Review Article

A Comprehensive Review on Nutraceuticals as Emerging Neuroprotective Agents in Neurodegenerative Diseases

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ABSTRACT

A rising global health concern, neurodegenerative diseases (NDDs) like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS) afflict millions of people, mostly the elderly. Complex, interconnected mechanisms such as oxidative stress, mitochondrial dysfunction, abnormal protein aggregation, neuroinflammation, and excitotoxicity are involved in the pathogenesis of various illnesses. various pathways ultimately result in gradual death of neurons. Despite their partial efficacy, conventional pharmaceutical treatments frequently have negative side effects and are unable to address the complex nature of neurodegeneration. The antioxidant, anti-inflammatory, anti-apoptotic, and metal-chelating qualities of nutraceutical bioactive substances obtained from natural food sources have made them promising neuroprotective agents. The neuroprotective mechanisms of important nutraceuticals, such as curcumin, resveratrol, omega-3 fatty acids, vitamin E, B-complex vitamins, Bacopa monnieri, and Centella asiatica, are thoroughly examined in this review. These substances work by altering important signaling pathways such Nrf2/ARE, NF-κB, PI3K/Akt, MAPK, and SIRT1/AMPK. Along with current drawbacks such limited bioavailability, lack of standardization, and insufficient large-scale clinical trials, clinical evidence suggesting their therapeutic potential in neurodegenerative disorders is presented. Additionally discussed are future prospects such as combination therapy, nanoformulations, and individualized dietary plans. As safe, multi-targeted adjunct therapy for the management and prevention of neurodegenerative disorders, nutraceuticals have great potential.

Keywords: Nutraceuticals, neurodegenerative illnesses, oxidative stress, neuroprotection, Parkinson's disease, Alzheimer's disease, neuroinflammation, and curcumin.

INTRODUCTION

One of the most crippling disorders are neurodegenerative diseases, which are typically linked to gene mutations, the buildup of aberrant proteins, elevated reactive oxygen species (ROS), or the death of neurons in a particular area of the brain[1].

A vast range of chronic illnesses with a very complex etiology are included in the category of neurological aliments. Peripheral or central nervous system disorders might result from a diet low in nutrients. Every year, about 10 million people worldwide suffer from neurological illnesses, and this number is predicted to increase[2].

Due to decreased or changed hormone production, increased oxidative stress, and neuro-inflammation, the prevalence rate is higher in older individuals than in younger ones[3].

Nutraceuticals have been employed to enhance brain health because they directly affect cellular processes like neurogenesis, synaptogenesis, synaptic transmission, neuro-inflammation, oxidative stress, cell death modulation, and neuronal survival. Similarly, complex brain processes including neuro-regeneration, neuroprotection, neuroplasticity, memory, and cognition are similarly modulated by nutraceuticals[4].

NDDs such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) can cause dementia and depression, which can lead to increased mortality and morbidity (disabilities) and a significant financial burden. Additionally, because NDDs are closely linked to aging, the incidence rate is higher in older adults than in younger ones due to decreased or changed hormone production, increased oxidative stress, and neuro-inflammation[5].

Approximately 5–6 million people worldwide, mostly elderly, suffer with Parkinson's disease (PD), the most prevalent neurological movement condition. Due to the progressive loss of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNpc), which innervates the striatum, the disease is characterized by a constellation of motoric deficits, including resting tremor, bradykinesia (slowness in movements), postural instability, and rigidity[6].

The abnormal buildup of amyloid plaques and neurofibrillary tangles in the brain is the cause of AD, a brain disease marked by a progressive and permanent decrease in cognitive function[7].

Target-based therapies, including neurotransmitter modulators, direct receptor agonists/antagonists, second messenger modulators, stem cell-based therapies, hormone replacement therapy, neurotrophic factors, and regulators of mRNA synthesis and its translation into disease-causing mutant proteins, have been developed using the understanding of the etiology of neurodegenerative diseases. Even while these tactics are excellent ways to slow down neurodegenerative processes, they frequently have negative side effects and unidentified long-term repercussions[8].

