acid in the brain may be a target for curcumin (120, 121). Reducing arachidonate turnover can be related to down-regulating gene expression and cytosolic phospholipase A2 enzyme activity induced by curcumin (120, 123-125). Curcumin also decreased the brain protein levels and activity of cyclooxygenase 2 (COX-2) as well as the brain concentration of prostaglandins that are arachidonate metabolites produced by COX-2 (124-126). Accumulating evidence indicates that inflammation plays a role in the pathogenesis of neurodegenerative diseases and disorders, and that curcumin has anti-inflammatory effects that may contribute to its therapeutic effectiveness (13, 14, 60, 127-129). Some data suggest that curcumin exerts anti-inflammatory effects (e.g., suppression

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of *COX-2* expression, inhibition of IL-1β and TNF-α production, and enhancement of Nf-Kβ inhibition (130-132). However, there is a broad range of evidence suggesting that curcumin also exhibits anti-inflammatory properties under certain experimental conditions such as drug abuse (44- 46, 77). Chronic curcumin therapy has shown a significant decrease in lipopolysaccharide (LPS)-induced elevation of brain prostaglandin E2 (PGE2) synthesis in rats (130). Curcumin reduced LPS-induced upregulation of *COX-2* and PGE2 production in rat primary glial cells (130, 133). Similarly, it has been observed that curcumin significantly decreased *COX-2* expression and PGE2 production in experimental procedures in neurodegenerative models (122, 130). Several studies have found that curcumin modulates the NOS-NO pathway (122). A recent study found that curcumin pretreatment decreased NOS activity in the ischemic rat model (48, 134). In addition, curcumin has been shown to decrease *NOS* expression and NO production in rat brain tissue (134, 135). TNF-α is a cytokine which promotes inflammation. Many studies have shown that curcumin treatment has resulted in a significant dose-dependent reduction in TNF-α secretion by normal inflammatory cells, especially in brain cells (42, 136). Other studies later also stated that curcumin decreases the development of TNF-α in neurodegenerative events (14, 129, 137). Furthermore, another study indicated that curcumin treatment decreased *in vivo* development of TNF-α in mice treated with LPS (138, 139). In addition, in a rat model of morphine, nicotine, and alcohol mediated neurodegeneration, curcumin was found to decrease hippocampal TNF-α levels (44-46, 77). Conclusively, the summarized studies show that the effect of curcumin on TNF-α varies under different experimental conditions, with most studies suggesting that it inhibits TNF-α synthesis. In subjects with neurodegenerative diseases (128, 129), IL-1β is a pro-inflammatory cytokine. IL-2 is a cytokine that is anti-inflammatory. Numerous studies have shown that curcumin increases the secretion of IL-2 (140, 141). On the other hand, several studies have shown that curcumin does not substantially alter IL-2 levels (138, 142) or decrease IL-2 production (141). Taken together, these data indicate that curcumin inhibits IL-2 development certifying that this neuroprotective agent has an anti-inflammatory impact (143). IL-4 is a cytokine which causes inflammation. The effect of curcumin on IL-4 synthesis in neurodegenerative events (142, 144, 145) was investigated in few studies relative to other inflammatory mediators. Many of those studies showed that curcumin reduced levels of IL-4 (138, 145, 146). Nevertheless, tests have also shown that curcumin doesnot affect this cytokine (8). IL-6 is a cytokine that is pro-inflammatory. Numerous studies have shown that curcumin in neurodegenerative events attenuates IL-6 production (46, 60, 127, 147). Overall, these data suggest that curcumin's effect on IL-6 varies with different experimental conditions. IL-10 is a cytokine with anti-inflammatory influence. Most of the studies that investigated the effect of curcumin on IL-10 found that it decreased the production of IL-10 (121, 148). About the anti-inflammatory action of curcumin evidence, it has been approved that curcumin reduced the production of INF-γ, as pro-inflammatory cytokine, at blood level in neurodegenerative disease. (141). Similarly, evidence has shown that curcumin reduced the production of INF-γ in serum and brain tissue during the neurodegeneration process (27, 149). Predominantly, most of the studies reviewed found that curcumin inhibits INF-γ synthesis, which is a clear indication of possible anti-inflammatory effects (150-152). Some earlier studies have also shown that curcumin induces anti-inflammatory effects on brain regions such as hippocampus and amygdala, which may have protective effects against neurodegenerative diseases, because curcumin can function as a neuroprotective agent,

