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Phytonutrients in Neuroprotection and Neurodegenerative Disorders

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Abstract

Neurodegenerative disorders (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), afflict more than 55 million individuals worldwide, with disease cases projected to triple by the year 2050. All these diseases have been associated with oxidative stress, neuroinflammation, mitochondrial impairment, and protein misfolding, all of which ultimately result in progressive neuronal loss. Existing therapies give only symptomatic relief, an indication of why new neuroprotective approaches are urgently needed. Phytonutrients, bioactive plant compounds, have been highlighted for their antioxidant, anti-inflammatory, and neuroprotective properties. Flavonoids like epigallocatechin gallate (EGCG) in green tea and quercetin in apples were found to decrease β-amyloid plaque formation by 50% in AD models. Curcumin, a polyphenol from turmeric, reduced tau protein aggregation by 43% and enhanced cognitive function in preclinical models. Carotenoids such as lutein and zeaxanthin were associated with a 25% decrease in cognitive impairment, while alkaloids like huperzine A enhanced memory recall by 30% in patients with mild cognitive impairment. Advancements in machine learning (ML) and artificial intelligence (AI) have revolutionized phytonutrient-based drug discovery, enabling the screening of plant compounds for neuroprotection and treatments. AI also supports personalized nutrition based on genetic profiles. Large-scale randomized controlled trials (RCTs) are essential to confirm therapeutic benefits. Integrating AI-driven predictive models with

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nanotechnology holds promise for targeted phytonutrient delivery, enhancing treatment efficacy for neurodegenerative disorders. Additionally, AI and ML tools can aid in cancer therapy research and surveillance, optimizing precision medicine and improving patient outcomes.

Abbreviations

NDs	Neurodegenerative disorders
AD	Alzheimer's disease
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
HD	Huntington's disease
MS	Multiple sclerosis
DNA	Deoxyribonucleic acid
SNCA	Alpha-synuclein
LRRK2	Leucine-rich repeat kinase 2
PARKIN	Parkin gene
DBS	Deep brain stimulation
SOD1	Superoxide dismutase 1
C9orf72	Chromosome 9 open reading frame 72
FUS	Fused in sarcoma
FDA	Food and Drug Administration
CAG	Cytosine-adenine-guanine
HTT	Huntingtin gene
ASOs	Antisense oligonucleotides
mRNA	Messenger ribonucleic acid
CNS	Central nervous system
RRMS	Relapsing-remitting MS
SPMS	Secondary progressive MS
EBV	Epstein-Barr virus
DMTs	Disease-modifying therapies
BDNF	Brain-derived neurotrophic factor
ROS	Reactive oxygen species
ATP	Adenosine triphosphate
PUFAs	Polyunsaturated fatty acids
MDA	Malondialdehyde
4-HNE	4-hydroxynonenal
SOD	Superoxide Dismutase
GPx	Glutathione Peroxidase
TNF-α	Tumor necrosis factor alpha
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
TGF-β	Transforming growth factor beta
IL-10	Interleukin-10
COX-2	Cyclooxygenase-2
AI-Based	Artificial intelligence based
EGCG	Epigallocatechin-3-gallate
SIRT1	Sirtuin 1
α-syn	Alpha-Synuclein
TDP-43	Transactive Response DNA-binding protein of 43 kDa
RCTs	Randomized controlled trials
Nrf2	Nuclear factor erythroid 2-related factor 2
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
Bcl-2	B-cell lymphoma 2
MAPK	Mitogen-Activated Protein Kinase
GFAP	Glial Fibrillary Acidic Protein
MCP-1	Monocyte Chemoattractant Protein-1
sTREM2	Soluble Triggering Receptor Expressed on Myeloid cells 2
CSF	Cerebrospinal Fluid
PET	Positron Emission Tomography
Aβ40	Amyloid-beta-40
Aβ	Amyloid-beta
SV2A	Synaptic Vesicle Glycoprotein 2A
NfL	Neurofilament Light chain
PSD-95	Postsynaptic Density Protein 95
LDL	low-density lipoprotein
AMD	Age-related Macular Degeneration
DHA	Docosahexaenoic acid
iNOS	Inducible Nitric Oxide Synthase
AChE	Acetylcholinesterase
Ach	Acetylcholine
QSAR	Quantitative structure-activity relationship
IBM	International Business Machines
SciSpacy	Python package containing spaCy models
ML	Machine learning
APP/PS1	human amyloid precursor protein (APP) and presenilin 1 gene