Due to their potential health advantages when regularly and optimally ingested as part of a diverse diet, functional foods and nutritional supplements common sources of nutraceuticals are starting to receive awareness on a global scale[6].

Therefore, any nutraceuticals with strong antioxidant, anti-inflammatory, anti-protein aggregation, and anti-apoptotic properties that can cross the blood-brain barrier (BBB) and suppress aberrant mitochondrial dynamics all of which are multifaceted and have a high bioavailability rate would be an effective treatment agent against NDDs to slow the progression of neuronal degeneration[5].

Pathophysiology of Neurodegeneration

The gradual loss of neuronal structure and function that eventually results in neuronal death is referred to as neurodegeneration. It is a defining feature of conditions like multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). Despite the clinical differences between these conditions, oxidative stress, mitochondrial dysfunction, protein aggregation, neuroinflammation, and excitotoxicity are among the molecular mechanisms they have in common. Neuronal injury and disease progression are accelerated by these interrelated mechanisms[9].

Stress caused by oxidation:

When the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) surpasses the antioxidant defense capabilities of cells, oxidative stress results. Due to their high oxygen consumption, lipid-rich membranes, and comparatively poor antioxidant mechanisms, neurons are extremely vulnerable. Lipids, proteins, DNA, and mitochondria are all harmed by excess ROS, which reduces neuronal survival. Alzheimer's, Parkinson's, and Huntington's diseases are all closely linked to oxidative stress[10].

Dysfunction of Mitochondria:

The production of ATP, calcium homeostasis, and apoptosis regulation are all handled by mitochondria. Mitochondrial anomalies, including faulty electron transport chain activity, impaired ATP synthesis, excess ROS production, altered mitochondrial dynamics, and defective mitophagy, are frequent in neurodegenerative illnesses. Dysfunction results in synaptic failure and neuronal death because neurons rely significantly on the energy supply from the mitochondria[9].

Mitochondrial Dysfunction in Alzheimer's Disease vs Parkinson's Disease[11].

