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Nutraceuticals against Neurodegeneration: A Mechanistic Insight

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Abstract: The mechanisms underlying neurodegenerative disorders are complex and multifactorial; however, accumulating evidences suggest few common shared pathways. These common pathways include mitochondrial dysfunction, intracellular Ca^{2+} overload, oxidative stress and inflammation. Often multiple pathways co-exist, and therefore limit the benefits of therapeutic interventions. Nutraceuticals have recently gained importance owing to their multifaceted effects. These food-based approaches are believed to target multiple pathways in a slow but more physiological manner without causing severe adverse effects. Available information strongly supports the notion that apart from preventing the onset of neuronal damage, nutraceuticals can potentially attenuate the continued progression of neuronal destruction. In this article, we i) review the common pathways involved in the pathogenesis of the toxicants-induced neurotoxicity and neurodegenerative disorders with special emphasis on Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Multiple sclerosis (MS) and Amyotrophic lateral sclerosis (ALS), and ii) summarize current research advancements on the effects of nutraceuticals against these detrimental pathways.

Keywords: Neurodegeneration, mitochondria, calcium, oxidative stress, inflammation, nutraceuticals.

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1. INTRODUCTION

Neurodegenerative diseases are one of the most debilitating conditions and usually associated with mutated genes, accumulation of abnormal proteins, increased reactive oxygen species (ROS) or destruction of the neurons in a specific part of the brain [1-5]. Improved experimental models, modern research techniques and research in the field of neuroscience have advanced our understanding about the unique mechanisms of the onset and expansion of the neurodegeneration and toxicants-induced neurotoxicity. Among several recognized mechanisms, the damage to neuronal mitochondria, intracellular Ca^{2+}overload, uncontrolled generation of ROS, sustained inflammatory condition or any combination of these are the common busy high-roads for neurotoxicity [6-14]. Increased oxidative stress and mild chronic inflammation are the host of multiple disorders, including neuronal disorders. On the other hand, Ca^{2+} homeostasis across the membrane (cellular, endoplasmic reticulum (ER) and mitochondrial) is critical for a variety of cellular physiological functions. The multiple order of calcium concentration [Ca^{2+}] gradient across the membrane is precisely regulated through several specialized mechanisms. Any event that perturbs these mechanisms leads to the persistent increase in the intracellular and intra-organelle (ER and mitochondria) [Ca^{2+}], which has been linked to the pathogenesis of several neurodegenerative disorders [15-17]. Among these mechanisms, mitochondrial damage has gained particular attention, as perturbation of its function triggers activation of neurotoxic pathways such as deregulation of Ca^{2+} homeostasis, generation of ROS from the electron transport chain (ETC) and impaired cellular energy production [18]. Although, the causative factor for the onset of these signaling may differ, the progression of toxicants-induced neuronal damage and neurodegenerative disorders largely involves the same shared mechanisms, reinforcing the importance of these pathways as common targets for the intervention strategies. Advancement in our understanding of the mechanisms underlying the neuronal damage has made it possible to design interventions that can potentially delay the onset and/or prevent further expansion of the unabated neurodegeneration [19, 20].

Utilizing the knowledge of the etiology of the neuro-degenerative diseases, target-based therapies such as neuro-transmitter modulators, direct receptor agonists/antagonists, second messenger modulators, stem cells-based therapies, hormone replacement therapy, neurotrophic factors as well

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as regulators of the mRNA synthesis and its translation into disease-causing mutant proteins have been developed [21-28]. Although, these strategies are great tools to mitigate the neurodegenerative processes, such treatments are often associated with adverse effects and long-term unknown consequences [22, 25, 29, 30]. Neural transplantation and stem cells-based therapies are emerging with a great hope to fight against the range of neurodegenerative diseases [31-33]. Despite unprecedented advancement in these fields of research, the therapeutic applications of such novel tools are still far from reaching the clinics. So, there is a need to identify a safer alternative treatment option that can be employed over long duration to fight against the debilitating neuronal conditions. Nutraceuticals, which can simultaneously act on multiple targets to improve the overall neuronal health, appear to be an attractive option [34-39]. In the present article, we have reviewed mitochondrial dysfunction, intracellular Ca^{2+} overload, oxidative stress and inflammation as common pathways involved in the neuronal damage and evaluated current research advancements on the effects of some selected nutraceuticals on these pathways.