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cognitive enhancer, and mood stabilizer during neurodegeneration due to the role of the hippocampus in cognitive and mood-related behavior (153, 154). Recent research has shown that curcumin prevents the development of inflammatory processes and induces cognitive function (learning and memory) and mood improvement in neurodegenerative diseases and other related conditions including drug abuse mediated neurodegeneration. Accordingly, there is a correlation between the anti-inflammatory effects of curcumin and its effects on cognition enhancement. (44, 46, 85). Studies concluded that certain parts of curcumin neuroprotective properties are mediated by inhibition of neuro-inflammatory pathways in the hippocampus and amygdala, leading to improved cognition and mood-related actions throughout neurodegeneration occurrences (85, 153). The mechanism associated with curcumin's anti-inflammatory effects is still obscured. Among the pharmacological activities of curcumin, CREB activation or GSK-3β inhibition are those which have been documented repeatedly to modify inflammatory responses of different types (44, 46, 155). A strong piece of evidence for a link between CREB and GSK-3β and inflammation (155) has been shown. A growing body of evidence has shown that GSK-3β enhances the function of the NF- κ B (key transcription regulator for a range of immune and inflammatory responses) resulting in increased inflammation in mice (156, 157). Furthermore, previous findings have confirmed that inhibition of GSK-3β or CREB activation by curcumin has reduced the production of pro-inflammatory mediators under different conditions (158, 159). Significant results have shown that the GSK-3β (inhibition)-associated anti-inflammatory effect of curcumin is not exclusively triggered by the inactivation of NF- κB. Another downstream target of GSK-3β is the transcription factor signal transducer and transcription activator (STAT). Inhibition of GSK-3β by curcumin has been found to result in reduced STAT activation, which plays a crucial role in decreasing pro-inflammatory cytokine secretion (160-163). Similar work has also shown that curcumin induces CREB (activation)-associated anti-inflammatory responses that lead to its neuroprotective effectiveness (46, 160, 164). Summary of multiple studies, results about curcumins anti-inflammatory effects on various animal models and cell lines is indicated in Table 2.

Modulation of oxidative stress

The brain is sensitive to reactive oxygen species (ROS) development because it does not only metabolize 20% of total body oxygen, but also has a restricted antioxidant capacity (165). Consequently, free radical generation exceeds antioxidant capacity. Oxidative stress can lead to degradation of the membrane, cellular dysfunction, and apoptosis (165). Increased oxidative neuronal stress (OxS) has deleterious effects on signal transduction, structural plasticity, and cellular resilience, often by inducing lipid peroxidation in membranes, proteins and genes (166, 167). Additionally, studies show that curcumin exerts neuroprotective effects on oxidative stress. Many studies assessed plasma levels of the metabolism markers (oxidative/energy), thiobarbituric acid reactive substances (TBARS) (a direct index of cell lipid peroxidation), superoxide dismutase (SOD), catalase (CAT), and neuron-specific enolase (NSE) compared to controls in subjects during neurodegenerative disease occurrences (168-174). The elevated SOD/CAT ratio results in increased OxS, and is mainly reflected by elevation in the concentration of hydrogen peroxide in cells (167). Through resistance to OxS, curcumin has proven to exert antioxidant and neuroprotective impact. Similarly, curcumin therapy has been shown to avoid excitotoxicity by inhibiting oxidative stress in brain cells (175, 176). Glutathione, as the main antioxidant in the brain, plays a key role in preventing oxidative damage (177). Previou research found that chronic curcumin therapy

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Table 2. Summary of multiple studies of curcumin anti-inflammatory effects on various animal models and cell lines.

Cell line/Animal model	Dose, concentration and duration or protocol of treatment.	Major outcomes and results	Ref.
Animal mouse model fetal brain injury	LPS was used to induce mouse fetal brain injury model and the effects of maternal administration of curcumin (40 mg /kg) on the fetal mouse brain were evaluated.	The maternal administration of curcumin alleviates neuro-inflammation in the fetal brain caused by administration of LPS. Long-term consumption of curcumin may improve the neurological outcomes of pre-maturity neonates from dams suffering from infection / inflammation.	120
HAPI cells have been incubated with their compound and curcumin.	Concentrations of 0.1, 0.5, 1, 10, and 50 μM for 24 h prior to the MTT assay.	The compound is a novel anti-inflammatory agent for the treatment of many neurodegenerative disorders in which microglial activation is a critical step in their pathogenesis. In addition, it has the unique property of mediating both iNOS and COX-2 actions.	123
Molecular docking	All ligand structures have been either downloaded from the PubChem Database or manually drawn using the Marvin Sketch program. In addition to curcumin, a total of 28 curcumin analogs were selected for the studies.	Four analogs, namely rosmarinic acid, tetrahydrocurcumin, dihydrocurcumin and hexahydrocurcumin, showed a better binding than curcumin. Curcumin analogs have also been found to possess anti-inflammatory activity. This study may lead to a better understanding of inhibition of PLA2 by curcumin analogs.	124
Human recombinant microsomal enzyme PGE synthase-1, prostaglandin H2(PGH2), and prostaglandin E2(PGE2) were exposed to multiple curcumin structures.	Seven curcumin structure analogues 1, 3, 6, 7, 9, 11, 12 and 17 are exposed to Phospholipase A2, Cyclooxygenase, Lipo-oxygenase and Microsomal Prostaglandin E Synthase-1.	Several derivatives have been able to inhibit the activity of Phospholipase A2, Cyclooxygenase, Lipo-oxygenase, and Microsomal Prostaglandin E Synthase-1.	125
Animal brain trauma model (rat)	Using curcumin supplementation to counteract the effects of traumatic brain injury on homeostasis membrane disruption.	They found that TBI had damaged plasma membranes as evidenced by an increase in lipid peroxidation marker 4-hydroxynonenal (4-HNE) levels. The TBI reduced the NR2B subunit of the NMDA transmembrane receptor.	126
Primary endothelial cells and cornea of the mouse	Curcumin doses ranging from 0 to 20 μM	Curcumin inhibited endothelial cell proliferation in a dose-dependent manner and its derivatives demonstrated significant inhibition of bFGF-mediated comeal neo vascularization in the mouse.	127
Microglial cell culture BV2.	Concentrations of 0,2, 4, 8,16 μM were used for increased nuclear factor kB (NF-kB) and activator protein 1 (AP-1) DNA bindings induced by LPS.	Curcumin limits the expression of COX-2 by inhibiting the binding of AP-1, NF-k beta and its DNA.	131
Female ICR mice (6±7 weeks of age)	1, 5 or 25 mmol curcumin was used 30 min before cyclooxygenase-2 was induced by phorbol ester in the mouse skin	Curcumin inhibits the expression of TPA-induced COX-2 by blocking the ERK and NF-kB signaling cascades that provide a molecular basis for the suppression of tumor promotion as well as inflammation in mouse skin by this chemo-preventive phytochemical	132