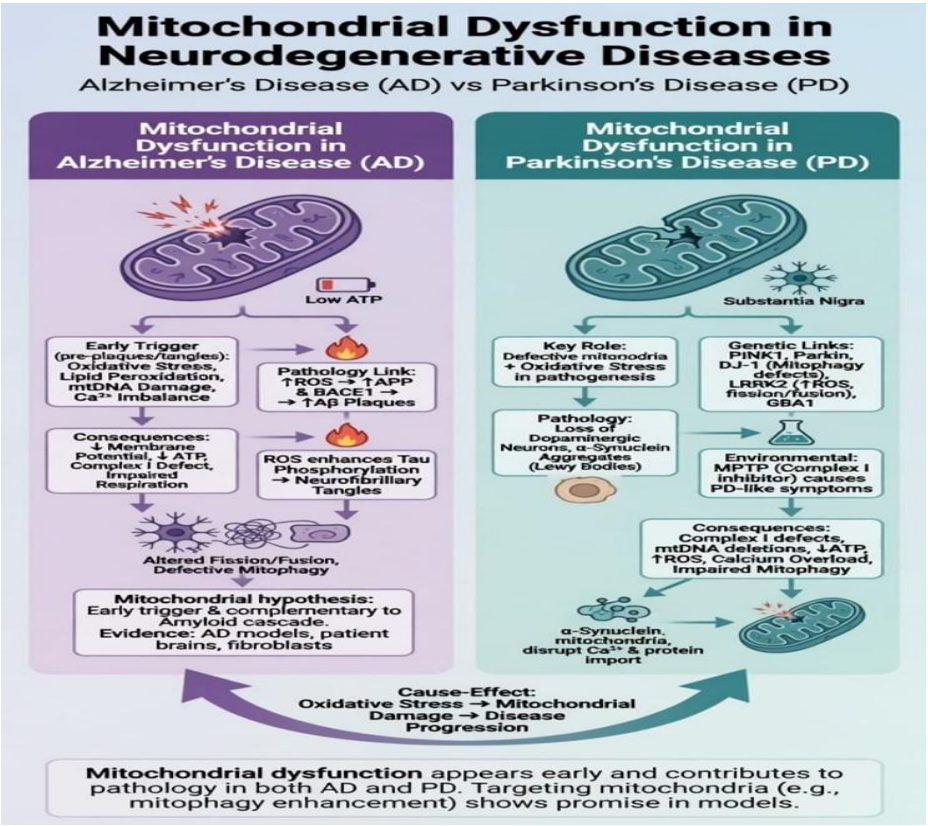

Figure 1: Mitochondrial Dysfunction in Neurodegenerative Disorders Alzheimer's Disease vs Parkinson's Disease.

Aggregation of proteins (amyloid, α-synuclein):

In many neurodegenerative illnesses, misfolded proteins build up and create hazardous clumps. Examples consist of: Tau tangles and amyloid-β plaques in Alzheimer's illness, Parkinson's disease: α-Synuclein Lewy bodies, Aggregates of mutant huntingtin in Huntington's illness, TDP-43 additions in ALS.

These aggregates eventually cause neuronal death by interfering with cellular transport, mitochondrial activity, proteasomal breakdown, and synaptic transmission[12].

Neuroinflammation:

Activation of microglia and astrocytes in reaction to damage or the buildup of toxic proteins causes neuroinflammation. In addition to ROS and nitric oxide, activated glial cells release inflammatory cytokines such TNF-α, IL-1β, and IL-6. Prolonged inflammation exacerbates brain damage and accelerates the course of illness. These days, persistent neuroinflammation is thought to be a key component of the majority of neurodegenerative diseases[13].

Excitotoxicity:

Neuronal damage brought on by overstimulation of glutamate receptors, particularly NMDA receptors, is known as excitotoxicity. Excessive calcium influx, mitochondrial damage, ROS production, enzyme activation, and apoptosis result from this. Stroke, ALS, Alzheimer's, Parkinson's, and Huntington's diseases are all frequently linked to excitotoxicity[14].

NUTRACEUTICALS:

The words "nutrition" and "pharmaceutical" are combined to form the phrase "nutraceutical." It was initially used in 1989 by Stephen DeFelice to characterize foods or dietary components that offer health or medical benefits, such as illness prevention and treatment[15].

Biologically active substances derived from natural food sources, including plants, animals, microbes, and marine items, are known as nutraceuticals. Nutraceuticals are ingested in concentrated forms as capsules, powders, pills, beverages, or fortified foods, in contrast to regular foods[16].

Because they may promote health beyond simple nutrition, nutraceuticals have attracted a lot of scientific interest. Antioxidant, anti-inflammatory, immunomodulatory, anti-aging, cardioprotective, and neuroprotective qualities are primarily responsible for their therapeutic effects[17].

Because oxidative stress, chronic inflammation, mitochondrial dysfunction, and aberrant protein aggregation are important pathological mechanisms in diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis, nutraceuticals are especially useful in neurodegenerative disorders[18].

Curcumin, resveratrol, omega-3 fatty acids, flavonoids, coenzyme Q10, and probiotics are examples of natural substances that have demonstrated promise in lowering neuronal damage and enhancing cognitive performance. As a result, nutraceuticals are being used more often as preventative or supplemental treatments for neurological conditions[19].

Nutraceutical Categories:

Nutraceuticals can be categorized according to their source, chemical makeup, and mode of action.

Conventional Nutraceuticals:

These are naturally occurring food-based compounds that are eaten unaltered. Fruits, vegetables, grains, dairy, herbs, and fermented foods are among them. Garlic, turmeric, soybeans, berries, green tea, and yogurt are a few examples[20].