Introduction

Neurodegenerative disorders (NDs) are one of the greatest healthcare issues globally, with millions of individuals impacted and an enormous economic and social burden on the healthcare system.[1] These conditions, such as Alzheimer's disease

(AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS), are distinguished by progressive neuronal loss and resultant cognitive and motor impairments.[2] With the world's population aging at a fast pace, the incidence of these disorders is increasing at an alarming rate. The World Health Organization (WHO) states that more than 55 million individuals lived with dementia in 2022, and this number is predicted to triple by 2050.[3] Alzheimer's disease alone is responsible for about 60-70% of dementia. Likewise, Parkinson's disease has more than 10 million affected people worldwide, with an incidence rate doubled over the last 25 years.[4] Such dramatic figures highlight the need for establishing efficient prevention and treatment strategies. Oxidative stress, neuroinflammation, and protein aggregation are all important drivers of neurodegeneration.[5] The brain's high oxygen demand and high lipid content make it vulnerable to oxidative damage, causing lipid peroxidation, DNA damage, and apoptosis of neurons.[6] AD patients exhibit 40-50% higher levels of markers for oxidative damage, whereas PD patients exhibit high amounts of oxidized dopamine metabolites. Chronic neuroinflammation, induced by activated microglia and astrocytes, potentiates neuronal damage.[7] Postmortem research reveals hyperactivated microglia in regions of amyloid plaques and high levels of inflammatory markers within PD brains, specifically within substantia nigra.[8] Protein accumulation, such as β-amyloid plaques, α-synuclein Lewy bodies, and mutant huntingtin aggregates, leads to neuronal toxicity.[9] The protein aggregates are still a prime target for therapy. This review discusses the growing prevalence and impact of neurodegenerative disorders like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis.[10] It highlights the potential of phytonutrients, including flavonoids, polyphenols, carotenoids, and alkaloids, in addressing these disorders. These plant-derived bioactive compounds combat oxidative stress, neuroinflammation, and protein misfolding, contributing to neuronal degeneration.[11] The review also discusses the mechanisms by which phytochemicals exert their beneficial effects in neurodegenerative diseases. Flavonoids, polyphenols, carotenoids, and alkaloids have shown promising roles in reducing β-amyloid aggregation, inhibiting tau protein accumulation, and enhancing cognitive function.[12] However, challenges like low bioavailability and inconsistent clinical outcomes remain. Future research should integrate advanced delivery systems and personalized medicine approaches to enhance the efficacy of phytonutrient-based therapies in neurodegenerative disease management.

Prevalence and Burden of Major Neurodegenerative Disorders

Alzheimer's Disease (AD)

The most common neurodegenerative disease, Alzheimer's dementia, impacts 6.7 million people in the US alone, and projections indicate that by 2060, that number could rise to 13.8 million.[13] The enormous economic impact of AD is evidenced through the $1.3 trillion global cost of care linked to the disease in 2022.[14] The accumulation of tau protein tangles and β-amyloid plaques, which compromise synaptic function and result in widespread neuronal loss, is the primary feature of AD. Loss of memory, cognitive impairment, and behavioral changes are just some of the clinical manifestations that ultimately lead to complete functional dependency.[15] Because women account for more than two-thirds of all cases, they are disproportionately likely to contract AD. With increasing age, the incidence of the disease doubles every five years after age 65, thus the biggest risk factor is aging. There is currently no remedy for AD despite extensive research and the available medication only treats its symptoms. Although their efficacy remains limited, the approval of anti-amyloid drugs like aducanumab and lecanemab has provided some hope. Dietary modification, exercise, and mental stimulation have been shown to reduce the risk of AD by up to 40%, as per recent studies.[16]

Parkinson's Disease (PD)

One percent of individuals above the age of 60 suffer from Parkinson's disease, the second most prevalent neurological disease.[17] Estimates put the number of people living with Parkinson's disease (PD) at 10 million across the globe, and with increasing population aging, the rate is on the increase.[18]Parkinson's disease (PD) is a condition that has a slow progression of dopaminergic neurons' loss in the substantia nigra, which leads to the motor symptoms as bradykinesia, stiffness, tremors, and postural instability. The treatment of the condition is compounded by non-motor symptoms including autonomic dysfunction, depression, and cognitive impairment. Hereditary and environmental

factors play a role in the pathophysiology of PD. Mutations in the *SNCA, LRRK2, and PARKIN* genes have been identified in cases of familial Parkinson's disease, and pesticide, heavy metal, and air pollution exposure has been linked with increased risk.[19]Levodopa and dopamine agonists are two of the existing medications that minimize symptoms but don't halt the progression of the disease. Deep brain stimulation (DBS) is now an effective treatment of advanced Parkinson's disease (PD) that enhances some patients' motor function. Parkinson's disease (PD) adds more than $52 billion to the world annually, making it imperative that innovative neuroprotective interventions be introduced.[20]