2. MECHANISMS OF NEURONAL DAMAGE

2.1. Mitotoxicity-mediated Neuronal Damage

Mitochondrial damage underlies the pathogenesis of several types of toxicants-induced acute neurotoxicity and neurodegenerative diseases [40-48]. Unlike other organelles, the regulation of mitochondrial functions is under the control of two genomes: nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Mutations in either of these genomes can result in the mitotoxicity-mediated neurodegeneration [49]. Mitochondrial dysfunction could affect distinct compartments of a single neuron or a specific region of the brain. Widely studied glutamate neurotoxicity by Ca^{2+} influx is also primarily attributed to the mitochondrial permeability transition pore (MPT) [40, 45]. The neuro-toxicant, 1-methyl-4-phenylpyridinium (MPP^{+}), as generated from the mono amine oxidase (MAO)-catalyzed oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) within the brain, is concentrated inside the mitochondria of the dopaminergic cells and inhibits Complex I of the respiratory electron transport chain (ETC), which contributes to the development of Parkinson's disease (PD) [50, 51]. Poly ADP ribose polymerase (PARP) activation-associated neuronal cell death (both apoptotic and necrotic forms) after cerebral ischemia is mediated by cyclophilin D (CypD)-dependent MPT [50, 51]. Neurotoxicity that occurs with various chemotherapeutic agents such as taxanes [52], bortezomib [53] and platinum compounds [54] is also associated with the mitochondrial dysfunction.

Pathophysiology of several neurodegenerative diseases such as Alzheimer's disease (AD), PD, Huntington's disease (HD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) largely involves damaged mitochondria [55-59]. Several mitochondrial-dependent molecular mechanisms such as inhibition of mitochondrial ETC's complexes, generation of ROS, perturbations of mitochondrial clearance mechanisms, altered functioning of the enzymes involved in tricarboxylic acid cycle, impairment of mitochondrial dynamics, and interference with the timely supply of the functional mitochondria to the specific sites within a neuron could contribute to the pathogenesis of neuronal injury and neurodegenerative diseases [40, 41, 43-46]. Defective ETC (Complex I) in the substantia-nigra has been considered as a central cause of the sporadic form of PD [50, 51, 57, 60, 61]. Mitochondrial abnormalities also underlie the neuronal damage in AD [55, 62] and ALS [59, 63, 64]. Neuronal degeneration in MS and in experimental autoimmune encephalomyelitis (EAE) is also attributed to the abnormal activities of Complexes I and IV of the ETC as well as the loss of mitochondrial membrane potential ($\Delta\Psi_m$) [65, 66]. Evidence from pre-clinical and clinical studies suggested the role of mitotoxicity in the pathogenesis of neuronal degeneration in HD [56, 67-70]. Mutant huntingtin, the gene responsible for the development of HD, is reported to directly impair mitochondrial functions [71]. Defective mitochondrial Complex II, III and IV have been found in the postmortem tissue from HD patients [72, 73]. Several studies have concluded a positive relationship between mtDNA fragmentation in striatal and cortical neurons and the development of HD [74].

Collectively, these findings suggest that mitochondrial damage is the primary event observed in toxicants-induced neurotoxicity as well as various neurodegenerative diseases. Owing to complex interplay between mitotoxicity, oxidative stress and sustained inflammatory status, it has always remained unclear if mitochondrial damage is the cause or consequence of neuronal damage. Several lines of evidence suggest that mitotoxicity-associated intracellular Ca^{2+} overload, oxidative stress and inflammation are the leading causes for the development of neurodegeneration [43]. The role of Ca^{2+}overload, oxidative stress and inflammation in the development of neurotoxicity and neurodegeneration has been discussed below.

2.2. Ca^{2+} Overload-mediated Neuronal Damage

Research about the role of Ca^{2+} ions in neurotoxicity and neurodegenerative diseases started in 1970s [75, 76]. In general, the $[Ca^{2+}]$ in extracellular space remains in millimolar range, while inside cells, it remains in micromolar range [75, 77-79]. This multiple order of $[Ca^{2+}]$ difference across plasma membrane under normal physiological conditions is attributed to the selective permeability of plasma membrane, the dynamic functions of the several adenosine triphosphate (ATP)-dependent Ca^{2+}-ATPase pumps and sodium/calcium exchange system that actively pumps Ca^{2+}ions outside the cells [17, 80, 81]. Moreover intracellular low level of $[Ca^{2+}]$ is maintained by the buffering functions of ER and mitochondria by virtue of their ability to store the Ca^{2+}ions [17, 47, 82]. Storage of Ca^{2+} inside the ER occurs after active transport of cytoplasmic Ca^{2+} through ATP-dependent pumps in the ER membrane [17]. However, uptake of cytoplasmic Ca^{2+} into mitochondria occurs through a membrane protein known as electrophoretic uniporter present in the mitochondrial outer membrane [47]. Cellular events that compromise integrity of the plasma membranes or the functions of ATP-dependent Ca^{2+}-ATPase pumps/uniporter system can potentially be responsible for rise in intracellular $[Ca^{2+}]$. In addition to these mechanisms, Ca^{2+} accumulation in neuronal cells can also occur through several other routes such as activation of