Unconventional Nutraceuticals:

These are foods that have been fortified to increase their nutritional content or altered using biotechnology. Genetically modified crops, calcium-fortified milk, and vitamin-enriched cereals are a few examples[21].

Functional Foods:

Functional foods are those that offer physiological advantages above and beyond simple nourishment. Oats (beta-glucan), flaxseed, probiotic yogurt, and soy protein products are a few examples[22].

Nutritional Supplements:

Vitamins, minerals, amino acids, fatty acids, enzymes, and plant extracts are all included in these concentrated preparations. Vitamin D, omega-3 capsules, ginseng, and ginkgo biloba are common examples[23].

Herbal Nutraceuticals:

Bioactive substances obtained from plants that have therapeutic effect, such as ginsenosides from ginseng, curcumin from turmeric, and catechins from green tea, are frequently utilized to treat chronic illnesses[24].

Prebiotics and Probiotics:

These enhance immunity, metabolism, and gut-brain axis communication while promoting the equilibrium of the gut microbiota. They are being investigated more and more in neurological conditions[25].

Mechanism of Action of Nutraceuticals in Neurodegenerative Disorder:

Progressive neuronal loss, cognitive decline, motor dysfunction, oxidative stress, inflammation, mitochondrial impairment, and apoptosis are the hallmarks of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, and multiple sclerosis. Through a variety of methods, including as antioxidant activity, anti-inflammatory effects, anti-apoptotic actions, metal chelation, and modification of intracellular signaling pathways, nutraceuticals have neuroprotective effects. They are promising supplementary treatments for neurodegenerative diseases because of their multitargeted effect[1,7,26,27,28].

Activity of Antioxidants

One of the main pathogenic factors in neurodegeneration is oxidative stress. Neuronal lipids, proteins, and DNA are harmed by excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which ultimately results in neuronal death[1].

Free radicals are neutralized and endogenous antioxidant defenses are strengthened by nutraceuticals such curcumin, resveratrol, quercetin, vitamin E, vitamin C, coenzyme Q10, and green tea polyphenols. They raise glutathione levels, catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) activity. This lessens damage to the mitochondria and lipid peroxidation[7,29,30.]

For instance:

Curcumin inhibits lipid peroxidation and scavenges reactive oxygen species.

Resveratrol enhances the antioxidant state of mitochondria.

Green tea polyphenol, or EGCG, shields dopaminergic neurons from oxidative damage.

Reduction of Inflammation

Progressive neuronal injury is a result of persistent neuroinflammation caused by activated microglia and astrocytes. Inflammatory mediators such TNF-α, IL-1β, IL-6, nitric oxide (NO), and prostaglandins are released by these activated cells.

By blocking inflammatory enzymes such nuclear factor-kappa B (NF-κB), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), nutraceuticals reduce proinflammatory mediators[1,7,24.]

For instance:

Curcumin suppresses the release of IL-1β and TNF-α.

Microglial activation is decreased by omega-3 fatty acids.

NF-κB signaling is suppressed by quercetin.

The Effect of Anti-Apoptosis

Oxidative stress, calcium excess, inflammatory cytokines, and mitochondrial malfunction all cause neuronal death. By controlling pro-apoptotic and anti-apoptotic proteins, nutraceuticals stop planned cell death. They raise Bcl-2 expression and reduce Bax, caspase-3, caspase-9, and cytochrome c release. Neuronal survival is maintained in this way[7,27.]

For instance:

Curcumin inhibits the activation of caspase.

Resveratrol inhibits the signaling of mitochondrial apoptosis.

In Alzheimer's models, tocotrienols decrease neuronal death.

Chelation of Metals

Oxidative stress, amyloid aggregation, and α-synuclein toxicity are all facilitated by abnormal iron, copper, and zinc buildup in the brain. Metal-chelating nutraceuticals bind excess metals and lessen the production of ROS caused by metals[7,31.]