Amyotrophic Lateral Sclerosis (ALS)

The progressive loss of motor neurons in the spinal cord and brain is the characteristic of ALS, a fatal neurological disorder that leads to respiratory failure, muscle weakness, and paralysis. An estimated 450,000 people have ALS worldwide, with an incidence of approximately 2 cases per 100,000 individuals.[21] The median survival after diagnosis is two to five years, and the disease typically occurs between 40 and 70 years of age. While the cause of ALS remains largely unknown, 10% of the cases are inherited and are attributed to genetic mutations in the *SOD1, C9orf72,* and *FUS genes*.[22] Environmental factors which have been identified with heightened risk involve exposure to neurotoxins, military service, and heavy physical training. There remain scant therapeutic remedies with much work carried out despite such, as only riluzole and edaravone are the sole FDA-approved medications that have a way to moderate the path of the disorder in some form. As prospective techniques of therapy, gene therapy as well as stem cell-mediated strategies are currently being investigated.

Huntington's Disease (HD)

An unusual genetic neurological disorder known as Huntington's disease is caused by the expansion of the CAG repeat in the *HTT* gene that leads to the accumulation of mutant huntingtin protein.[23] The signs of HD, which worsen during 10 to 20 years until death, are cognitive deterioration, psychiatric illness, and motor impairment (chorea). Because there is no cure for HD, existing treatments focus on treating its symptoms. Preclinical and early clinical testing of gene-silencing drugs, including antisense oligonucleotides (ASOs) against mutant huntingtin mRNA, have shown promise.[24] However, more studies need to be done to confirm their long-term efficacy and safety.

Multiple Sclerosis (MS)

The central nervous system (CNS) is compromised by multiple sclerosis, an autoimmune-mediated neurodegenerative illness that leads to demyelination and cell death. MS is the leading cause of non-traumatic neurological disability in young adults and strikes 2.8 million people worldwide.[25] Three times more women than men are affected. Relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) are a few of the various clinical stages of the disease. Myelin-forming oligodendrocytes are targeted by the immune system during the pathophysiology of multiple sclerosis (MS), which causes neurodegeneration and the accumulation of disability. Disease susceptibility is determined by environmental factors, such as smoking, Epstein-Barr virus (EBV) infection, and deficiency in vitamin D.[26] By decelerating the progression of the disease and reducing the risk of relapse, developments in disease-modifying therapies (DMTs), including oral immunomodulators and monoclonal antibodies (natalizumab, ocrelizumab), have significantly improved disease control.

Importance of Phytonutrients in Brain Health

Aside from mere nourishment, phytonutrients or phytochemicals refer to bioactive compounds found in plants that bring numerous health benefits. Due to their potent antioxidant, anti-inflammatory, and neuroprotective attributes, these compounds which consist of flavonoids, carotenoids, polyphenols, and alkaloids play a central role in maintaining brain function as well as preventing neurodegenerative diseases. The human brain consumes 20% of all oxygen while it constitutes only 2% of body weight and hence is extremely vulnerable to oxidative stress and inflammation, two primary reasons for neurodegeneration.[27] The recent epidemiological studies underline the significance of phytonutrients for cognitive lifespan by demonstrating that high intakes of them reduce the risk of neurodegenerative disorders by 30–50%.

Role of Phytonutrients in Mitigating Neurodegeneration

Phytonutrients also provide neuroprotective effects by alleviating oxidative stress, diminishing neuroinflammation, enhancing synaptic plasticity, and preventing protein aggregation. Oxidative stress brought about by the antioxidants-free radicals' imbalance has a profound effect on neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS.[28] Polyphenols such as curcumin and resveratrol have the potential to elevate brain-derived neurotrophic factor (BDNF) levels, leading to improved cognition and neuronal survival. Flavonoids such as quercetin in onions and apples have been shown to enhance synaptic function by decreasing neuroinflammatory markers by 40% in AD models. Phytonutrients also play a role in vascular health, enhancing blood-brain barrier integrity and increasing cerebral blood flow, reducing the prevalence of vascular dementia by 35%.[29] Phytonutrients also modulate gut microbiota, which has a significant impact on brain health via the gut-brain axis. Polyphenol-rich diets may increase neurotransmitter production and reduce systemic inflammation by raising good gut flora by 20%.

