Effects of Curcumin on Mitochondria in Neurodegenerative Diseases

Running Title: Curcumin, mitochondria and neurodegeneration

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Abstract

Neurodegenerative diseases (NDs) result from progressive deterioration of selectively susceptible neuron populations in different central nervous system (CNS) regions. NDs are classified in accordance with the primary clinical manifestations (e.g. parkinsonism, dementia or motor neuron disease), the anatomic basis of neurodegeneration (e.g. frontotemporal degenerations, extrapyramidal disorders or spinocerebellar degenerations) and fundamental molecular abnormalities (e.g. mutations, mitochondrial dysfunction and its related molecular alterations). NDs include the Alzheimer disease (AD), Parkinson disease (PD) among others. There is growing evidence that mitochondrial dysfunction and its related mutations in the form of oxidative/nitrosative stress and neurotoxic compounds play major roles in the pathogenesis of various NDs. Curcumin, a polyphenol and nontoxic compound, obtained from turmeric, has been shown to have a therapeutic beneficial effect in various disorders especially on the CNS cells. It has been shown that curcumin has considerable neuro- and mitochondria-protective properties against broad-spectrum neurotoxic compounds and diseases/injury-associating NDs. In this article, we have reviewed the various effects of curcumin on mitochondrial dysfunction in NDs.

Keywords: Curcumin; Neurodegenerative Diseases; Mitochondrion; Mitochondrial dysfunction; Neuroprotection.

Introduction

Turmeric (*Curcuma longa* L.) is a common golden-colored spice from a member of the ginger family (Zingiberaceae) which is a rhizomatous herbaceous perennial flowering plant (Angiosperms) (1, 2). The powdered rhizome of turmeric has been used in traditional medicine as a curative compound as well as in Asian cuisines as a food additive and beverage industries as a coloring agent (3, 2). Curcuminoids are biologically active and are one of the main components of turmeric, which based on soil conditions and origins, contain 2% to 9% of the turmeric compounds. Curcuminoids consist of curcumin/diferuloylmethane (the major component), demethoxycurcumin, bis-demethoxycurcumin and cyclic curcumin (the minor component) (4, 2).

Over the past half a century, curcuminoids in particular curcumin, have displayed a growing interest in a broad range of biological/pharmacological research. The anti-bacterial properties of curcumin were reported for the first time in 1949 (5, 6). Since then growing number of studies have focused on the potential therapeutic properties of curcumin in a myriad conditions and shown to have antioxidant (7), anti-tumoral (8-10, 3, 1), lipid-modifying (11, 12), hepatoprotective (13, 14), vasculoprotective (15), cardioprotective (16), pulmonoprotective (17), neuroprotective (18), anti-thrombotic (19), immunomodulatory (20, 21), anti-diabetic (22), analgesic (23), anti-inflammatory especially anti-neuroinflammatory (24-27) as well as microglia-activation inhibitory (2) properties.

Curcumin (1,7-bis-(hydroxy-3-methoxyphenyl)-1,6-heptadiena-3,5-dione; $C_{21}H_{20}O_6$) is a natural polyphenol compound with molecular weight of 368.38 g/mol. It contains two ferulic acid residues joined by a methylene bridge (28, 6). It is a hydrophobic molecule, mostly insoluble in water, poorly soluble in hydrocarbon solvents (e.g. cyclohexane, hexane) and easily soluble in polar solvents (e.g. ethanol, methanol, DMSO, acetonitrile, chloroform, ethyl acetate) (6). Biological activities and therapeutic properties of curcumin take place in three functional groups: an aromatic o-methoxy phenolic group, α, β-unsaturated β-diketo moiety and a seven carbon linker (28). In addition to its various therapeutic properties, owing to the hydrophobic tendency, presence of an active methylene group and a β-diketone moiety, curcumin has poor bioavailability/pharmacokinetics and degraded easily via aldo-keto reductase in the liver (29, 2). Numerous studies are being conducted to improve the bioavailability and pharmacokinetics property of curcumin.

NDs are a heterogeneous group of disorders that are characterized by the progressive deterioration of the function and structure of the selectively vulnerable neuron populations in the CNS (30). NDs are showing a growing trend worldwide as well as worsening mortality and morbidity especially in the elderly (31). The individual NDs can be classified by their clinical presentations and symptoms, with pyramidal and extrapyramidal movement impairments (also known as ataxias) and cognitive or behavioral impairments (also known as dementia) being the most common (32, 33). NDs comprise AD, PD and PD-related disorders, Huntington disease (HD), Spinal muscular atrophy (SMA), amyotrophic lateral sclerosis [ALS; also known as motor neuron

diseases (MND)], dementia with Lewy bodies (DLB), Spinocerebellar ataxia (SCA), corticobasal degeneration (CBD), Frontotemporal dementia (FTD) and its variants, progressive supranuclear palsy (PSP), Prion disease and other dementia/ataxia-related NDs (34). NDs are mostly incurable and the current therapeutic strategies are aimed at symptomatic relief and/or restraining the disease progression (35). NDs not only reduce the life expectancy and health-related quality of life (HRQoL) in patients but also take a heavy toll on family members and impose striking financial strains on global healthcare systems (36, 37). Hence, it is an urgent necessity to develop more effective therapeutic strategies to cope with the growing burden and health-related consequences of NDs.