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Cell line of human colon cancer (colo 205 cells)	Multiple time-conducting concentrations were used in colo 205 cells and inflammatory biomarkers were evaluated.	Curcumin inhibited Cox-2 levels, but promoted Cox-1 levels in colo 205 cells. Curcumin also inhibited levels of MMP-2 and promoted levels of MMP-9, but did not affect levels of MMP-7. Also Dibenzoyl methane (DBM), trimethoxy dibenzoyl methane (TDM), tetrahydro curcumin (THC) and curcumin effectively inhibited the release of arachidonic acid and its metabolites in lipopolysaccharide (LPS)-stimulated RAWcells and A23187-stimulated HT-29 cell.	133 and 134
Male Sprague-Dawley rats models of hypoxia ischemic brain damage (HIBD).	A set of curcumin (0, 20, 40, 60, 80 mg / kg) was tested in the trials. The 40 mg / kg dose was chosen for the final brain damage induction experiments.	Curcumin protects the BBB ultrastructure and therefore reduces the brain edema following HIBD by lowering the HIBD-induced increase in nitric oxide synthesizes activity and AQP-4 protein expression.	135
Animal model alcohol dependence in adult mice	Four groups with N = 10–12/group: (a) vehicle (corresponding to: physiological saline or 0.1 per cent DMSO, 10 ml /kg), (b) ethanol (1 g / kg), (c) curcumin (40 mg / g) followed by ethanol, (d) DMSO (10 ml / kg) followed by ethanol.	Curcumin can affect acute memory deficits caused by ethanol are mediated, at least in part, by suppressing the activity of nitric oxide synthesizes in the mice's brain.	136
Animal model of male albino mice with neuropathic pain	Curcumin (60 mg / kg) was injected into a neuropathic pain model.	Uncontrolled 4-week-long diabetes in mice is associated with increased glucose levels of nitrite and TNF-α. Once daily curcumin was administered, nitrite and TNF-α levels were inhibited.	137
The murine of BV2 microglia cell line	The cells were exposed to different concentrations (10, 30, 40, 50μM) of curcumin.	Curcumin plays an important role in the attenuation of LPS-induced inflammatory reactions in microglial cells and that mechanisms involve the down-regulation of PI3K / Akt signaling.	140
T-cell clones and part of the cytomegalovirus chain.	The cells were exposed to different concentrations (10-100μM) of curcumin.	Oral curcumin administration significantly inhibited IL-2 therapy-induced urinary nitrite / nitrate excretion and nitric oxide synthesizes tumor tissue expression, and further increased IL-2 therapy-induced survival prolongation in the murine Meth-A ascites tumor model.	141
Mononuclear cells in peripheral blood	Curcumin (20 μg / ml) was used and IFN-(10 ng / ml), IFN-l (10 ng / ml) and IL-12 (100 ng / ml) were measured.	Curcumin has a differential effect on IL-12 and IFN-α/β not only by differential effects on STAT4 phosphorylation, but also on the upstream receptor level.	142
Human lymphocytes	Various concentrations of curcumin (2.5, 5, 10, 50μg)	Curcumin has profound immunosuppressive effects mediated by inhibition of IL-2 synthesis, mitogen, and IL-2 induced activation of human lymphocytes.	144
Human keratinocyte cell line	Various concentrations (2-100μg) of curcumin have been exposed to the cell line.	Curcumin attenuates the expression of TNF- α induced IL-1ß, IL-6, and TNF- α in HaCaT cells as well as inhibition of TNF- α induced NF-kB, p38 MAPK, and JNK activation.	148 and 149
Male Wistar rats (90–110 days) infected with Tripanosoma Evansi.	Doses of 0, 20 or 60 mg /kg curcumin after infection.	Curcumin inhibited AChE activity and improved immunological response by pro-inflammatory cytokines.	150
Healthy adult male mice with intracerebral	The dose of 100 mg /kg was used for the ICH model	Curcumin would reduce the number of cerebral T-lymphocytes in experimentally induced ICH mice.	151