voltage-sensitive Ca^{2+}channels, receptor-operated Ca^{2+} channels (N-methyl-D-aspartate (NMDA)), ATP-dependent Ca^{2+} channel (P2j receptor), cyclic nucleotide-gated Ca^{2+} channels, Ca^{2+} channels coupled to G protein receptors and are sensitive to inositol 1,3,4,5 tetrakisphosphate [83]. Notably, the plasma membrane, ER and mitochondria can only handle rise in intracellular Ca^{2+} up to certain extent. Persistent rise in intracellular Ca^{2+} leads to disturbed ER and mitochondrial Ca^{2+} homeostasis, which has been linked to the pathogenesis of various neurodegenerative diseases [16, 17]. Excitotoxicity is also related to the influx of Ca^{2+} ions into the neurons [84]. Further, some pathological conditions such as cerebral ischemia and traumatic brain injury are also associated with an abrupt increase in intracellular [Ca^{2+}] [85, 86]. Sudden rise in intracellular [Ca^{2+}] is an immediate threat to the cell, as it triggers a cascade of neurotoxic events, including mitotoxicity and cessation of ATP synthesis, over-activation of several Ca^{2+}-dependent hydrolytic enzymes such as proteases, phospholipases, nucleases, nitric oxide synthase and phosphatases [87, 88]. These events lead to the onset of neurotoxicity, impaired neuronal functions and eventually death of the neuronal cells. This explains why the maintenance of the intracellular Ca^{2+} ions homeostasis is of crucial importance for the survival of the neuronal cells. Exposure to several neurotoxic chemicals result in the perturbed intracellular Ca^{2+} homeostasis, which eventually leads to the death of neuronal cells [89]. Increased intracellular [Ca^{2+}] is not only implicated in the traumatic and toxicants-induced neurotoxicity, but several neurodegenerative diseases also have the same underlying mechanisms [90-93]. In AD, amyloid-beta (Aβ)-induced neuronal cell death is associated with the dysregulation of Ca^{2+}-dependent pathways [93-95]. Moreover, deregulation of the intracellular Ca^{2+} could explain the selective destruction of dopaminergic neurons in the PD [96]. Neuronal destabilization and injury in MS is due to the overactivation of the Ca^{2+}-dependent proteases, calpain and protein phosphatases [97]. Opening of the MPT due to mitochondrial Ca^{2+} overload and release of the Ca^{2+} ions from the ER by mutant huntingtin is considered as the mechanism of the neuronal death in HD [71, 98]. Collectively, this information indicates that the death of the neuronal cells in toxicants-induced neurotoxicity and neurodegenerative disease follow the common [Ca^{2+}]-dependent mechanisms. However, further studies are needed to understand the downstream pathway that precisely orchestrate the expansion of high intracellular [Ca^{2+}]-mediated death of neuronal cells in neurodegenerative diseases.

2.3. Oxidative Stress-mediated Neuronal Damage

Excessive production of ROS as a result of the imbalance among cellular biochemical processes gives rise to a condition known as oxidative stress [99]. ROS and reactive nitrogen species (RNS)-mediated damage to cellular macromolecules is involved in the pathogenesis of several neurodegenerative diseases [14, 100, 101]. Nervous system is particularly vulnerable to the oxidative stress due to several reasons such as: i) high oxygen consumption due to higher demand of energy (ATP), ii) relatively lower level of the endogenous antioxidants reserve, iii) abundance of polyunsaturated lipids, which are particularly susceptible to free radical attack, in the plasma membrane of large neuronal cells, iv) high levels of redox-active transition metals, v) presence of excitatory amino acids and neurotransmitters, whose metabolism can produce ROS, and vi) almost complete dependency of the neuronal cells on the membrane-dependent dynamic synaptic transmission for the effective communication [102-107]. These characteristics make neuronal cells an easy target for the ROS- and RNS-mediated damage. Although, initial events after MPP^+ exposure is the inhibition of Complex I in ETC, subsequent oxidative stress is the underlying cause of the PD like condition [108]. The loss of dopaminergic and serotonergic nerve terminals in the methamphetamine (METH) and 3,4-methlyenedioxymethamphetamine (MDMA) drug abusers has been attributed to the oxidative stress [109, 110]. Neuronal degeneration and Aβ neurotoxicity in AD patients is associated with the oxidative damage to DNA, RNA, proteins and lipids [111-116]. Oxidative damage to DNA [117-119] and protein [120, 121] has been reported in the nigro-striatal region of the brain in PD. Oxidation of dopamine to a reactive 6-hydroxydopamine (6-OHDA) provides an important endogenous mechanism for the development of PD like condition [122-124]. Iron, a transition metal, overload has been recognized to play a key role in the Lewy body formation in PD [125]. Perturbed homeostasis of redox-active and inactive metals has been associated with the affected area in the brain of AD [113, 114] and PD [126-129]. Oxidative stress-induced mutations in the gene encoding for the ubiquitous Cu/Zn-superoxide dismutase (SOD-1) enzyme [130] and damage to the proteins, lipids and DNA [131-133] have been associated with the familial and sporadic forms of the ALS. Pathology of MS is no different when the detrimental effect of the oxidative stress is considered. ROS and RNS produced by the activated microglia and mononuclear cells play a major role in the pathogenesis of MS. Oxidative damage to nDNA, mtDNA and decreased level of endogenous antioxidants [134-136] have been linked to the demyelination [137] and axonal injury in MS and EAE [138]. Increased incidence of the oxidative DNA strand breaks and exacerbated lipofuscin, a pigment produced by the reaction of cellular amino compounds with the aldehydic products of the oxidative damage to tissue macromolecules, is associated with HD [139, 140]. Significant increase in the levels of 8-OH-dG in nDNA has been found in the postmortem tissue of HD cases [141]. All these evidences clearly indicate a causal relationship between the oxidative stress and neuronal cell death in neurodegenerative diseases and toxicants-induced neurotoxicity. This implies that interventional agents such as antioxidants, metal chelators and those able to boost the cellular endogenous antioxidants may offer a therapeutic strategy to prevent the continued progression and sometimes even initiation of the diseases.