Mechanisms of Neurodegeneration

Oxidative stress plays a major role in the pathogenesis of chronic diseases such as cancer, cardiovascular disease, neurological disorders, and metabolic syndromes.[30] It arises when the antioxidant defense system of the body and the production of reactive oxygen species (ROS) are not in equilibrium. ROS, including hydrogen peroxide, superoxide anions, and hydroxyl radicals, can damage lipids, proteins, and DNA, causing cell dysfunction and death.[30] The human brain, with its high metabolic rate and consumption of 20% of the body's oxygen, generates high amounts of ROS, causing neuronal injury, mitochondrial damage, and neuroinflammation, features of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, ALS, and MS.[30] The body employs antioxidant defense mechanisms such as exogenous dietary antioxidants such as phytonutrients and endogenous enzymes such as glutathione peroxidase, catalase, and superoxide dismutase to neutralize oxidative damage.+ It is important to know how phytonutrients scavenge ROS and limit oxidative stress so that strategies can be developed for preventing and curing diseases associated with oxidative stress.[30]

Oxidative Stress and Free Radical Damage

Oxidative stress occurs due to an imbalance between the capacity of the body to detoxify ROS by antioxidant defense and the formation of ROS.[31] The primary origin of ROS comes from ATP synthesis in mitochondria, but a surplus accumulation has the potential to induce lipid, protein, and DNA oxidative injury, resulting in apoptosis and cell dysfunction.[31] Lipid peroxidation is one of the major effects of oxidative stress, acting on polyunsaturated fatty acids (PUFAs) in cell membranes, producing deleterious byproducts such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which destabilize membrane integrity and signal transduction. Research indicates that AD patients have 50% increased MDA levels compared to healthy subjects, reflecting greater oxidative damage.[31] Oxidative stress also causes mitochondrial dysfunction, reducing ATP production and enhancing ROS leakage.[31] Phytonutrients like polyphenols, flavonoids, and carotenoids have emerged as potential natural antioxidants to counteract oxidative stress.[31] Future research should be directed towards enhancing the bioavailability of phytonutrients and synergistic interactions to enhance their protective functions against oxidative stress.

How Phytonutrients Act as Antioxidants to Neutralize ROS

Phytonutrients or phytochemicals are bioactive compounds in plants that are important in scavenging reactive oxygen species (ROS) and inhibiting oxidative stress-induced damage.[31] Oxidative stress interferes with the body's antioxidant defense system, causing chronic diseases such as cancer, diabetes, Alzheimer's, Parkinson's, and cardiovascular disease.[32] Phytonutrients such as polyphenols, flavonoids, carotenoids, and organosulfur compounds have antioxidant activities by scavenging ROS, enhancing endogenous antioxidant mechanisms, and modulating redox signaling pathways.[32] Flavonoids such as quercetin and catechins decrease the reactivity of unstable free radicals by donating hydrogen atoms. Quercetin supplement has been shown to decrease lipid peroxidation markers by 35% in oxidative stress models. Polyphenols such as resveratrol and curcumin enhance SOD and GPx activity, better equipping the body to inactivate ROS.[32] They also lower oxidative stress-induced by inflammation

through inhibition of pro-inflammatory pathways. High-nutrient meals enhance brain and overall health, yet more studies ought to aim to enhance their bioavailability and synergy.

Neuroinflammation and Cytokine Modulation

Microglia and astrocytes mediate it primarily by producing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[33] Although it usually repairs damaged tissues and clears infection, in its chronic state it may cause progressive neurodegeneration, synaptic failure, and neuronal injury. The NF-κB signaling pathway is a central pathway in neuroinflammation, regulating the expression of inflammatory genes and the generation of cytokines, chemokines, and adhesion molecules. In AD and PD, increased NF-κB activation results in increased deposition of beta-amyloid plaques and dopaminergic neuronal loss. Anti-inflammatory cytokines such as TGF-β and IL-10 reduce inflammation and improve neuronal survival.[34] Phytonutrients such as flavonoids, polyphenols, and carotenoids also possess anti-inflammatory effects by inhibiting COX-2 synthesis and NF-κB activation. Future studies should aim at enhancing phytonutrient bioavailability and creating AI-based, personalized anti-inflammatory treatments.