For instance:

Curcumin chelates Cu^{2+} and Fe^{2+} ions.

Iron-induced α-synuclein aggregation is inhibited by EGCG.

Quercetin inhibits oxidative damage and binds transition metals.

Signaling Pathway Modification

Numerous intracellular signaling pathways related to inflammation, protein aggregation, and neuronal survival are regulated by nutraceuticals[1.]

Key routes consist of:

a) The Nrf2/ARE Pathway

It activates glutathione enzymes, SOD, CAT, HO-1, and other antioxidant genes.

b) The NF-κB Pathway

It inhibits the activation of microglia and inflammatory cytokines.

d) The Akt/PI3K Pathway

It prevents apoptosis and encourages neuronal survival.

e) MAPK Pathway (p38, JNK, and ERK)

It regulates stress reactions, apoptosis, and inflammation.

f) The SIRT1/AMPK Pathway

It enhances cellular energy metabolism and mitochondrial biogenesis[7,26,32.]

For instance:

SIRT1 is activated by resveratrol.

Curcumin inhibits the JNK and NF-κB pathways.

PI3K/Akt and MAPK signaling are modulated by quercetin.

PART IN PARTICULAR DISEASES:

Alzheimer's illness

Amyloid-β aggregation inhibition, Decrease in oxidative stress, Enhancement of cognitive performance.

Parkinson's illness

Dopaminergic neuron protection, Decrease of neuroinflammation, Enhancement of motor skills.

Huntington's illness

Decrease in oxidative damage, Enhancement of mitochondrial performance.

Amyotrophic Lateral Sclerosis (ALS)

Decrease in excitotoxicity Amyotrophic Lateral Sclerosis (ALS), Effects of neuroprotective antioxidants[1,5,41.]

Major Nutraceuticals and Their Neuroprotective Roles in Neurodegenerative Disorders[1,5,33-40.]

Table 1: Major Nutraceuticals and Their Neuroprotective Roles in Neurodegenerative Disorders.

Nutraceuticals	Source	Mechanism	Main Effects in Neurodegenerative Disorders
Curcumin	Turmeric	Reduces ROS scavenging, ↑ SOD & catalase, ↓ lipid peroxidation, NF-κB inhibition, ↓ amyloid-β aggregation	Antioxidant, anti-inflammatory, antiamyloid
Resveratrol	Grapes, Berries	Enhances SIRT1 & Nrf2 activation, ↑ mitochondrial function, ↓ pro-inflammatory cytokines, modulation of apoptosis	Antioxidant, Mitochondrial Protection
EGCG	Green tea	Enhances Free radical scavenging, metal chelation, ↓ amyloid-β fibrils, MAPK & PI3K/Akt modulation	Neuronal Survival, antiapoptoic
DHA&EPA (OMEGA-3)	Fish oil, marine sources	Reduces pro-inflammatory cytokines, ↑ synaptic plasticity, membrane integrity, gene regulation.	Synaptic Support, antiinflammatory
Vitamin E	Vegetable oils, nuts	Lipid-soluble antioxidant, ↓ lipid peroxidation	Protection of neuronal membrane
B-Complex Vitamins (B6,B12,Folate)	Grains, leafy greens, meat	Homocysteine metabolism regulation	Reduces cognitive decline
Bacopa monnieri	Brahmi plant	Enhances antioxidant enzymes, ↓ oxidative stress, improved synaptic transmission	Cognitive enhancement, antiinflammatory
Centella asiatica	Gotu kola	Increase BDNF, ↓ oxidative stress, promotes neuronal growth	Memory improvement, neuronal growth

EVIDENCE AND CLINICAL TRIALS:

According to clinical research, a number of nutraceuticals may help treat neurodegenerative conditions like Parkinson's, Alzheimer's, and Huntington's diseases. Curcumin, resveratrol, coenzyme Q10, omega-3 fatty acids, and epigallocatechin-3-gallate (EGCG) have all been tested in human trials. When administered as an adjuvant therapy to standard treatment, these nutraceuticals showed potential improvements in mitochondrial function, inflammatory state, oxidative stress indicators, and cognitive performance. In long-term intervention studies, several multinutrient formulations have also demonstrated a slowing of cognitive deterioration in prodromal Alzheimer's disease[5,42.]