NDs are characterized by many micro-processes resulting in progressive neuronal dysfunction and death. These include specific protein accumulations, mitochondrial dysfunction, oxidative/nitrosative stress, proteotoxic stress and its related abnormalities in ubiquitin proteasomal and autophagosomal/lysosomal systems, excitotoxicity, apoptosis (also known as programmed cell death) and uncontrolled neuroinflammation (38-41). There is overwhelming evidence of mitochondrial dysfunction and mutations in the pathogenesis of various NDs. Mutations in the mitochondrial DNA (mtDNA), impaired mitochondria dynamics (e.g. shape, size, distribution, fission-fusion, movement), abnormalities in complexes of the electron transport chain (ETC) and partial inhibition of mitochondrial ATP production giving rise to overproduction of free radicals. This will lead to damage of the biomolecules (e.g. lipids, proteins and DNA), neuroinflammation, tissue damage and consequent cellular apoptosis in CNS which are the major hallmarks of NDs (40, 42).

It has been reported that native curcumin and its micellized (43)/micronized (44)/hybridized (45)/nano-sized (46) forms, as well as its derivatives (47)/synthetic analogs (48) and its synergistic combination with other compounds (49) have the excellent capacity for scavenging intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) (50, 51). In addition, it protects the mitochondrial dysfunctions/impairments by 1. retaining mitochondrial membrane potential ($\Delta\Psi m$)/the activities of all four mitochondrial complexes (complex I, II, III and IV) (48) and Bax/Bcl-2 ratio (52); 2. enhancing/increasing mitochondrial fusion activity, mitochondrial biogenesis and synaptic proteins (53); 3. reducing fission machinery (53), mitochondrial swelling, lipid peroxidation, protein carbonylation (44), levels of oxidized lipids (49) neuroinflammation (54), apoptosis (55-57), cytochrome c, caspase-3 and -9 activation and mitochondrial depolarization (58); 4. modulating/targeting the phospho-CREB-BDNF signaling (54) and the nuclear factor (erythroid-derived 2)-like 2 (also known as Nrf2 or NFE2L2; a transcription factor) (59) and 5. restoring the glutathione (GSH) levels and superoxide dismutase (SOD) (44).

These findings suggest that utilizing curcumin and its related compounds as a neuroprotective agent with modulatory/protective effects on mitochondrial impairments and mitophagy (60) could be a promising approach for the treatment of NDs. Due to the association between NDs and mitochondrial dysfunction, we review in detail about the effects and underlying mechanisms of curcumin on the mitochondria in NDs *in vitro, in vivo* and in clinical trials.

Neurodegenerative Diseases

At present, there is no definitive treatment for curing the NDs. , The current therapeutic strategies are just capable of symptomatic relief and/or managing the overall symptoms as well as restraining the disease progression such as dopaminergic treatments for parkinsonism (e.g. PD, PD-related disorders and movement impairments) (61), cholinesterase inhibitors for cognitive disorders (62), antipsychotic drugs (also known as neuroleptics or major tranquilizers) for behavioral and psychological symptoms of dementia (63), analgesics for pain reduction (64), anti-inflammatory medications for ameliorating disease progression (2), and deep-brain stimulation, a medical device, to stop tremor and refractory movement disorders (65).

Although recent advances have shed more light into the pathophysiology of NDs, the exact etiology of NDs remain to be fully elucidated. The etiology of NDs could be multifactorial and heterogeneous, albeit credible evidence has emphasized that aging, genetic background, accumulated/misfolded proteins and environmental/external factors (e.g. lifestyle and chemical exposure) are potentially linked with the onset of these diseases (66, 67).

The NDs are typically described by specific misfolded and aggregated proteins (68); however, the affected neuron populations and disease severity differ for each NDs (41). However, NDs share many substantial micro-processes associated with gradual neuronal dysfunction and death such as proteotoxic stress and its related abnormalities in ubiquitin–proteasomal and autophagosomal/lysosomal systems, synaptic toxicity, excitotoxicity, oxidative stress, apoptosis, cell-death-related signaling pathways and neuroinflammation (33, 54).

AD is the most common form of dementia with a growing impact on NDs-related global health challenges affecting more than 50 million individuals. It is projected that AD cases in 2030 and 2050 will rise to 82 and 152 million respectively (69). Aβ peptides accumulation and their deposition into β-amyloid plaques (also known as Aβ plaques), as well as the neurofibrillary tangles aggregation into misfolded and hyperphosphorylated tau protein, are the leading causes and the accelerator of AD and AD-related pathology (41). Neurotoxic metals (e.g. lead, mercury, aluminum, cadmium, arsenic), as well as metal-based nanoparticles and some pesticides, are reported to increase Aβ peptides and the neurofibrillary tangles aggregation. This leads to Aβ plaques and hyperphosphorylation of Tau protein and the consequent onset of AD and AD-related pathology (67). Energy deficiency due to mitochondrial dysfunction is a crucial characteristic of AD and AD-related dementias.

PD and PD-related disorders are the second most common NDs with more than 6 million cases or 1-2 individual per 1000 of the population worldwide affected (70). This group of disorders predominately affect dopaminergic (dopamine-producing) neurons in a specific area of the brain called substantia nigra (41). The exposure to several metals (e.g. lead and manganese), industrial chemicals and pollutants (71), solvents and some pesticides (72) are significantly associated with the mitochondrial dysfunction, metal homeostasis alterations and proteins aggregation such as a-synuclein, which is a key constituent of DLB and a pivotal factor in PD pathogenesis (67).

Moreover, nuclear genome mutations in the PINK1 and Parkin genes have been implicated in PD-related NDs pathology (73). DLB is the second most common dementia which is characterized by progressive cognitive impairment, psychiatric and behavioral disturbances and parkinsonian motor symptoms (74).

HD is an autosomal dominant neurodegenerative disorder with choreoathetosis, behavioral as well as psychiatric disturbances and dementia that is caused by excessive CAG repeats in the short arm of chromosome 4p16.3 in the Huntingtin gene. The more CAG repeats (36 CAG repeats or more) the earlier will be the onset of the disease (75, 76). Prion disease is a group of rare NDs that can affect both humans and animals (77). Prion is a type of protein that can fold abnormally leading to the onset of prion disease which is also known as transmissible spongiform encephalopathies.