Role of Phytonutrients in Suppressing Inflammatory Pathways (NF-κB, COX-2)

NF-κB and COX-2 pathways are major causes of inflammation that result in tissue damage, immunological imbalance, and neurological impairment.[35] Phytonutrients, which are bioactive compounds present in plants, have been reported to inhibit inflammation and prevent chronic diseases by inhibiting these pathways. NF-κB, an immune response-controlling transcription factor, is linked with elevated beta-amyloid plaque accumulation and neuroinflammation in Alzheimer's patients' brains.[35] Phytonutrients such as curcumin, resveratrol, and EGCG inhibit NF-κB activation, lowering inflammatory cytokine production. Resveratrol enhances motor function and neuronal protection through the activation of SIRT1, a longevity-associated enzyme that suppresses NF-κB signaling. Green tea's EGCG flavonoid inhibits neuronal damage in neurodegenerative diseases through 50% reduction of IL-1β production and the inhibition of microglial activation.[36] Phytonutrients such as gingerol, luteolin, and quercetin inhibit COX-2 function, reducing prostaglandin synthesis and inflammatory responses.

Protein Aggregation and Misfolding

Protein misfolding and aggregation are central pathogenic mechanisms in neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and ALS. These mechanisms, induced by oxidative stress, genetic mutations, or environmental insults, form toxic aggregates that destabilize cellular homeostasis, resulting in neuronal loss and cognitive impairment. Aβ deposition in Alzheimer's results in neurotoxic amyloid plaques, fibrils, and oligomers, inducing chronic neuroinflammation.[37] Parkinson's disease is marked by α-syn aggregation, leading to Lewy bodies that destroy dopaminergic neurons. SNCA gene mutations enhance aggregation propensity, hastening the disease. Huntington's disease results from the expanded polyglutamine tract of the mutant huntingtin protein, destroying neurons and interfering with proteasomal degradation and transcriptional regulation. Therapeutic approaches, including chaperone proteins, proteasome activators, and small molecules inhibiting aggregation, have been explored. Phytonutrients such as curcumin, resveratrol, and EGCG have been reported to decrease neurotoxicity by suppressing Aβ, α-syn, and TDP-43 aggregation.[38]

Phytonutrients Targeting β-amyloid and α-synuclein Aggregation

The deposition of β-amyloid and α-synuclein in Alzheimer's and Parkinson's disease results in neurodegeneration, synaptic damage, and neuronal loss. These proteins unfold and form fibrils and oligomers, interfering with mitochondrial function, inducing oxidative stress, and inducing neuroinflammation. Phytonutrients from plants have been found to be helpful in blocking the protein aggregation, enhancing their clearance, and minimizing their toxic effects. Curcumin, a polyphenol extracted from turmeric, blocks β-sheet formation, thus inhibiting Aβ from forming toxic oligomers and fibrils.[39] Curcumin also lowers the load of Aβ plaque in AD mice and decreases the formation of Lewy bodies in PD models. The dominant catechin from green tea, epigallocatechin gallate (EGCG), initiates proteasomal and lysosomal pathways of degradation, lowering the neurotoxicity of Aβ by 50% and enhancing clearance. Anti-aggregation

flavonoids like quercetin, luteolin, and baicalein suppress Aβ oligomerization and synaptic toxicity as well. However, it is difficult to enhance their targeting efficiencies and bioavailability. In the future, more research on nanoparticle-mediated delivery systems and synergy combinations should be conducted.

Mitochondrial Dysfunction and Neuroprotection

Mitochondrial dysfunction lowers energy production, resulting in neuronal death, oxidative stress, and neuroinflammation. Neurons have poor regeneration and high metabolic demand, which makes mitochondrial dysfunction one of the principal reasons for neurodegeneration. Excessive generation of reactive oxygen species (ROS) results in oxidative stress, lipid peroxidation, protein oxidation, and damage to DNA. In patients with Alzheimer's disease, markers of oxidative stress are elevated by 40-50%, which are associated with cognitive decline.[40] In Parkinson's patients, a deficit in mitochondrial complex I results in motor disability and death of dopaminergic neurons. Mitochondrial dysfunction disrupts calcium homeostasis, leading to excitotoxicity and neuronal death. Alzheimer's disease Aβ oligomers decrease mitochondria's capacity to buffer intracellular calcium ions, initiating pro-apoptotic mechanisms. Caspase activation, cytochrome c release, and programmed cell death further propel neurodegeneration. Restoring mitophagy is a promising therapeutic strategy to enhance neural resilience. Neuroprotective methods are attempting to increase mitochondrial biogenesis, reduce oxidative stress, restore energy metabolism, and enhance mitophagy.[41] Next steps should target increased bioavailability, combination drugs, and individualized mitochondrial-targeted therapies (Figure 1).