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hemorrhage (ICH).			
Microglial cell	Various concentrations (1-50µg) of curcumin have been exposed to the cell line.	Curcumin blocked the production of pro-inflammatory and cytotoxic mediators such as NO, TNF-alpha, IL-1alpha, and IL-6 produced by Abeta(25-35)/IFN-gamma-and LPS-stimulated microglia.	152
Animal model of renal ischemia/ reperfusion (rats)	Curcumin (10-100 mg /kg) was used prior to ischemia/ reperfusion.	Curcumin pretreatment decreases the pulmonary apoptotic pathway by substantial inhibition of TGF-β and caspase-3 in the kidney and lung tissues.	153
Animal model of Gulf War Illness	Dose of 30 mg /kg in 0.1 ml of 33 % DMSO for the treatment of the sequel of the model.	Curcumin treatment enhanced antioxidant gene expression and normalized multiple gene expression related to mitochondrial respiration, inflammation and oxidative stress with normalized mitochondrial respiration that underlie better memory and mood function mediated by curcumin therapy.	154
Animal model of cognitive defect by in diabetic rats.	Dose 100(mg /kg /day, IP) following induction of diabetes.	Nicotin-Curcumin reverses the effects of diabetes mellitus on Bax, Cyt-c, Cleaved Caspase-3, and Bcl-2 protein expression in rat hippocampus CA1 tissue.	155
Animal model of acrylamide-induced spatial memory impairment in male rats	Curcumin (90 mg / kg curcumin by oral gavage) was used in rats treated with acrylamide.	Curcumin alleviated ACR-induced spatial memory impairment through reversing tau abnormalities and P-CREB reduction in the hippocampus	159
Animal model of arsenic mediated alterations in NMDA receptor.	The oral dose of 20 mg /kg was given to rats treated with arsenic.	Curcumin exercises its neuroprotective influence, affecting the PI3K /Akt pathway, which may affect NMDA receptors and downstream signaling through TrKβ and BDNF in arsenic induced cognitive deficits in the hippocampus.	161
The endometrial cancer cell line	Various concentrations of curcumin (10–50mM) were used for 72 h.	Curcumin has increased PIAS-3 expression in cancer cells. And Curcumin suppresses JAK-STAT signaling by activating PIAS-3, thereby attenuating STAT-3 phosphorylation and tumor cell growth.	162
Acute spinal cord injury in the animal model (rat)	Curcumin was administered at 40 mg /kg by intraperitoneal injection following spinal cord injury.	Curcumin has a moderately protective effect on spinal cord injury and may be associated with inhibition of overexpressed AQP4 and GFAP and activated JAK / STAT signaling pathway.	163
Primary microglia Cells	Various concentrations (2-100µg) of curcumin have been exposed to cell line	Curcumin may increase phosphorylation and association with JAK1/2 of SHP-2, which inhibits the initiation of JAK-STAT inflammatory signaling in activated microglia and inhibits the up-regulation of nitric oxide synthase and COX-2 inactivated microglia.	164
Rodent cortical neurons	Curcumin between 1.25 and 10µM	Curcumin-induced increase in phosphorylate cyclic AMP response element binding protein (CREB) and curcumin neuroprotection may be mediated via BDNF /TrkB-MAPK /PI-3K-CREB signaling pathway.	165

increased glutathione levels in primary cultivated rat cerebral cortical cells, and that the effects of curcumin on glutathione levels were dose-dependent in rodent and human experimental procedures with neurodegenerative disease (178-180). Curcumin therapy in neurodegenerative

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diseases greatly decreases the levels of lipid peroxides in the brain tissues and increases the antioxidant status (13, 87, 181-183). Curcumin has also been shown to decrease the SOD levels in preclinical experiments relative to animals subjected to a prefrontal cortex animal model of mania (ketamine) (184). Many previous studies demonstrated curcumin's neuroprotective function and explained its mechanism, some of which showed that curcumin can inhibit neurotoxicity by modulating the oxidative stress event (9, 61, 185). For its antioxidant and radical scavenging properties, curcumin is marketed as the main constituent of turmeric (8, 9). Curcumin strengthens systemic markers of oxidative stress and induces increased activation of the antioxidant balance in substance misuse and other circumstances causing neurodegeneration in humans and animals (44-46, 77). Studies have shown that curcumin can effectively scavenge free radicals in neural damage (38). According to current evidence, curcumin mainly contributes to the reduction of lipid peroxidation in human and animal subjects treated with alcohol (46, 186). Curcumin can prevent neurotoxicity damage by scavenging of these free radicals and inhibiting lipid peroxidation processes (187). Curcumin, therefore, may protect the neural cell membrane from oxidative damage by exerting great efficacy to prevent lipid peroxidation (188). In this scenario, curcumin treatment in animal models (by multiple doses of 5, 10, 40 and 60 mg/kg) in rodents will inhibit neurodegenerative agent malicious effects, and reduce the amount of MDA and lipid peroxidation in brain tissue (31, 44, 46, 57, 189). Previous studies have reported that curcumin has neuroprotective properties; these findings demonstrate the role of curcumin, mediated by the reduction of free radicals in neural cells that are impaired by neurodegenerative disease (3, 107). has Also, it was shown that various doses of curcumin can increase reduced glutathione content and decrease oxidized glutathione levels in animal models of neurodegenerative disease and associated neurodegenerative disorders (190). Curcumin also neutralizes the adverse effects on the glutathione circle of certain neurotoxic agents (190). These findings were also supported by previous studies demonstrating that curcumin can increase the levels of glutathione in subjects suffering from neurodegenerative disorder (60, 183, 191). It seems that some parts of the neuro-protective properties of curcumin are mediated during the neurodegenerative phase through the modulation of the glutathione circle (183). Curcumin has also been shown to have possible effects on glutathione recovery in vital organs like the brain, liver and kidneys (3, 8). The neuroprotective effects of curcumin were shown to be mediated by the glutathione pathway (3, 183). Curcumin has been shown to increase glutathione and activate the glutathione pathway, and to decrease the development of glutathione sulfide in some subjects diagnosed with drug abuse who suffer from neurodegeneration in their brain (178, 191). Curcumin's antioxidant effects in the regulation of the glutathione pathway against the incidence of neurodegeneration damage have been well established, and it has been shown that an adequate balance between oxidized and reduced glutathione is a crucial factor in the efficacy of the human brain metabolism system (178, 192). In addition, curcumin has been shown to preserve mitochondrial biogenesis and antioxidant physiognomies in strategic organs especially in brain areas (24, 25, 193). Curcumin induces increased production of SOD, glutathione peroxidase (GPx), CAT, and glutathione reductase (GR) activating antioxidant defenses in the brain of neurodegenerative disorder subjects (49, 194). Curcumin has been shown to play a critical role by preserving SOD and GPx activity in neural cells and reversing the CAT inhibition caused by the toxic agent (49). These curcumin functions will eventually contribute to a reduction in lipid