2.4. Inflammation-mediated Neuronal Damage

Emerging evidence underscores an active role of neuro-inflammation in the pathophysiology of neurodegenerative diseases [142]. The initiation and subsequent propagation of the neuroinflammation appear to rely on the interaction between glia, immune cells and neurons. Immunologic privileges of brain owing to absence of physical connection between central nervous system and classical lymphatic

system has recently been challenged with identification of functional and classical lymphatic system in the brain [143] suggesting an important role in the pathogenesis of neuronal diseases. Macrophages are present in the brain near glia and microglia and play a fundamental role in the inflammation-mediated neurodegenerative disorders. In the disease state, activated microglia mediate neuronal injury through the production of pro-inflammatory factors such as cytokines and chemokines [144]. Production of pro-inflammatory cytokines and chemokines leads to the trans-endothelial migration of immune cells across the blood-brain-barrier [145]. Several mechanisms have been identified for the microglia-mediated phagocytic and cytotoxic actions that are responsible for neuronal damage. The first and foremost mechanism is phagocytic oxidase (PHOX)-mediated oxidative stress-induced neurotoxicity [145, 146]. Unlike healthy brain, when PHOX (normally expressed at high levels in microglia) is acutely stimulated by inflammatory condition, it causes oxidative stress by rapidly producing high levels of superoxides ($O2^-$).

Inflammatory activation of PHOX also causes activation of microglia [146] resulting in the production of TNFα, IL-1β and inducible NO Synthase (iNOS) [147, 148]. Thus, PHOX activation provides an important link between inflammation and oxidative stress [149]. Thus, inhibition of PHOX has been reported as a potential therapeutic strategy for several neuroinflammatory conditions. iNOS is expressed in microglia, astrocytes and is upregulated during inflammation [150, 151], resulting in increased NO production and thereby RNS leading to neuronal death through the inhibition of the mitochondrial cytochrome oxidase in the neurons [145, 152, 153]. Increased iNOS expression during inflammation may potentiate the neuronal death by hypoxic condition, as it can compete with cytochrome oxidase for the molecular oxygen [153, 154]. However, it should be noted that, activation of either NADPH oxidase (NOX/PHOX) or production of NO through iNOS expression alone is not sufficient to induce neurotoxicity, but their combined activation underlies the mechanism of inflammatory neurodegeneration [145, 155]. Apart from this, chemokines secreted by astrocytes play multiple roles in the pathology of a chronic inflammatory neurodegenerative disease such as AD [154, 156, 157]. Given the self-perpetuating cyclic nature of inflammatory processes in the progression of neurodegeneration [158], intervention with the natural compounds having strong anti-inflammatory activities may offer a safer way to prevent or at least reduce the progression of such devastating diseases.

2.5. Interplay between Intracellular Mitotoxicity, Ca^{2+} Accumulation, Oxidative Stress and Inflammation

Although, each mechanism discussed above can independently mediate neuronal damage, they are highly interlinked with each other and often co-exist. Every single mechanism can serve as an initiation point for the vicious cycle. But perturbation in. Ca^{2+} homeostasis has immediate cytotoxic consequences Ca^{2+} overload, as observed during excitotoxicity, is sensed by the ER, mitochondria and membrane bound Ca^{2+}-transporter pumps. ER and mitochondria operate to re-establish intracellular Ca^{2+} homeostasis. Continued uptake of Ca^{2+} by mitochondria through Ca^{2+} uniporter results in the dissipation of $\Delta\Psi_m$, hindering ATP synthase activity. Inhibition of ATP synthesis impairs the regulatory functions of ATP-dependent Ca^{2+}-ATPase pumps located in the membrane of ER and cell. This causes further accumulation of Ca^{2+} in the cytoplasm of the cells. Continuous overload of Ca^{2+} increases ROS production through interference with the ETC [159]. Ca^{2+}overload can activate constitutively expressed NOS in the neuronal and endothelial cells of the brain to produce excess amount of NO [160, 161]. Coproduction of NO and $O2^-$ leads to the formation of highly reactive $NOO2^-$. Furthermore, $NOO2^-$ can itself augment its formation through the inactivation of Mn-SOD. ROS and RNS irreversibly bind with the respiratory complexes and inhibit ATP synthesis.