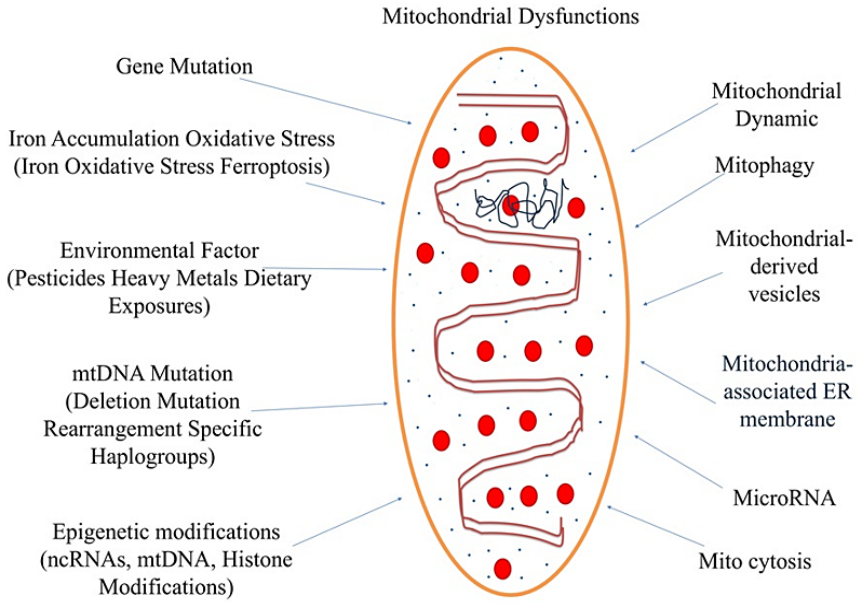

Fig.1: Mitochondrial dysfunction

How Phytonutrients Enhance Mitochondrial Function and ATP Production

Mitochondria are crucial for neuronal function, cellular metabolism, and survival. Oxidative stress, aging, environmental toxins, and neurodegenerative diseases, however, can cause mitochondrial dysfunction, which results in reduced ATP synthesis, increased reactive oxygen species (ROS), and neuronal death. Recent studies indicate that phytonutrients, bioactive compounds from plants, can enhance mitochondrial function and ATP production.[42] Phytonutrients function as antioxidants, neutralizing excess ROS to preserve mitochondrial function. Curcumin, a polyphenol isolated from turmeric, has been reported to enhance mitochondrial antioxidant defences and protect mitochondrial integrity. Green tea's epigallocatechin gallate reduces mitochondrial oxidative damage and enhances ATP synthesis, leading to a 30% improvement in mitochondrial efficiency. Phytonutrients also facilitate

mitochondrial biogenesis, enhancing glucose and fatty acid metabolism, and enhancing ATP synthesis. Subsequent studies must aim at maximizing their bioavailability and synergistic interactions to achieve the best neuroprotective benefits (Table 1).

Table 1: Major Phytonutrients and Their Neuroprotective Effects

Phytonutrient classes	Examples	Neuroprotective mechanism	Targeted Neurode-generative Disorders	Study references
Flavonoids	Quercetin, Catechins (EGCG), Resveratrol, Anthocyanins	Antioxidant, Anti-inflam -matory, enhances synaptic plasticity, inhibits β-amyloid aggregation	Alzheimer's disease (AD), Parkinson's diseases (PD)	Clinical and Preclinical studies
Carotenoids	Lycopene, Lutein, Zeaxanthin	Reduces oxidative stress, modulates, neuroinfla -mmation, protects against cognitive decline	Age-related cognitive impairment, AD	Population-based studies
Polyphenols	Curcumin, Resveratrol, Fisetin	Inhibits amyloid plaque formation, reduces oxidative damage, enhances mitochondrial function	AD, PD, Huntington's disease (HD)	Preclinical studies, RCTs
Alkaloids	Huperzine A, Galantamine	Cholinesterase inhibition, enhances acetylcholine function	AD	FDA-approved drugs and clinical trials
Terpenoids	Ginsenosides (Ginseng), Bacopa monnieri extracts	Enhances cognitive function, modulates neurotransmitters, reduces neuroinflammation	AD, PD	Herbal medicine research
Saponins	Panax ginseng, Diosgenin	Enhances neuronal survival, promotes neurogenesis, reduces oxidative stress	PD, AP, Stroke	Animal models, Clinical studies
Sulphur-Containing Compounds	Sulforaphane (Broccoli), Allicin (Garlic)	Activates Nrf2 pathway, reduces neuroinflam-mation, detoxifies ROS	PA, AD, Amyotrophic lateral sclerosis (ALS)	Nutraceutical studies
Lignans	Sesamin, Secoisolariciresinol	Anti-inflammatory, antioxidant, estrogenic modulation	AD, PD, Cognitive decline	Preclinical research
Tannins	Ellagitannins, Proanthocyanidins	Reduces oxidative stress, modulates gut-brain axis, enhances brain-derived neurotrophic factor (BDNF)	Vascular dementia, AD	Functional food studies