FTD is an umbrella term given to a heterogeneous group of clinical syndromes and is the leading cause of early-onset dementia in patients under 65. It results from neurodegeneration within the frontal and anterior temporal lobes, insular cortex and subcortical structures. The major hallmarks of FTD are early changes in emotion and behavior, language, and motor skills (31). ALS/MND is a fatal motor neuron disorder that is characterized by progressive deterioration of the upper and lower motor neurons at the spinal or bulbar level (78). The exact etiology of ALS/MND remains to be elucidated. Mutations of superoxide dismutase 1 have been proposed as the most common cause of this fatal motor neuron disorder (79).

The Roles of Mitochondria in NDs

Although the adult brain is about 2% of the body mass, it consumes more than 20% of energy supply in the form of ATP. Most of the brain energy is consumed for synaptic transmission which is crucial for synaptic plasticity (80). Mitochondria are dynamic organelles and the powerhouses of cells. The mitochondria are not only responsible for production of the majority of energy currency represented by ATP but also have a variety of crucial roles including regulation of calcium homeostasis, biogenesis of haem, fatty acid synthesis, biogenesis of iron–sulfur (Fe–S) proteins, apoptosis and population maintenance through fission and fusion (81, 82). There is overwhelming evidence that mitochondrial dysfunction and mutations play major roles in the aging and pathogenesis of various NDs (42).

Brain-derived neurotrophic factor (BDNF) pathway is a fundamental pathway for regulating the synaptic transmission and plasticity of neurons. These processes require a high amount of energy consumption and ca^{2+}-buffering. For ca^{2+}-buffering, mitochondria must be moved to the proper locations. The role of the BDNF pathway in mitochondrial movement and distribution has been increasingly recognized. This suggests that mitochondrial movement and distribution play a crucial role in BDNF-mediated synaptic transmission and plasticity (83). Hence, impairment of mitochondria could affect the synaptic transmission and synaptic plasticity which are the important neurochemical foundation of learning and memory. Intensifying the BDNF pathway could be associated with a higher mitochondrial movement and distribution.

The cAMP response element-binding (CREB) protein is a ubiquitous transcription factor. After phosphorylation, it can promote the transcription of cAMP response element-regulated genes especially mitochondrial genes and it related protein biogenesis (84). However, dysregulation of the CREB transcriptional cascade is reported that have a direct link with the mitochondrial dysfunction and the progression of NDs (85).

The human mtDNA contains genetic coding information of 13 proteins which are the core constituents of the mitochondrial electron transport chain (ETC) complexes I-IV that are embedded in the inner membrane (86). ETC is one of the major hallmarks of mitochondria for energy production in cells through the redox (reduction and oxidation) reactions. Since the major part of ATP is generated by ETC the proper functioning of this chain is fundamental for the CNS cells. Dysfunction in ETC complexes via genetic or exogenous factors could contribute greatly to the onset of NDs. It is reported that neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) suppresses the protein NADH-CoQ reductase in Complex I from pumping the protons across the mitochondrial membrane leading to inhibition of the electrochemical gradient formation and subsequent hindering ATP production and energetic failure (87).

In addition to mtDNA mutations, nuclear DNA mutations are also associated with mitochondrial dysfunction and subsequent NDs. It is reported that nuclear genome mutations in genes encoding α-synuclein, parkin (88), PINK1 (89) and LRRK2 (90) lead to a molecular link between mitochondrial dysfunction and subsequent oxidative stress contributing to PD and PD-related NDs pathology. Mutations in amyloid protein precursor (APP), presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes cause autosomal dominant forms of early-onset AD (91). PSEN1 and PSEN2 mutations impact the mitochondrial function by deregulating the ca^{2+} signaling leading to mitochondrial metabolic defects (92). On the other hand, APP mutations lead to a serious reduction in respiratory activity and enhance glycolysis as well as reduce the mtDNA transcripts (93).

ETC is responsible for most of the ROS production in the cells. GSH and SOD are the natural antioxidants in the cells especially in mitochondria responsible for ROS scavenging. Several studies have reported that patients with NDs have a significant reduction of these antioxidants (94). On the other hand, mitochondria dysfunction leads to an increase in the levels of lipid peroxidation and protein carbonylation which has been identified as the potential intensifier of ROS and/or free-radical productions (95, 96).

Nrf2, a basic leucine zipper protein, is amongst the most pivotal cell defense mechanisms against exogenous and/or endogenous stressors. Nrf2 targets variety of genes such as a vast range of antioxidant enzymes, proteins bound up in xenobiotic detoxification, repair and damaged-proteins elimination, inhibition of neuroinflammation as well as other targeted transcription factors which have fundamental role in retaining the cellular redox homeostasis by regulation, utilization, and generation of GSH and NADPH (97). It is reported that Nrf2 defends neurons against mitochondrial neurotoxic compounds, reduced GHS and imbalanced mitochondrial ROS production as well as improving the function and integrity of mitochondria. Besides, in many

mitochondrial-related disorders especially NDs the function of Nrf2 is suppressed by several processes (98, 59).

ΔΨm generated by proton pumps of ETC complexes I, III and IV is a fundamental component of mitochondria. It results from the redox reactions associated with the activity of the Krebs cycle and is responsible for the storage of energy. ΔΨm plays a crucial role in mitochondria homeostasis by eliminating mitochondria dysfunction. The association of proton gradient (ΔpH) and ΔΨm, form the transmembrane potential of hydrogen ions and can harness ATP production. The levels of ΔΨm and ATP production are relatively steady with limited fluctuations leading to normal physiological activity (99). Alterations of mitochondrial function such as reduction of ΔΨm is highly linked to generating more oxidative stress-inducing early apoptosis (100). In short, long-term decline or the rise of ΔΨm levels may promote adverse effects on cell viability and could be a reason for generating various pathologies especially NDs in CNS (101).