The evidence that is now available has a number of limitations, despite encouraging results. Small sample numbers, brief treatment durations, inconsistent dosing schedules, and diverse patient groups are common features of clinical studies. Results interpretation is made more difficult by variations in formulation bioavailability and the absence of established outcome markers. Therefore, before routine clinical recommendations of nutraceuticals in neurodegenerative illnesses can be established, large-scale randomized controlled trials remain necessary[43.]

Overall, human research suggests that some nutraceuticals may provide additional neuroprotective effects; nonetheless, at this time, they should be regarded as supplements rather than substitutes for traditional medication[5.]

Future Prospectives:

Nanonutraceuticals:

In order to increase the treatment efficacy in neurodegenerative illnesses, advanced nanoformulations are being created to improve the bioavailability, stability, and targeted administration of nutraceuticals across the blood–brain barrier[44.]

Combination Therapy:

Targeting several pathological pathways such oxidative stress, inflammation, and mitochondrial dysfunction, nutraceuticals are increasingly being investigated in conjunction with traditional pharmaceutical treatments to generate synergistic benefits[44,45.]

Customized Nutrition:

In order to optimize the prevention and management of neurodegenerative illnesses, future approaches will concentrate on tailored nutraceutical therapies based on genetic, metabolic, and lifestyle factors[44.]

Limitations&Challenges:

Low Bioavailability

The therapeutic efficacy of many nutraceuticals in neurodegenerative illnesses is greatly diminished by their quick metabolism, low absorption, and restricted capacity to pass the blood–brain barrier[44.]

Absence of Standardization

Inconsistent clinical results and challenges in developing standardized treatment regimens are caused by variations in the composition, dosage, and preparation of nutraceuticals[44].

Regulatory Concerns:

Concerns about safety, quality control, and clinical validation arise since nutraceuticals are frequently not subject to the same strict regulatory regimes as medicines[44].

CONCLUSION

With few treatment options, neurodegenerative disorders continue to be a significant global burden. Multi-targeted therapeutic approaches are required due to the progressive nature of diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, and multiple sclerosis, which are caused by interrelated pathological mechanisms like oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein aggregation. Nutraceuticals are a potential and rapidly developing class of naturally occurring bioactive substances that can target several neurodegenerative pathways at once. Through antioxidant, anti-inflammatory, anti-apoptotic, and neuroregenerative mechanisms, agents like curcumin, resveratrol, EGCG, omega-3 fatty acids, and plant-based extracts like Bacopa monnieri and Centella asiatica have shown notable neuroprotective activity in preclinical and emerging clinical studies. Despite this possibility, there are still a number of obstacles.

The clinical translation of nutraceuticals is still hampered by poor bioavailability, quick systemic metabolism, inadequate blood-brain barrier penetration, a lack of standardized formulations, and a dearth of large-scale randomized controlled trials. Additionally, inconsistent quality control and therapeutic validation result from their regulatory classification. Future approaches that hold great potential for improving results include nanonutraceutical delivery methods, synergistic combination therapy with traditional medications, and customized dietary plans based on metabolic and genetic analysis. It is concluded that nutraceuticals are useful complimentary agents in the prevention and adjunct care of neurodegenerative illnesses, even though they do not yet completely replace traditional medication. To create standardized therapy guidelines and integrate nutraceutical-based interventions into routine neurological care, strong clinical evidence from carefully planned trials is desperately needed.

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