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peroxidation, and thus boost the harmful effects of the signaling pathway to neurodegeneration (7, 12). As indicated by *in vivo* and *in vitro* studies, the effect of curcumin on the antioxidant defense mechanism, lipid peroxidation levels, neural cell ROS and NOS levels have been confirmed (195). Through activating GR, curcumin enhances the conversion of oxidized to reduced glutathione, thereby shielding neuronal cells from the initiation of oxidative stress in neurodegenerative diseases (196). As disused above, some parts of curcumin-induced neuroprotection mediated through its properties in improving cognition of neurodegenerative diseases and disorders were due to its anti-inflammatory and anti-apoptosis properties (16). In line with this idea, some previous studies showed that curcumin induces antioxidant effects on brain areas such as hippocampus and amygdale, and may reduce cognitive deficits throughout neurodegeneration (153, 197). These studies have shown that curcumin can inhibit lipid peroxidation and ROS and NOS production in hippocampus and amygdale, and also stimulate antioxidant enzyme activity such as SOD, GPx, and GR in the mentioned brain region, and that this antioxidant mechanism will probably function as a neuroprotective agent, cognitive enhancer and mood stabilizer during neurodegeneration occurrences (44-46, 198). Such findings indicated that certain portions of curcumin neuroprotective properties as a cognitive enhancer were mediated by inhibition of oxidative stress damage in the hippocampus and amygdala, resulting in normalization of memory and mood-related actions throughout neurodegeneration occurrences (44-46, 198). All of these studies have shown that curcumin possesses the potential capacity for free radical scavenging and activation of antioxidant enzyme in neural cells exposed to neurotoxic or neurodegenerative agents and neurodegenerative disease subjects in both animals and humans. In addition, as oxidative stress is involved in most neurodegenerative event studies, curcumin's possible protective role as an antioxidant against this form of failure has been investigated. Summary of multiple studies results about curcumins antioxidant effects on various animal models and cell lines is indicated in Table 3.

Upregulation of mitochondrial function

With transcriptional control (199), mitochondria plays a key role in cells including energy homeostasis, metabolism, signaling and apoptosis. Transcriptional mechanisms that control biogenesis and function of mitochondria may shed light on potential therapeutic approaches to modulate mitochondrial function (200). Many human diseases, particularly neurodegenerative diseases (200), are associated with mitochondrial dysfunctions. Curcumin prevents the mitochondrial release of proteins associated with apoptosis (25, 193, 201, 202). Weak punctata cytoplasmic immunostaining indicated that under normal conditions cytochrome c (Cyt c) is located in the intermembrane space of the mitochondria (203). In damaged areas, Cyt c is released into the cytoplasm from the mitochondria, causing extreme neuronal, cytoplasmic staining (203). Apoptosis-inducing factor (AIF) is another protein that is usually located in the mitochondrial space of the intermembrane, translocating from injured cells into the nucleus (199, 203). Curcumin treatment decreased the number of AIF positive nuclei 24 h after treatment in the hippocampus, and immunoblotting confirmed that curcumin inhibited the AIF release from the mitochondrial fraction in neurodegenerative animal modeling (204, 205). Recent studies have shown that curcumin in hippocampal cells induced an increase in mitochondrial mass leading to increased production of ATP with major improvements in mitochondrial efficiency (45, 113, 206). This increase in mitochondrial mass was associated with an increase in mRNA levels of mitochondrial biogenesis transcription factors (84, 193), some of which

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Table 3. Summary of multiple studies of curcumin antioxidant properties and its effects on mitochondrial function on various animal models and cell lines.