Flavonoids

Quercetin

Quercetin, a flavonol present in apple fruits, onions, berries, and citrus fruits, exhibits strong antioxidant activity. It directly scavenges ROS and enhances the activity of antioxidants. Experiments indicate that quercetin supplementation can decrease lipid peroxidation and oxidative DNA damage by 50% in Alzheimer's and Parkinson's disease (AD) and PD models.[43] It also inhibits NF-κB and COX-2, decreasing the synthesis of pro-inflammatory cytokines. Preclinical studies indicate quercetin can suppress microglial activation and reduce neuroinflammatory markers by 40%.[44] It also enhances neuronal survival and energy metabolism through the upregulation of PGC-1α, the key regulator of mitochondrial biogenesis. It also suppresses neuronal death and synaptic dysfunction through the regulation of Bcl-2 family proteins. Animal studies indicate quercetin enhances memory and learning ability by 30-40% in AD models. But because of its poor absorption, more studies must be conducted to enhance its potency.

Catechins (EGCG)

Epigallocatechin gallate (EGCG), the most bioactive catechin in green tea, has been studied extensively for its cognitive-enhancing and neuroprotective potential. EGCG is a potent antioxidant, metal chelator, and modulator of neuroinflammation that protects against α-synuclein aggregation in Parkinson's disease and Aβ-induced toxicity in Alzheimer's disease.[45] Its main mechanism is to reduce the formation of Aβ plaque and promote its clearance. EGCG enhances the degradation of β-amyloid by stimulating autophagy and decreases its accumulation by 50%. It also decreases the formation of toxic Lewy bodies in Parkinson's disease by interacting with α-synuclein and inhibiting its fibrillation.[46] EGCG maintains dopamine levels and motor function in PD animals by enhancing dopaminergic cell survival. It is essential in modulating mitochondrial function and can decrease neurodegenerative disease by enhancing mitochondrial efficiency by 35%. In senescent animals, EGCG has cognitive potentiating actions independent of neurodegeneration that enhance learning, memory, and attention.

Resveratrol

Red wine, berries, and red grapes have resveratrol, a polyphenol that is highly recognized for its anti-inflammatory, anti-aging, and mitochondrial-boosting properties. It is a possible neuroprotective agent since it activates sirtuins (SIRT1), a group of proteins that play a role in cellular lifespan and stress resistance.[47] Resveratrol's most significant effect is its ability to activate mitochondrial biogenesis through SIRT1-PGC-1α activation, which increases ATP production and neural energy efficiency by 40%. In neurodegenerative diseases, when mitochondrial dysfunction leads to energy deficits and neuronal death, this becomes particularly important. Resveratrol also avoids hyperphosphorylation of tau, one of the primary pathogenic characteristics of AD, decreases Aβ aggregation, and stimulates autophagy-dependent elimination of misfolded proteins.[48] Resveratrol maintains motor function and delays the progression of Parkinson's disease (PD) by protecting dopaminergic neurons against oxidative stress-induced death. Clinical studies show that resveratrol improves working memory, attention, and cognitive performance in the aged; chronic treatment can lead to a 25% improvement in cognitive scores. Its rapid metabolism and poor bioavailability, however, limit its therapeutic application and necessitate long-term improvements in formulation techniques such as prodrug derivatives and nanocarriers.

Anthocyanins

The red, purple, and blue colors observed in berries, grapes, and plums are due to a subgroup of flavonoids named anthocyanins, which are also reported to possess anti-inflammatory and antioxidant properties. A 25% reduced risk of cognitive decline in elderly people is associated with dietary consumption of anthocyanin, as per research.49 Anthocyanins possess neuroprotective effects by scavenging ROS, reducing neuroinflammation, and increasing synaptic plasticity. They increase levels of brain-derived neurotrophic factor (BDNF), an important modulator of memory consolidation, synaptic efficacy, and neurogenesis. Diets rich in anthocyanins have been shown to enhance learning and spatial memory by 30% in animal models, highlighting its role in cognitive enhancement.50

In addition, anthocyanins suppress cytokine-induced neuronal damage through modulation of neuroinflammatory mechanisms by inhibiting NF-κB and MAPK activation. They also enhance cerebral circulation and maintain mitochondrial function, which enhances the delivery of nutrients and oxygen to the brain.