Excessive production of ROS and RNS can induce DNA stand break, which leads to the activation of DNA repair enzymes such as PARP. Activated PARP causes depletion of cellular NAD^+, which severely compromises ATP synthesis. Thus, oxidative and nitrosative stress can indirectly lead to the accumulation of cytoplasmic Ca^{2+} by depriving the functions of ATP-dependent Ca^{2+} pumps. Furthermore, ROS and RNS can directly inactivate ATP-dependent Ca^{2+} pumps by reacting with the soft nucleophile, such as thiol group, and contribute towards the cytoplasmic overload of the Ca^{2+} ions. Moreover, mitochondrial dysfunction in the neuro-degenerative diseases leads to the deregulation of the Ca^{2+} ion homeostasis [162, 163]. This provides a direct link between mitochondrial damage and intracellular Ca^{2+} overload. Mitochondria serve as primary site for the generation of the oxidative and nitrosative stress. The proximity of mtDNA to the sites of ROS and RNS generation and lack of protective histones makes it highly vulnerable for ROS-induced damage [164]. Literature evidences suggest that ROS- and RNS-mediated cellular damage activates glial cells to produce NO and pro-inflammatory cytokines with subsequent formation of RNS [147, 155]. Activated glial cells also release H_2O_2, which is converted to hypochlorous acid (HOCl), a highly toxic pro-oxidant [165]. Thus, a vicious cycle of Ca^{2+} overload, oxidative stress and inflammation mediates the progression of neurodegenerative diseases. This makes it challenging to distinguish the sequence of the events.

3. NUTRACEUTICALS: BRIEF OVERVIEW

Although, our understanding about the mechanisms involved in the neuronal damage has increased in recent years, we are yet to identify natural compound-based therapeutic agents that positively improve the overall neuronal health. One of the major disadvantages of the currently available therapeutic agents against the neuronal damage is that chronic use of these agents results in the multiple adverse effects. Therefore, protective strategies including nutraceuticals-based and other cost-effective therapies are warranted. The term "Nutraceutical" was coined by Dr. Stephen DeFelice, the then Chairman of the Foundation for Innovation Medicine, in 1989 [166]. Nutraceuticals are food-based products that not only supplement the diet but also help in the prevention and/or treatment of a wide variety of diseases and disorders [167]. About 2000 years ago, Hippocrates correctly stated that "Let

food be your medicine and medicine be your food" [168]. According to the epidemiological studies carried out in the 1980s by Professors Doll and Peto for the World Health Organization, it has been postulated that appropriate nutrition could prevent approximately 35% of cancer deaths, and as many as 90% of certain cancers could be avoided by dietary supplementation [169]. As stated above, several mechanistic studies found that mitotoxicity, intracellular Ca^{2+} overload, oxidative stress and inflammation are the primary reasons for the number of neurodegenerative disorders including AD, PD, HD, MS and ALS [55, 96, 111, 142]. Nutraceuticals by virtue of their better tolerance and ability to act on multiple cellular pathways appear to be favorable candidates for the long-term consumption as required for the management of chronic ailments such as neurodegenerative disorders. Currently nutraceuticals have received considerable global interest because of their presumed safety and potential nutritional and therapeutic effects.

Some nutraceuticals such as resveratrol, α-lipoic acid, coenzyme Q10 (ubiquinone), β-carotene, lycopene, astaxanthin and curcumin, to name a few, are potent antioxidants and have showed therapeutic effects against several diseases by neutralizing oxidative stress, boosting the endogenous antioxidant levels and stabilizing mitochondrial functions [37-39, 170-173]. Several studies have suggested beneficial effects of a wide variety of nutraceuticals against various neurodegenerative disorders; however, the present review focuses on nutraceuticals for which mechanistic evidences for neuroprotection are available (Table **1**).

In general, the neuroprotective effects of nutraceuticals can be attributed, but not limited, to their ability to scavenge free radicals, chelate transition metals, improve antioxidant reserve and anti-inflammatory effects. At the molecular level, nutraceuticals regulate several signaling pathways which are known to play role in the cell survival and stress response such as Nrf2/ARE, mitogen-activated protein kinase (MAPK) [174], protein kinase C (PKC) [175], Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) [176, 177], MEK/ERK/CREB, PI3K/AKT [178, 179] and insulin-signaling pathways [180, 181]. As nutraceuticals act on multiple molecular pathways, they are anticipated to improve overall neuronal health. Nonetheless, we have categorized the available evidences for some nutraceuticals-mediated neuroprotection (Table **1**) based on the primary effect as concluded from the respective study. Major pathways involved in neuronal damage and nutraceuticals-mediated neuroprotection are depicted in Fig. **1**.