Cell line/Animal model	Dose, concentration and duration or protocol of treatment.	Major outcomes and results	Ref.
Cortical astrocytes and neurons cell culture	Concentration of 5, 10, 20, 50 or 100 µM curcumin for 24 hours on cortical neurons	Curcumin reduced GSSG and increased GSH. Increased cell viability also reduced oxidative stress related gene expression. Curcumin also decreased caspase 3 and Bax and increased protein Bcl-2.	39, 179
Dopaminergic neuronal cell line [(1RB3AN27 (N27)] and Parkinson's animal model.	Concentration of 20, 50 or 100 µM curcumin for 24 hours on cortical neurons or doses of 10-50 mg / kg in Parkinson's animal model.	Curcumin significantly decreased GSSG, lipoid peroxidation, ROS, H2O2 and increased GSH and inhibited cell death.	180 and 192
Neuronal Cell Culture (Human SK-N-SH) and Animal Model (athymic) Alzheimer's Disease	Concentrations of 250 nM, 500 nM, 1 M, 2.5 M, and 5 M curcumin for 48 hours on cell culture and doses of 25 mg / kg administered intraperitoneally for 4-6 weeks for animals.	Curcumin decreased lactate dehydrogenase, lipoid peroxidation, ROS, H2O2 and inhibited Caspase 3 and 9 and increased cell density.	181
Rat model of cognitive defect by homocysteine	Curcumin treatments were performed for 10 days as 5,15 and 45 mg /kg, gavage	Increases in neurogenesis and memory recognition, and decreases in lipid peroxidation and anion superoxide.	88 and 182
Animal model of neur-otoxicity induced by fluoride	Doses of 10 and 20 mg /kg and 30 mg /kg for 2 weeks.	Curcumin improves nerve damage and reduces lipid peroxidation.	183
Rat model of sporadic dementia of Alzheimer's type (SDAT)	Doses of 80 mg /kg for three weeks.	Curcumin decreased (MDA), thiobarbituric reactive substances, hydrogen peroxide, protein carbonyl, and GSSG; increased levels of GSH and its dependent enzymes (Glutathione peroxidase, glutathione reductase, and increased activity of choline acetyltransferase (ChAT).	184
Animals model of ketamine-induced mania (rat).	Doses of 20 and 50 mg / kg curcumin for 14 days i.p.	Improved behavioral dysfunction and increased Catalase, Superoxide dismutase and decreased Thiobarbituric acid reactive species formation	185
Animal models of nicotine morphine and alcohol induced neurotoxicity	Doses of 10, 20, 40 and 60 mg / kg curcumin for 21 days i.p.in nicotine or alcohol-dependent rat	Decreased nicotine and/or induced apoptosis, oxidative stress and inflammation and increased levels of P-CREB and BDNF. Curcumin also decreased prostaglandin levels E(1), E(2), F(2alpha) and D(2) in rats treated with alcohol.	45,46, 47 and 187
Animal model of cerebral ischemia(rat)	Treatment of Curcumin (200 mg / kg / day, i.p.) at three different times (immediately, 3 hours and 24 hours after ischemia)	Reduced dead cells and biomarkers of apoptosis in cortex and also decreased oxidative stress biomarkers.	189

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Cortical neuron of the animal that induced excitotoxicity by glutamate	Concentrations of 0, 1,26, 2,6, 6 and 10μM curcumin for 24 hours on cortical neurons	Curcumin inhibits apoptosis in glutamate-induced cell death and up regulates BDNF and TrkB expression	58
Animal model of corticosterone induced depression (rat)	Doses of 5, 10, 20 and 10μM curcumin for 3 weeks.	Curcumin inhibits oxidative stress and cell death, and up-regulates BDNF and TrkB expression and confers antidepressants.	190
Animal model of cerebral ischemia reper fusion(rat)	Rats were pre-treated with either a low (50 mg / kg, intraperitoneal injection) or a high (100 mg / kg, intraperitoneal injection) curcumin dose for 5 days.	Increased mitochondrial uncoupling protein 2 and increased mitochondrial biogenesis. Nuclear factor-erythroid 2-related factor 2 (Nrf2) to the antioxidant response element (ARE) has also been increased.	194
Animal model of focal cerebral ischemia-reperfusion(rat)	Doses of 100 mg/kg and 300 mg/kg.	Curcumin improves the symptoms of nerve damage and infarction volume and reduces the water content of the brain and relieves neuronal apoptosis (Bax level) and also increases the expression of p MEK, p ERK, p CREB, Bcl 2.Alos reduces lipid peroxidation and increases superoxide dismutase.	72, 50 and 192
Cell culture from animal model of brain injury (rat)	Curcumin concentrations (2.5, 5.0, 10 and 25 mM) after 1 hour of brain injury.	Curcumin inhibits cell degeneration, lactate dehydrogenase, volume of infarction and inhibits cell death. Activate the Akt / Nrf2 pathway in the treated rat.	196
Cerebral artery occlusion induced focal cerebral ischemia in rats	Curcumin administered 100 and 300 mg / kg, i.p. 30 minutes after the occlusion of the cerebral artery	Increase the activity of superoxide dismutase, glutathione peroxide and decrease lipid peroxidation and peroxynitrite.	197
Animal model of Gulf War Illness in rat	Curcumin treatment for 30 days	Enhanced neurogenesis, restrained inflammation and oxidative stress with normalized mitochondrial respiration.	154
Animal model of diabetic rat	Curcumin (100 mg / kg b.w.) was administered to the diabetic group after induction and for eight weeks.	Curcumin significantly improved blood glucose level, redox status, cellular stress, and decreased INF-γ and Bax levels, down-regulated GRP78 and ATF-4 expression, meanwhile, up-regulated Bcl2 and ChAT expression in the hippocampus.	199