Mitochondria also play a prominent role in the extrinsic/death receptor and intrinsic/mitochondrial apoptosis pathway, which is a fundamental process for growth, homeostasis and immunomodulation in mammalian cells. Apoptosis is initiated by multiple forms of cellular stress stimuli/DNA damage including oxidative stress/ROS/RNS and endoplasmic reticulum stress, radiation and drugs (e.g. chemotherapeutic agents) (102, 40). In this process, pro-apoptotic Bcl-2 homology domain 3 only (BH3-only) proteins (e.g. Bad, Bid, Bim and NOXA) activate Bcl-2 pro-apoptotic family members (e.g. Bax and Bak) and consequently they translocate to the mitochondria. Bax and Bak also induce the cytochrome c release into the cytosol. This promotes the assembling of apoptosome (Apaf-1 and caspase-9) and subsequent activation of executioner caspase-3, -6, -7 initiating the cell death. Moreover, Bcl-2 family has a group of anti-apoptotic members such as Bcl-2, Bcl-xL, Mcl-1 and Bcl-w. For the proper functioning of the cells, the ratio between anti-apoptotic (e.g. Bcl-2, Bcl-xL) and pro-apoptotic (e.g. Bax and Bak) members of Bcl-2 family proteins must be steady. Unbalancing the anti-apoptotic and pro-apoptotic members of Bcl-2 family proteins leads to neuronal damage/death and NDs (103, 104). Moreover, the extrinsic pathway can also crosstalk to the intrinsic apoptosis pathway by an amplification induced by caspase-dependent activation of Bid protein (105).

Microglial cells are the innate immune system cells residing in the CNS. In circumstances such as an invasion of pathogens and the formation of Aβ plaques, microglial cells are converted to the activated state. To defend against the pathogenic invaders and eliminate the Aβ plaques, activated-microglia have the capability of generating neuroinflammation by releasing broad-range of compounds such as inflammatory mediators and neurotoxic compounds. These compounds are a double-edged sword for defending the neurons or affecting the neurons viability and CNS integrity. The chronic expression of several compounds such as TNF-α, IL-1β, PGE2, IL-6, IFN-γ, ROS and RNS could be destructive to cells (106, 2). Long-standing neuroinflammation and chronic expression of several compounds will strikingly affect the neuronal viability and the survival of neural precursor cells by unbalancing the anti-apoptotic and pro-apoptotic members of Bcl-2 family proteins and targeting mitochondria as well as extrinsic and intrinsic apoptosis

pathway (107, 108). Moreover, astrocytic mitochondrial dysfunction including change in intracellular calcium, GSH, SOD and specific neurotoxic compounds production have been implicated by various studies to be associated with the onset of NDs (109).

In short, mitochondrial impairments/dysfunction in the CNS neurons results in mitochondrial depolarization and reduction of mitochondrial dynamics/movements, distribution and fission, as well as releasing cytochrome c/ROS/RNS and subsequent neuronal damage and apoptosis. Moreover, many genetic alterations and related suppression on proteins production are associated with a higher incidence of mitochondrial dysfunction and its molecular consequences. Hence, mitochondrion and its related abnormalities are promising therapeutic targets for neurological disorders and NDs (**Figure 1**).

Molecular Targets of Curcumin on mitochondria in NDs

It has been shown that many exogenous and endogenous factors such as aging, nuclear- and mt-DNA mutations, drugs, neurotoxic compounds and misfolded/aggregated proteins, leads to mitochondria dysfunction, which is markedly linked to the onset and pathogenesis of NDs (30). NDs have a significant effect on the life expectancy and HRQoL (37); however, the existing medications are just capable of symptomatic relief or managing the overall symptoms. It is a priority to develop more effective drugs to face the growing trend of mortality and morbidity of NDs. Curcumin is a natural polyphenol and nontoxic compound stemmed from *Curcuma longa* L., which has a highly pleiotropic and broad-range of targets in cells especially the cell-relating to NDs. Moreover, curcumin's structure makes it possible to cross the blood-brain barrier (BBB) (2). There is growing evidence on the beneficial therapeutic properties of curcumin on various aspects of cells associated with NDs especially for their dysfunctional/impaired mitochondria (**Table 2**). In this section, we discuss the molecular targets of curcumin on mitochondria in NDs.

Various neurotoxic compounds and/or drug are increasingly being recognized as external risk factors linked to the mitochondria-mediated onset of various NDs. For instance, long-term alcohol abuse induces oxidative stress, activates the neuroinflammation pathways, increases the caspase-3, -9, -8 and also changes the Bcl-2/Bax ratio (decreases Bcl-2 and increases Bax proteins). Mitochondria are responsible for regulating the neurotoxicity induced by long-term alcohol abuse, however, these compounds promote the cytochrome c and decrease mitochondria biogenesis (110-112). Curcumin has neuro- and mitochondria-protective effects by reversing the withdrawal effects of the alcohol-induced neurodegeneration and also improves neuronal survival by reducing apoptosis, oxidative stress, neuroinflammation and perturbation in phospho-CREB-BDNF signaling. Moreover, curcumin improves the alcohol-induced reduction in the SOD, GSH, oxidized GSH and GSH reductase activity. Curcumin also decreases the levels of TNF-α and IL-1β as well as reduces the Bax and Bax/Bcl-2 ratio (54).