3.1. Nutraceuticals Targeting Mitochondrial Dysfunction

Neurons are vulnerable to mitochondrial damage [182, 183]. Several nutritional supplements have been tested for their ability to preserve mitochondrial functions and thereby offer protection against the neurodegenerative diseases. Curcumin, derived from the turmeric, ameliorated 6-hydroxydopamine-induced neurotoxicity in MES23.5 cells by partially restoring the $\Delta\Psi_m$, increasing the level of Cu-Zn SOD and suppressing an increase in intracellular ROS and translocation of NF-κB, a transcription-factor involved in inflammation [55]. α-lipoic acid, another potent mitochondrial stabilizer, protected neurons *in vitro* and *in vivo* against the chemotherapy, hypoxia, Aβ and other toxicants-induced neurotoxicity by improving the mitochondrial functions and physiology [184-189]. Several clinical trials have been initiated or completed for α- lipoic acid in patients with diabetic neuropathy [190] and peripheral neuropathy associated with the cancer chemotherapy [191]. Astaxanthin protected mitochondria of the cultured nerve cells and boosted energy production, without increasing the production of ROS [192, 193]. Coenzyme Q10 is another powerful mitochondrial antioxidant that protects neuronal cells by preserving the functions of mitochondria in stroke, epilepsy, striatal excitotoxic lesions produced by the mitochondrial toxin (Complex II inhibitor) and several other neurodegenerative disorders [67, 194-196]. Several clinical trials with Coenzyme Q10 suggested its beneficial effects in neurodegenerative disorders [197, 198]. These evidences strongly substantiate the ability of nutraceuticals to fight against the onset and progression of neurodegenerative disorders by primarily preserving the mitochondrial functions.

3.2. Nutraceuticals Targeting Calcium Overload

The neuroprotective effect of blue berry-extract against Aβ was mediated by its ability to antagonize increase in intracellular Ca^{2+} and aggregated Aβ-induced ATP leakage [207, 208]. Despite being a potentially effective therapeutic strategy [227], only few studies are available that examine the ability of nutraceuticals to antagonize intracellular Ca^{2+} overload. With the help of advanced *in-silico* tools, further mechanistic studies are required to identify some potential nutraceuticals that can prevent the pathological rise in intracellular $[Ca^{2+}]$.

3.3. Nutraceuticals Targeting Oxidative Stress

A large number of nutraceuticals exert both direct and indirect antioxidant effects by scavenging ROS and inducing the expression of cytoprotective proteins in a Nrf2-dependent manner, respectively [37-39]. Nrf2-antioxidant response element (ARE) signaling pathway has been identified as a promising therapeutic target for neurodegenerative diseases [228].

Pre-treatment with L-sulforaphane, an isothiocyanate compound found in broccoli and other cruciferous vegetables, markedly inhibited dopamine quinone-induced neuronal death by decreasing accumulation of ROS, attenuating membrane damage and preventing DNA fragmentation in dopaminergic cell lines (Cath. and SK-N-BE (2)C) and in mesencephalic dopaminergic neurons. Also, L-sulforaphane and tert-butylhydroquinone protected neurons and astrocytes against H_2O_2-induced oxidative stress in a mixed neuron-astrocyte culture system through stimulation of the Nrf2-antioxidant response element (ARE) transcriptional pathway. Activation of Nrf2 pathway induces transcription of various antioxidant genes such as γ-glutamylcysteine ligase (GCL), the rate limiting enzyme in the synthesis of glutathione (GSH), MnSOD, hemeoxygenase and NAD(P)H:quininereductase [205, 229]. Blue berry diet is also known to exert neuroprotection through alteration in ROS signaling through CREB and MAP-kinase signaling pathways [206]. Possible mechanisms for the neuroprotective effect of resveratrol are related to its antioxidant properties and its

Table 1. Summary of the molecular neuronal effects of emerging nutraceuticals.

S. N.	Nutraceuticals	Targeted Mechanism(s)	Implication	Refs.
1.	Curcumin	• Restored the mitochondrial membrane potential, • Suppressed increase in intracellular ROS • Inhibited pro-inflammatory signaling through NF-κB or toll-like receptors • Inhibited Aβ-induced MAP kinase activation and the phosphorylation of ERK-1/2 • Inhibited phosphorylation of JNK1/2 and c-Jun • Decreased malondialdehyde levels, cytochrome c and cleaved caspase-3 expression and increasing mitochondrial Bcl-2 expression	• Ameliorated 6-hydroxydopamine-induced neurotoxicity in MES23.5 cells • Inhibited pro-apoptotic signals in mouse models of encephalitis • Prevented Aβ-induced cell death in a human neuroblastoma cell line • Stabilized the blood brain barrier in MS • Protected C57BL/6 N mice and SH-SY5Y cells against dopaminergic neurotoxicity induced by MPTP or 1- methyl-4-phenylpyridnium ion- (MPP (+) • Protected rats against stroke	[17, 71, 199-204]
2.	α-lipoic acid	• Improved mitochondrial functions and physiology	Protected neurons *in vitro* and *in vivo* against the chemotherapy, hypoxia, Aβ, diabetic neuropathy and peripheral neuropathy associated with the cancer chemotherapy	[184-191]
3.	Astaxanthin	Boosted energy production by protecting mitochondria	Protected cultured nerve cells	[192, 193]
4.	Coenzyme Q10 (ubiquinone)	Preserved mitochondrial functions	Protection against stroke, epilepsy, striatal excitotoxic lesions produced by the mitochondrial toxin (Complex II inhibitor), malonate and several other neurodegenerative disorders	[56, 131, 194-196, 198]
5.	L-sulforaphane (isothiocyanate compound)	Decreased ROS and inhibited pro-inflammatory signaling through NF-κB or toll-like receptors	• Inhibited dopamine quinone-induced neuronal death • Stabilized the blood brain barrier in MS	[202, 205]
6.	Tert-butyl hydroquinone	Stimulated Nrf2-ARE transcriptional pathway	Protected neurons and astrocytes against H_2O_2-induced oxidative stress	[205]
7.	Blue berry	• Altered ROS signaling through CREB and MAP-kinase signaling pathways • Modulated inflammatory genes expression • Antagonized the increase in intracellular Ca^{2+} activity		[206-209]
8.	Resveratrol	• Antioxidant properties-mediated modulations of Aβ processing and up- regulation of the longevity-linked gene, sirtuin1 • Increased 5-HT activity	Antidepressant properties	[210, 211]
9.	Carnosic acid	Scavenged ROS	Neuroprotective action both in *in vitro* models of neuronal death and in *in vivo* models of neurodegeneration Protected neuroblastoma cells from H_2O_2-induced oxidative stress	[201, 212, 213]
10.	Rosmarinic acid			
11.	Aged garlic extract	Suppressed ROS generation and attenuated caspase-3 activation, DNA fragmentation and PARP cleavage	Protected PC12 cells against Aβ peptide-induced apoptosis	[214]
12.	Eugenol	Decreased 6-hydroxydopamine-induced lipid peroxidation and increased GSH level	Prevented 6-hydroxydopamine-induced reduction in the dopamine level in the mouse striatum	[215]
13.	Anthocyanins	Negatively regulated pro-oxidants and pro-inflammatory cytokines signaling pathways	Neuroprotection	[209, 216, 217]