involved neurogenesis transcription factors, and inhibit neurotoxicity (207). As a result, curcumin therapy rapidly induces an increase in activating Akt-Ser473 phosphorylation, and exerts inhibitory effects on GSK3β phosphorylation, as well as an increase in activating CREB- Ser133 phosphorylation, two mechanisms known to control peroxisome proliferator- activated receptor gamma coactivator 1-alpha (*PGC*-1α) expression (164, 194, 208). *PGC-1a* expression may be involved in the neuroprotective role of curcumin (208). Taken together, the results suggest that curcumin induces mitochondrial biogenesis via Akt/GSK3 or Akt/CREB//PGC-1a cascades, which elucidates the

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pleiotropic effects of curcumin, and also reveals novel beneficial effects through the preservation of mitochondrial functions (164, 194, 208, 209). Another study suggested that curcumin can modulate GSK3β in neurodegenerative animal models; GSK3β regulates mitochondrial energy metabolism (209). Consequently, inhibition of GSK3β in mice *in vivo* alters the metabolism of the hippocampus. This work shows that inhibition of GSK3β increases the mitochondrial respiration and membrane potential, and alters NAD(P)H metabolism (210). These metabolic effects are associated with increased stabilization of the PGC-1α proteins, increased nuclear localization, and increased transcriptional co-activation (210). Alteration of the hippocampal energy metabolism is correlated with increasing Pgc-1α in mice treated with the GSK3β inhibitor curcumin. These data indicate that curcumin has a metabolic effect on brain GSK3β. In addition, it can be concluded that GSK3β/PGC-1α axis may be essential in the metabolic integrity of the neurons leading to neuroprotection (193, 210, 211). Complex I (NADH dehydrogenase) and complex IV (cytochrome-c-oxidase) of the mitochondrial electron transport chain have been reported to be affected by drugs used to treat psychiatric or neurodegenerative diseases, including antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, anti-dementia, and anti-parkinsonian drugs. Recent data on the effects of curcumin on complex I and IV have been conducted. These studies assessed complex I and IV enzyme activity levels in the rodents brain, and revealed that curcumin increases complexes I and IV, which contribute to neural cell defense against neurodegenerative agents or events (22, 23, 52, 84, 211, 212). Taken together, these results indicate that curcumin could be a good alternative in the neurodegeneration to prevent or decrease nitrosative and oxidative stress as well as mitochondrial dysfunction. Therefore, in subjects suffering from neurodegeneration, curcumin may be useful for the prevention and/or treatment of oxidative stress and mitochondrial dysfunction.

Involvement of PI3/Akt/ GSK3 or PI3/Akt/ CREB/BDNF signaling pathways

As described above, the mechanism of curcumin neuroprotection is introduced by its anti-oxidant, anti-inflammatory, and anti-apoptotic system, which is mediated by two significant signaling pathways, PI3/Akt/GSK3 or PI3/Akt/CREB/BDNF (160, 164, 194, 213). Previous studies have shown that phosphatidylinositol 3-kinase (PI3K) activation (phosphorylation) of protein kinase B (Akt) results in Akt activation that may trigger neurodegenerative event inhibition (57, 214). GSK3β protein is an important biomarker for neurodegenerative diseases (215). Previous studies have shown that activation of GSK3β proteins (hyper-phosphorylation) by reduced activity of Akt causes toxic effects due to accumulation within cells (216, 217). According to previous studies, the reduction of Akt and thus the accumulation of hyper-phosphorylated GSK3β in neural cells causes mitochondrial dysfunction, and leads to neurotoxicity (218). According to previous studies, the reduction of Akt and thus accumulation of hyper-phosphorylated GSK3β in neural cells causes mitochondrial dysfunction and leads to neurotoxicity (218, 219). Many previous studies have shown that curcumin acts by activation of Akt and thus causes GSK3β hypo-phosphorylation in neural cells, leading to cell survival and protection against degenerative events (213, 220, 221). Given the importance of the PI3/Akt/GSK signaling pathway in the neuroprotective process of curcumin, this signaling pathway seems to mediate curcumin-induced neuroprotection and mitochondrial biogenesis (by regulation of oxidative stress, inflammation, and apoptosis) and behavioral disturbances. According to the above statement, GSK-3 can be considered as a significant

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way of mediating the neuroprotective effects of curcumin on major systems such as antioxidant, anti-apoptosis, and anti-inflammation by suppressing the development of IL-6 and the activation of astrocytes (79, 209, 222). PI3/Akt/GSK signaling pathway plays a crucial role on the neurobehavioral effects of curcumin, and is involved in the antidepressant and anxiolytic effects of curcumin (223-229). Curcumin has also been shown to regulate PI3/Akt / GSK3 not only directly but also through more complex network effects and downstream pathways affecting more than one serial molecular target signal (160). Significant correlation with PI3/Akt/GSK3 signaling and curcumin activation of events involving neurogenesis needs to be further evaluated. This could lead to the development of an understanding of the role of curcumin and the development of this agent as a new generation of neuroprotective combination with a clear mechanism of action and a signaling pathway.