Oxaliplatin, a platinum-based anti-cancer chemotherapy drug has dose-limiting side effects on the mitochondria by mediating the oxidative stress leading to damage the neurons (113, 114). Combination of curcumin and quercetin have demonstrated neuro- and mitochondrial-protective

effects against oxaliplatin side effects by significantly reducing the mitochondrial lipid peroxidation levels, protein carbonyl content and subsequent oxidative stress. It also improves the altered non-enzymatic and enzymatic antioxidants and ETC complexes enzymes of mitochondria (114).

Exposure of tert-butyl hydroperoxide (t-BHP) to neurons leads to ΔΨm loss and cytochrome c release and subsequent activation of caspase-3 and PARP cleavage and cell apoptosis. Curcumin has neuro- and mitochondrial-protective effects by abrogating the ΔΨm loss and cytochrome c release, suppressing the caspase-3 activation and altering the of Bcl-2 family expression as well as preventing the cellular GSH and decreasing intracellular ROS generation. In short, curcumin has the potential to attenuate tBHP-induced apoptosis in cortical neurons (115).

Aβ and APP can impair the mitochondria by localizing in the mitochondria membrane, interacting with mitochondrial proteins, disrupting the ETC and following synaptic activity reduction, increasing reactive oxygen species production, reducing the mitochondrial biogenesis and fusion activity, leading to mitochondrial and neuronal damage and consequent NDs (116, 49). It has been reported that curcumin can reverse the Aβ-withdrawal (and maybe APP-withdrawal) effects by reducing the mitochondrial dysfunction and its fission machinery, improving mitochondrial fusion activity and maintaining cell viability and mitochondrial dynamics, mitochondrial biogenesis, synaptic activity and synaptic proteins (53).

Rotenone, an insecticide and pesticide, has the potential to impair the cognitive function, affect the oxidative defense (e.g. by increasing lipid peroxidation, nitrite concentration and decreasing activity of superoxide dismutase, catalase and reduced glutathione level) and also influence the mitochondrial complex (II and III) enzymes activities (117, 118). It is reported that curcumin has the neuro- and mitochondrial-protective against rotenone-withdrawal effects by improving the behavioral alterations, mitochondrial ETC complexes enzyme activities, reducing ROS production and oxidative damage, preventing apoptosis as well as restoring the motor deficits and ΔΨm and enhancing the antioxidant enzymes (48, 118).

D-galactose, a reducing sugar, have the potential of inducing oxidative stress resulting in an alteration in mitochondrial dynamics and apoptosis of neurons. Additionally, D-galactose can impair the activity of the mitochondrial ETC complexes I, II and III. It also significantly increases the lipid/protein oxidation, diminish the levels of GSH and activate the caspase-3 (119, 49). Curcumin can markedly reduce the D-galactose effects on CNS cells by restoring the activity of the mitochondrial ETC complexes I, II and III, decreasing the levels of malondialdehyde, advanced oxidation protein products and protein carbonylation, increasing the GSH and oxidized GSH and reducing the expression of cleaved caspase-3 (49).

Various misfolded and aggregated proteins lead to the onset and progression of NDs. α-synuclein, an expressed neuronal protein, is the main protein affected in a group of neurodegenerative disorders called α-synucleinopathies, which are characterized by the presence of intracellular α-synuclein aggregation. α-synuclein can potentially lead to the onset of dementia in DLB, PD and

PD-related disorders (120, 121). α-synuclein aggregation leads to the induction of the cell death, intracellular ROS production, caspase-3 and -9 activations, mitochondrial depolarization and cytochrome c release. Curcumin has neuro- and mitochondrial-protective properties against the aggregated-α-synuclein neurotoxicity by reducing the cell death, intracellular ROS, caspase-3 and -9 activations, mitochondrial depolarization and cytochrome c release (58).

Hydrogen peroxide (H_2O_2) is the major source of oxidative stress and is considered to have a major role in various neurological disorders especially NDs. H_2O_2 has the potential ability to induce ROS production, apoptosis, caspase-3 and -9 activations and lipid peroxidation, reduce the mitochondrial depolarization, GSH and GSH peroxidase and increase the intracellular and extracellular release of ca^{2+}. It was reported that curcumin has the neuro- and mitochondrial-protective ability by reversing the detrimental effects of H_2O_2 (122).

1-methyl-4-phenylpridinium ions (MPP^+), the active metabolite of 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridin, exerts its neurotoxicity by inhibiting ATP production, stimulating superoxide radical formation, leading to mitochondria dysfunction and consequent CNS cell death (123). Curcumin significantly protects CNS cells against MPP^+-induced apoptosis. It also improves the mitochondrial function by attenuating the $\Delta\Psi m$ dysfunction and intracellular ROS production and expression of Bcl-2 (56).

Glutamate is the major excitatory neurotransmitter in the CNS. A mounting number of evidence suggests that perturbations in the systems using the excitatory L-glutamate may underlie the pathogenic mechanisms of a myriad of diseases such as epilepsy and chronic NDs. All neurons in the CNS have the N-methyl-d-aspartate subtype of ionotropic L-glutamate receptors mediating the post-synaptic $Ca2^+$ influx. Excitotoxicity resulting from the activation of NMDA receptors leads to the upregulation of GSH peroxidase 1, GSH disulfide, $Ca2^+$ influx, NO/ROS/H_2O_2 production, cytochrome c release, Bax/Bcl-2 ratio, caspase-3 activity, lactate dehydrogenase and malondialdehyde. It also downregulates GSH, GSH reductase, SOD and catalase thereby promoting cell apoptosis (124, 125). Curcumin has been shown to effectively protect CNS cells by reversing all the described glutamate-induced oxidative toxicity and excitotoxicity (125).