Table 1. contd….

S. N.	Nutraceuticals	Targeted mechanism(s)	Implication	Refs.
14.	The green tea flavonoid, epigallocatechin-3-gallate	Inhibited pro-inflammatory signaling through NF-κB or toll-like receptors	Stabilized the blood brain barrier in MS	[202]
15.	Mustard oil glycoside			
16.	Retinoic acid	Decreased inflammation through balancing T-lymphocyte populations in peripheral blood	Improve plasticity, regeneration, cognition and behaviour in MS patients	[218]
17.	Vitamin D	Anti- inflammatory activity	Protective in patients with MS, PD and AD	[219]
18.	Vitamin E	Decreased pro-inflammatory cytokines such as IL-1β and TNF-α	Decreased neuroinflammation and neuronal degeneration in the brain of rat with kainic acid-induced status epilepticus	[220]
19.	Omega-3 polyunsaturated fatty acid	Reduced inflammation	Improved neurologic recovery and attenuated white matter injury after experimental traumatic brain injury	[221]
20.	Apigenin	• Stabilized mitochondrial membrane potential • Modulated GABAergic and glutamatergic transmission	Protected neurons against copper-induced Aβ-mediated toxicity	[222, 223]
21.	Soy isoflavones	Modulated brain cholinergic system	Ameliorated age-related neuronal loss and cognition decline in male rats	[224]
22.	Isoflavones	Mimicked the effects of estrogen through estrogen receptor β in the brain	Improved cognitive function	[225]
23.	Emodin (3-methyl-1,6,8-trihydroxyanthraquinone), an anthraquinone derivative	Attenuated EGF receptor signaling	Protected rats against psychosis and ameliorating behavioral deficits	[226]