Another signaling pathway that is essential in the effects of curcumin on brain cells is PI3/Akt / CREB / BDNF (158, 160). Activation (phosphorylation) PI3Kfollowed by Akt phosphorylation causes activation (phosphorylation) of CREB which leads to BDNF synthesis (230, 231). During brain development and neurogenesis, CREB functions as a major transcription factor (231). CREB is activated in a phosphorylated state and several protein kinases in particular Akt phosphorylate this transcription factor, and transform CREB into its active form (232). CREB acts on DNA and promotes the production of BDNF protein which is important in neurogenesis and neuronal development (233). In addition, several previous studies have found that the neuroprotective effect of curcumin could be mediated by triggering the PI3/Akt/CREB/BDNF pathway and by this mechanism, encouraging cell survival and disrupting neurodegeneration cascades (28, 100, 160). Curcumin also inhibited pro-apoptotic molecules such as p53 and Bax by activation of PI3/Akt/CREB/BDNF (45). Curcumin pretreatment by modulation of PI3/Akt/CREB/BDNF inhibited the release of glutamate-induced mitochondrial cytochrome c, activation of caspse-3, and cleavage of lamin B1, the nuclear substrate for caspase-3, a crucial enzyme that mediates apoptosis (40, 41). Acute exposure to curcumin also protected cortical neurons through PI3/Akt/CREB/ BDNF and significantly reduced pro-inflammatory biomarkers (IFN-α, TNF-a, IL-8) and increased anti-inflammatory cytokines/compounds (IL-10, IL-1) (141, 143, 149). Strong association with PI3/Akt/CREB/BDNF signaling and curcumin neuroprotection offers further insight into the use of this agent in neurodegenerative events as a potent neuroprotective.

It should be noted that in the current review, PI3/Akt /BDNF and PI3/Akt/GSK3 signaling pathway was chosen for assessment, explanation and association of this signaling pathway with antioxidant, anti-inflammatory and anti-apoptosis effects of curcumin. The explanation for this choice is that there are many evidence on the role of these two signaling pathway impacts on neuroprotective and neurobehavioral effects of curcumin, and this has allowed us to better evaluate the neuroprotective efficacy of curcumin in both molecular and behavioral aspects. Therefore, we based this review on the mentioned signaling pathways and their association with antioxidant, anti-inflammatory, and anti-apoptotic effects of curcumin. Although there are some less important other signaling pathways proposed for the neuroprotective effects of curcumin in the literature to date, some parts of this signaling pathway include Akt/Nrf2 (nuclear factor-erythroid 2-related factor 2) which is essential in the neuroprotective effects of curcumin in hypoxia-induced oxidative damages (47, 194); TLR2/4-NF-B (toll-like receptors type 2 and 4/nuclear factor-B) which is

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important in the anti-inflammatory and immunomodulatory role of curcumin in brain cells (42); janus kinases (JAKs)/signal transducer and transcription protein activator (STATs), JAK2/STAT3, involving neuroprotective effects of curcumin inflammatory process during hypoxia induced neural cell damages (234); Nrf2-ARE (antioxidant responsive element) signaling pathways involving curcumin ability to increase the activity of antioxidant enzymes and attenuation of brain injury in the traumatic brain injury model (235); Wnt/β-catenin signaling pathways involving curcumin antioxidant effects against oxidative stress-induced injury in some neurodegenerative disease (236). In terms of the amount of data available on this miscellaneous signaling pathway and their role in curcumin neuroprotective effects, there was less information compared to PI3/Akt/ CREB/BDNF and PI3/Akt/GSK3 signaling pathways, and therefore we tried to focus our assessment on these two pathways. Given the importance of these two signaling pathways, they could provide useful clues for researchers to further assessing the effects of curcumin and its neuroprotective role, as these two signaling pathways known as two key highways between all signaling pathways and routes have a crucial role in comparison to other signaling pathways, and most neuroprotective agents (both herbal and synthetic) confer neuroprotective activity through these signaling pathways. It can therefore be suggested that PI3/Akt/ CREB/ BDNF and PI3/ Akt/ GSK3 signaling pathways have a high potential to be the target for modulation of oxidative stress, apoptosis and inflammation, cognition and mood-related disorders after curcumin administration, which may ultimately result in neuroprotection against 'neurodegenerative disorders or diseases. Thus, PI3/ Akt/ CREB/ BDNF and PI3/ Akt/ GSK3 signaling pathways have a high potential for targeting drug therapy and design in human studies phases.

Conclusion

The neuroprotective effects of curcumin are based on the fact that it modulates several homeostatic mechanisms involved in neurotrophic response, autophagia, oxidative stress, inflammation and mitochondrial function, in particular through PI3/ Akt/ GSK3 or PI3/ Akt/ CREB/ BDNF signaling pathways (Figure-5). In the present review, we reviewed a number of experimental and clinical studies focusing on the neurobiological properties and underlying mechanism of curcumin in the light of available evidence of its neurotrophic and neuroprotective properties. The current review also gathered new investigations on the mediation of PI3/Akt/GSK3 or PI3/Akt/CREB/BDNF signaling pathways for neuroprotective curcumin properties. Taken together, these findings provide a strong rationale for exploring curcumin as a potential treatment for neurodegenerative diseases.

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