Neurotoxic compounds such as manganese and aluminum have the capability to enhance the ETC activity of NADH dehydrogenase (complex I), succinic dehydrogenase (complex II) and cytochrome oxidize (Complex IV), increase the malondialdehyde, ROS production as well as induce mitochondria-related apoptosis such as caspase-3 and -9 activations, cytochrome c release and Bcl-2/Bax ratio (Bax increase, and Bcl-2 decrease). Curcumin exerts its neuro- and mitochondrial-protective effects on CNS cells especially microglial cells by reversing the effects of manganese- and aluminum-induced cytotoxicity/neurocytotoxicity (126, 57).

Nrf2 has a pivotal role in defending the CNS cells against the mitochondrial dysfunction and its neurotoxic compounds, reduced GHS and imbalanced mitochondrial ROS which is suppressed in NDs. Curcumin activates Nrf2 and Nrf2 target genes in the CNS cells decreases the level of intracellular ROS and attenuates the oxidative damage and mitochondrial dysfunction (127).

Cerebral ischemia can induce a rapid increase in lipid peroxidation and reduction in ΔΨm, increase cytochrome c release and caspase-3 activation thereby resulting in apoptosis. Cerebral ischemia also induces extensive neuronal death together with increasing the astrocytes and microglial cells activation. However, it has been reported that curcumin exerts its neuro- and mitochondrial-protective effects against ischemia-induced neurodegeneration by attenuating ischemia-induced neuronal death and glial activation as well as decreasing the lipid peroxidation, mitochondrial dysfunction and thereby apoptosis (55).

Curcumin analogs

Despite the myriad therapeutic beneficial effects of curcumin due to its hydrophobic tendency, presence of an active methylene group and a β-diketone moiety, curcumin has a poor bioavailability/pharmacokinetics and get metabolized easily via aldo-keto reductase in the liver, which hinders its *in vivo* and *clinical trial* use in many routes of administration (29, 2). Numerous studies have been looking into mechanisms to circumvent the unstable and poor bioavailability and pharmacokinetic properties of curcumin by designing and characterizing micellized (43)/micronized (44)/hybridized (45)/nano-sized (46) forms of native curcumin as well as its derivatives (47) and synthetic analogs (48).

Modification of curcumin not only enhance its bioavailability status but also amplify the neuro- and mitochondrial-protective effects of curcumin. For instance, curcumin pyrazole derivatives (e.g. C1-C6 and CNB-001) have significantly more protective properties on mitochondrial dysfunction and it related abnormalities by inhibiting the ΔΨm loss, attenuating intracellular ROS and enhancing nuclear translocation of Nrf2 (48, 59).

Curcumin micelles have been shown to have a better bioavailability status by improving solubility in different cells membranes. It has been shown that some micelles considerably improve the curcumin bioavailability up to 40-fold. Moreover, curcumin micelles are more effective in preventing mitochondrial swelling and oxidative stress than native curcumin (43).

Hybridization of compounds to curcumin is another approach to overcome its poor bioavailability and also potentially intensify the neuro- and mitochondrial-protection by another therapeutic compound. It is reported that curcumin and melatonin hybridization (two natural compounds) can potentiate the curcumin bioavailability and its function and can cross BBB could be even more significant and promising in neuroprotective approaches in NDs therapy (45).

Bioconjugates of curcumin such as di-demethylenated piperoyl, di-valinoyl and di-glutamoyl esters improve neuroprotective effects against nitrosative stress and mitochondrial dysfunction and damage (47). To compensate for the poor bioavailability of curcumin, curcumin encapsulated solid lipid nanoparticles (CSLNs) has been shown to significantly increase the activity of mitochondrial ETC complexes and cytochrome levels. Moreover, CSLNs also restore GSH levels and SOD activity. CSLNs markedly reduce the mitochondrial swelling, lipid peroxidation, protein carbonyls and ROS and also promote the Nrf2 antioxidant pathway (44). When encapsulated in nano-sized

PLGA curcumin exerts its neuro- and mitochondrial-protective effects through the regulation of NF-κB (p65) and also reduce the caspase-9a expression as well as the apoptosis by ameliorating CSF levels of TNF-α and IL-1β (46).

The Promise of Curcumin for NDs Therapy

Curcumin has the potential to protect the CNS cells against a myriad of conditions including NDs. It has been shown that curcumin not only protect mitochondrial dysfunction and inhibit neuronal death by targeting wide-range of crucial pathways including oxidative stress/ROS/RNS, intrinsic/extrinsic pathway of apoptosis, neuroinflammatory mediators as well as microglial cells activation and other glial cells, but also attenuate the neuronal loss by many diseases/injuries and neurotoxic compounds. Many conditions such as hypertension, diabetes, atrial fibrillation, ischemic, heart-disease, dyslipidemia and obesity have the potential to induce stroke especially ischemic stroke, which increases the risk of dementia up to five-fold (128). It has been shown that curcumin can protect the CNS cell against ischemia-induced mitochondrial dysfunction and the onset of NDs.

Due to its structural properties, it has poor bioavailability however, there is an increasing number of studies using nano-/micro-sized and encapsulated form of curcumin to enhance its bioavailability. By developing hybrid medications with curcumin and other natural compounds can potentiate the properties of curcumin even more which could be assessed in future clinical trials. Hence the use of curcumin is a promising therapeutic strategy to cope with the growing trend of NDs.