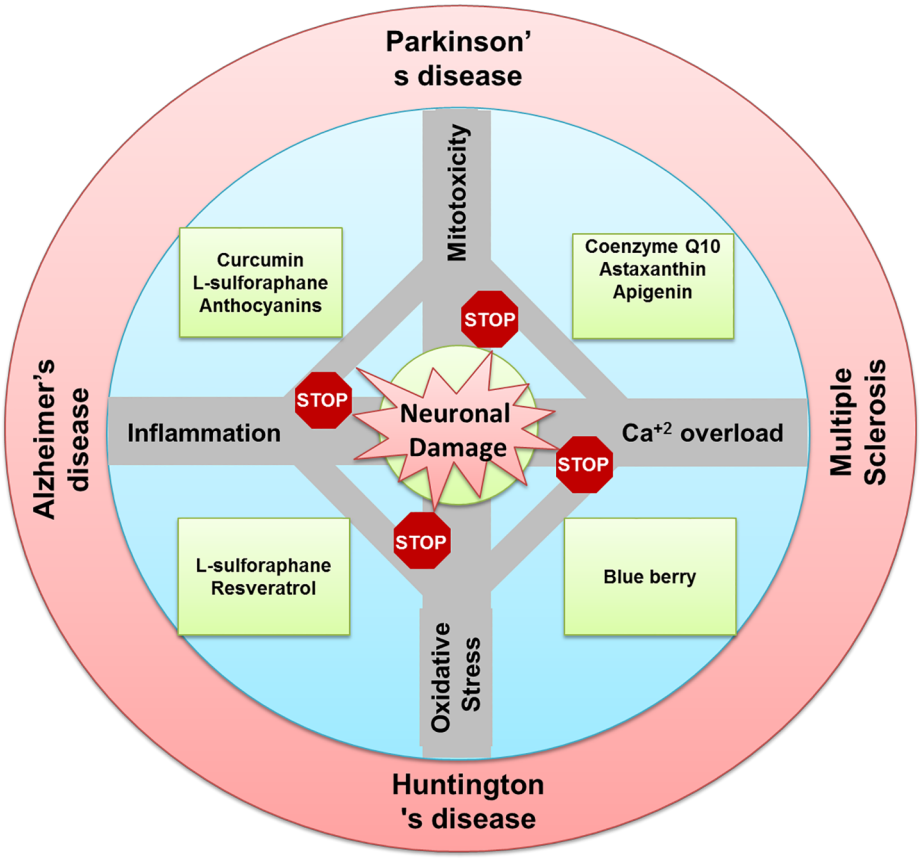

Fig. (1). A diagrammatic representation of the major pathways involved in neuronal damage and nutraceuticals-mediated neuroprotection.

capacity to modulate Aβ processing and up-regulation of the longevity-linked gene, sirtuin1 [211]. Curcumin decreased ROS and inhibited pro-apoptotic signals in mouse models of encephalitis [199, 201]. Carnosic acid and rosmarinic acid showed a neuroprotective action both *in vitro* and *in vivo* by scavenging ROS [201, 213]. Aged garlic extract protected PC12 cells against Aβ peptide-induced apoptosis by suppressing the generation of ROS and attenuating caspase-3 activation, DNA fragmentation and PARP cleavage [214]. Eugenol, a nutraceutical obtained from cloves, prevented 6-hydroxydopamine-induced reduction in the dopamine level in the mouse striatum by decreasing 6-hydroxydopamine-induced lipid peroxidation and increasing the GSH level [215]. Epidemiological studies have demonstrated that consuming foods rich in antioxidant vitamin supplements such as vitamin C and E are associated with a lower risk of developing PD [230]. However, at present, we are not aware of any conclusive clinical trials for these antioxidants against neurodegenerative disorders.

3.4. Nutraceuticals Targeting Inflammation

The neuroprotective effect of anthocyanins is known to be mediated through phospholipase A2 inhibition [216], which is adversely involved in a complex network of signaling pathways linking pro-oxidants and pro-inflammatory cytokines to the release of arachidonic acid and eicosanoid synthesis [217]. Blue berry diet showed neuroprotection through the modulation of genes expression involved in inflammation [209]. Curcumin inhibited the activation of NF-κB and prevented Aβ-induced cell death in a human neuroblastoma cell line, suggesting its possible role in the treatment for AD [11]. The green tea flavonoid, epigallocatechin-3-gallate, curcumin and the mustard oil glycoside are known to inhibit the pro-inflammatory signaling through NF-κB or toll-like receptors and stabilize the blood brain barrier in MS [202]. Retinoic acid, a metabolite of vitamin A, is known to increase tolerance and decrease inflammation, through balancing T-lymphocyte populations in peripheral blood, and thereby may improve plasticity, regeneration, cognition and behavior in patients with MS [218]. Vitamin D has been shown to alleviate various inflammatory markers in patients with MS, PD and AD [219]. Vitamin E supplementation reduced neuroinflammation and neuronal degeneration in the brain of rat with kainic acid-induced status epilepticus by decreasing the levels of astrocytic and microglial antigens (GFAP and MHC II, respectively) and pro-inflammatory cytokines such as IL-1β and TNF-α [220]. Omega-3 polyunsaturated fatty acid supplementation improved neurologic recovery and attenuated white matter injury after experimental traumatic brain injury by eliciting multifaceted protection against behavioral dysfunction, hippocampal neuronal loss, inflammation, and loss of myelination and impulse conductivity [221].

3.5. Nutraceuticals as Neurotransmitter Modulators

Apigenin, a flavonoid, protected neurons against copper-induced Aβ-mediated toxicity by relieving mitochondrial $\Delta\Psi_m$ dissipation [223] and modulating GABAergic and glutamatergic transmission in the cultured cortical neurons [222]. Moreover, soy isoflavones are known to influence the brain cholinergic system and ameliorate age-related neuronal loss and cognition decline in male rats [224]. Resveratrol, a non-flavonoid polyphenol, possesses antidepressant properties, which could be attributed to its ability to increase 5-HT level [210]. Thus, a few compounds have been identified to possess neuromodulatory activities that can be leveraged for the treatment of neurodegenerative disorders.

4. CONCLUSIONS

Mitotoxicity, calcium overload, oxidative stress and inflammation are the common pathways that are involved, often together, in the neuronal damage. Activation of these pathways, *viz*. mitochondrial dysfunction, intracellular Ca^{2+} overload, oxidative stress and inflammation, in neuronal damage is widely acknowledged, and it must be coupled with a change in the expression and function of hundreds to thousands of genes. We believe that the experimental studies utilizing advanced microarray-based investigations to identify the ability of nutraceuticals to antagonize such changes are the need of hour. At present limited information is available in this direction and further research is needed.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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