Conclusions

Based on *in vitro* (**Table 1**) and *in* vivo (**Table 2**) evidence, curcumin has an excellent potential to protect CNS cells against mitochondria-related pathology in a wide variety of NDs and against several stimulating factors (e.g. ischemia-induced neurodegeneration via mitochondrial dysfunction), neurotoxic compounds (e.g. aluminum, manganese, MPP, HO, D-galactose, rotenone and t-BHP), lifestyle-induced neurodegeneration (e.g. heavy alcohol usage), excitotoxicity-induced neurodegeneration (e.g. L-glutamate) and adverse effects of some existing medications on neurodegeneration (e.g. oxaliplatin) as well as pathologies induced by misfolded-/aggregated-/mutant proteins (e.g. Aβ, APP and α-synuclein). Moreover, curcumin exerts its mitochondria protecting properties by: 1. retaining ΔΨm/the activities of mitochondrial ETC complexes (48) and Bax/Bcl-2 ratio (52); 2. enhancing/increasing mitochondrial fusion activity, mitochondrial biogenesis and synaptic proteins (53); 3. reducing fission machinery (53), mitochondrial swelling, lipid peroxidation, protein carbonylation (44), levels of oxidized lipids (49) neuroinflammation (54), apoptosis (55-57), cytochrome c, caspase-3 and -9 activation, and mitochondrial depolarization (58); 4. modulating/targeting the phospho-CREB-BDNF signaling (54) and Nrf2 (59) and 5. restoring GSH levels and SOD (44).

In conclusion, curcumin is associated with biological properties on mitochondrial dysfunction and its related abnormalities and could be a potential therapeutic candidate for the management of various NDs.

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Figure legends

Figure 1. Genetic alterations (e.g. mutations) and environmental/external factors as well as their synergistic effects can induce the formation of reactive oxygen species (ROS), reactive nitrogen species (RNS) and other neurotoxic compounds, leading to accumulated/misfolded proteins and subsequent mitochondrial dysfunction. Mitochondrial dysfunction can contribute to neurodegeneration through several mechanisms including interference with cell signaling, redox state, microglial activation and lipid peroxidation. Curcumin can mitigate the destructive effects of ROS, RNS and other neurotoxic compounds by several mechanisms that result in blunted neurodegeneration. GSH: reduced glutathione, SOD: superoxide dismutase, ETC: electron transport chain.

Table 1. Effects of Curcumin on Mitochondria Function on NDs *in vitro*.

Author	Species and cell type	Agents	Dose	In vitro effects	Refs.
Liao et al. (2019)	PC12 cells	Six curcumin pyrazole derivatives	Dose- and time-dependent manner	Curcumin pyrazole derivatives potentially reduce ROS levels and protect the neurons by targeting and/or protecting mitochondria and nrf2 signaling pathway.	(59)
Daverey et al. (2016)	A172 (human glioblastoma cell line) and HA-sp (human astrocytes cell line derived from the spinal cord) astrocytes.	Curcumin	Dose- and time-dependent manner	Curcumin not only protected astrocytes from H_2O_2-induced oxidative stress but also reversed the mitochondrial damage and dysfunction induced by oxidative stress.	(129)
Cihangir Uguz et al. (2015)	SH-SY5Y cells	Curcumin and H_2O_2	5 mM curcumin and 100 mM H_2O_2	Curcumin effectively induced modulator effects on oxidative stress and the levels of intracellular Ca^{2+}, caspase-3 and -9.	(122)
Hagl et al. (2015)	PC12 cells	Curcumin micelles	0.1 μM and 10 μM	Curcumin micelles prevented mitochondria from swelling and was a suitable substance for the prevention of mitochondrial dysfunction and neurodegeneration.	(43)
Liu et al. (2011)	PC12 cells expressing inducible A53T α-synuclein	Curcumin	Dose-dependent manner	Curcumin reduced mutant α-synuclein-induced intracellular reactive oxygen species (ROS) levels, mitochondrial depolarization, cytochrome c release, and caspase-9 and caspase-3 activation.	(58)
Chen et al. (2006)	PC12 cells	Curcumin	Dose-dependent manner	Curcumin protected PC12 cells against MPP^+-induced cytotoxicity and apoptosis by inducing overexpression of Bcl-2, and reducing the loss of mitochondrial membrane potential, intracellular ROS and overexpression of iNOS.	(56)
van der Merwe et al. (2017)	PINK1 Knock Down SH-SY5Y cell line	Curcumin	Dose- and time-dependent manner	This study demonstrated that down regulation of PINK1 by specific siRNA resulted in features of mitochondrial dysfunction and increased cell	(130)

				death which were rescued and reversed by curcumin.	
Chang et al. (2014)	PC12 cells	Curcumin and glutamate	Dose- and time-dependent manner	Curcumin effectively protected PC12 cells against the glutamate-induced oxidative toxicity in two pathways: the glutathione-dependent nitric oxide-reactive oxygen species pathway and the mitochondria-dependent nitric oxide-reactive oxygen species pathway.	(125)
Chojnacki et al. (2014)	MC65 Cells	hybrid compounds of curcumin and melatonin (named 7)	Dose-dependent manner	7's antioxidant effects correlate well with its neuroprotective potency and these effects might be due to its interference with the interactions of amyloid-β oligomers within the mitochondria.	(45)
Mythri et al. (2011)	N27 cells	Bioconjugates of curcumin (Di-demethylenated piperoyl, di-valinoyl and di-glutamoyl esters)	Dose-dependent manner	Glutamoyl diester of curcumin showed the improved protection against peroxynitrite-dependent CI inhibition and protein nitration. Additionally, Di-glutamoyl curcumin protected dopaminergic neurons against MPP^+-mediated neuronal death.	(47)
Jayaraj et al. (2013)	SK-N-SH cells	CNB-001 and rotenone	2 μM curcumin and 100 nM rotenone	CNB-001 demonstrated protection against rotenone-induced toxicity by inhibiting mitochondrial ROS generation, retains $\Delta\Psi m$, and prevents apoptosis. Moreover, CNB-001 offered neuroprotection by its antioxidant, mitochondrial protective, and antiapoptotic properties.	(48)
Reddy et al. (2016)	SH-SY5Y cells	Curcumin and Aβ	Dose-dependent manner	After Aβ affections on mitochondria, curcumin enhanced mitochondrial fusion activity, reduced fission machinery, increased biogenesis and synaptic proteins.	(53)
Park et al. (2017)	BV-2 Microglial Cells	Curcumin and manganese	0.1–10 μM curcumin and 250 μM manganese	Curcumin prevented manganese-induced microglial cell death through the induction of HO-1 and regulation of oxidative stress, mitochondrial	(57)

				dysfunction, and apoptotic events.	
Zhu et al. (2004)	Primary cortical neurons culture	Curcumin and tBHP	2.5-20 μM/L curcumin for 18 h and 100 μM/L tBHP for 60 min	Curcumin treatment prevented cellular GSH and decreased intracellular ROS generation, and also attenuated tBHP-induced apoptosis in cortical neurons.	(115)

Table 2. Effects of Curcumin on Mitochondria Function on NDs *in vivo*.

Author	Species and cell type	Agents	Dose/route	In vivo effects	Refs.
Jiang et al. (2011)	male mice ($Nrf2^{+/+}$ and $Nrf2^{-/-}$) and their primary spinal cord astrocytes	Curcumin	Dose- and time-dependent manner	Curcumin activated Nrf2 and Nrf2 target genes in primary astrocytes, decreased the level of intracellular ROS, and attenuated oxidative damage and mitochondrial dysfunction.	(127)
Atamna et al. (2006)	Mouse model of AD and SH-SY5Y cell line	Curcumin	Dose- and time-dependent manner	Curcumin reduced oxidative stress in a mouse model for AD of Aβ-heme.	(131)
Sood et al. (2011)	Sprague-Dawley rats	Curcumin and aluminum	Oral gavage of 100 mg/kg body wt/day aluminum, and 50 mg/kg curcumin intraperitoneall y administration	Curcumin supplementation to aluminum-treated rats significantly normalized the activities of all the three mitochondrial complexes (complex I, II, IV) and reduced the content of GSH in the brain which wase altered following aluminum treatment.	(126)
Motaghinejad a et al. (2017)	Male wistar rats	Curcumin and alcohol	Dose- and time-dependent manner	Curcumin demonstrated neuro- and mitochondria-protection via reversing the withdrawal effects of the alcohol-induced cell degeneration, and improving neuronal survival by reducing apoptosis, oxidative stress, neuroinflammation and perturbation in CREB-BDNF signaling.	(54)
Hagl et al. (2015)	NMRI mice	Curcumin micelles	Orally gavaged of 1.75 µL curcumin micelles solution per gram body weight	Curcumin micelles prevented mitochondria from swelling and was a suitable substance for the prevention of mitochondrial dysfunction and neurodegeneration.	(43)
Sandhir et al. (2014)	Female Wistar rats	Curcumin encapsulated solid lipid nanoparticles (CSLNs)	Dose- and time-dependent manner, i.p. administration	CSLNs demonstrated a significant increase in the activity of mitochondrial complexes and cytochrome levels, also restored the GSH	(44)

				levels and superoxide dismutase activity and significantly reduced the mitochondrial swelling, lipid peroxidation, protein carbonyls and ROS.	
Eckert et al. (2013)	Senescence-accelerated mice	Curcumin	0.5 g curcumin per kg diet for 5 months.	Curcumin restored mitochondrial function by induction of the nuclear receptor PGC1a, and maybe a promising dietary agent that may slow down brain aging and prevent mitochondrial dysfunction.	(132)
Wang et al. (2005)	male Mongolian gerbils	Curcumin	i.p. administration of 30 mg/kg bwt	Curcumin administration significantly attenuated ischemia-induced neuronal death, glial activation and decreased lipid peroxidation, mitochondrial dysfunction, and the apoptotic indices.	(55)
Seo et al. (2010)	Tg2576 mice	Curcumin	500 ppm	Curcumin reversed motor function deficits of Tg2576 mice. Moreover, the enhanced lipid peroxidation and neuronal loss were partially suppressed by curcumin.	(133)
Zhang et al. (2017)	Male albino, Wistar rats	Curcumin	25 mg/kg bwt	Curcumin reduced the brain edema and water content, the level of IL-6 and TNF-α, Protein expression of p53 and Bax, and $\Delta\Psi m$	(134)
Waseem et al. (2016)	Male Wistar rats	Curcumin and quercetin	Dose-dependent manner	Curcumin and quercetin showed neuroprotective effects and regulated the neurotoxic effects of oxaliplatin exposure; they also attenuated oxidative stress as evident by mitochondrial dysfunction.	(114)
Banji et al. (2014)	Sixteen-week old healthy Wistar rats	Curcumin, D-galactose and hesperidin	150 mg/kg D-galactose subcutaneously 50 and 100 mg/kg curcumin orally; 10 and 25 mg/kg	Curcumin reduced the levels of oxidized lipids, proteins, cleaved caspase-3 expression and mitochondrial enzymes. Moreover, the combination of curcumin and hesperidin	(49)

			hesperidin orally	protected the morphological facets and improve the biochemical functions of neurons.	
Khatri et al. (2016)	Swiss albino male mice	Curcumin and rotenone	1 mg/kg rotenone i.p. administration and 50, 100 and 200 mg/kg of curcumin oral administration	Curcumin treatment markedly improved the rotenone-induced behavioral alterations, oxidative damage and mitochondrial enzyme complex activities as compared to negative control (rotenone treated) group, and demonstrated neuroprotective effects on PD.	(118)
Chang et al. (2015)	male Sprague–Dawley rats	Nanocurcumin	75/150/300 μg/kg/ day	Nanocurcumin exerted its neuroprotective effects through the upward regulation of NF-κB (p65) and reduced mitochondrion related caspase-9a expression	(46)