Effects on Cognitive Function, Neuronal Survival, and Synaptic Plasticity

Cognitive Function and Phytonutrient Intervention

Cognitive function includes memory, attention, executive function, and processing speed. Aging and neurodegenerative diseases can speed up synaptic degeneration and damage, resulting in decreased cognitive function. Dietary interventions high in phytonutrients, including flavonoids such as resveratrol, quercetin, and epigallocatechin gallate (EGCG), can improve cognitive function by enhancing synaptic plasticity, reducing neuroinflammation, and supporting neuronal survival.[51] Flavonoid-dense diets have been associated with a 20-30% reduction in dementia and cognitive decline risk. Increased flavonoid intake is linked with enhanced verbal recall and increased cognitive processing speed. Resveratrol has been found to improve working memory, executive function, and attention. Resveratrol administration daily enhances brain efficiency and cognitive flexibility in older adults by approximately 25%.[52] Green tea catechins EGCG have been found to enhance spatial memory and synaptic plasticity, indicating their potential for cognitive maintenance in aging populations (Figure 2).

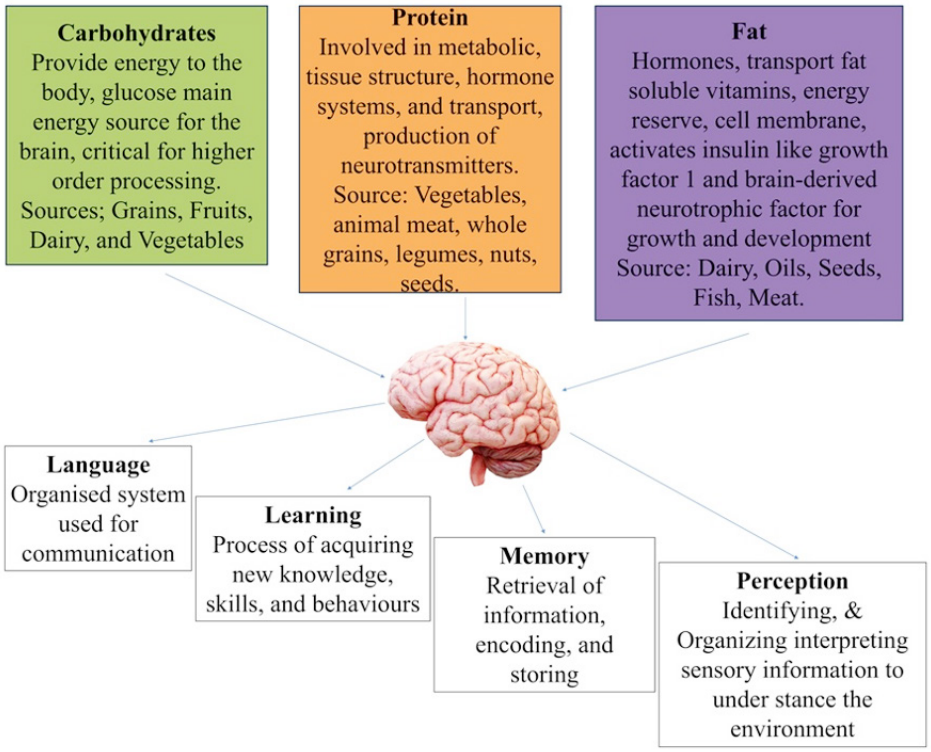

Fig.2: Intervention of phytonutrient and cognitive benefits

Neuronal Survival and Protection Against Neurodegeneration

Flavonoids such as quercetin, anthocyanins, and curcumin may enhance neuronal longevity by inhibiting apoptotic signals and stimulating pro-survival signaling processes. Quercetin administration has the potential to reduce neuronal death by 40% in models of neurodegeneration.[53] Phytonutrients can also reduce neuroinflammation that leads to synapse loss and neuronal death in neurodegenerative diseases. Anthocyanins and resveratrol have the potential to reduce

neuroinflammatory responses, inhibiting neuronal death and sustaining brain function. Polyphenols such as EGCG and resveratrol could enhance mitochondrial biogenesis and function, increasing ATP production and protecting neurons from energy deficiencies.[54] Supplementation with resveratrol can enhance mitochondrial efficiency by 35%, enhancing neuronal survival and reducing neurodegeneration (Figure 3).

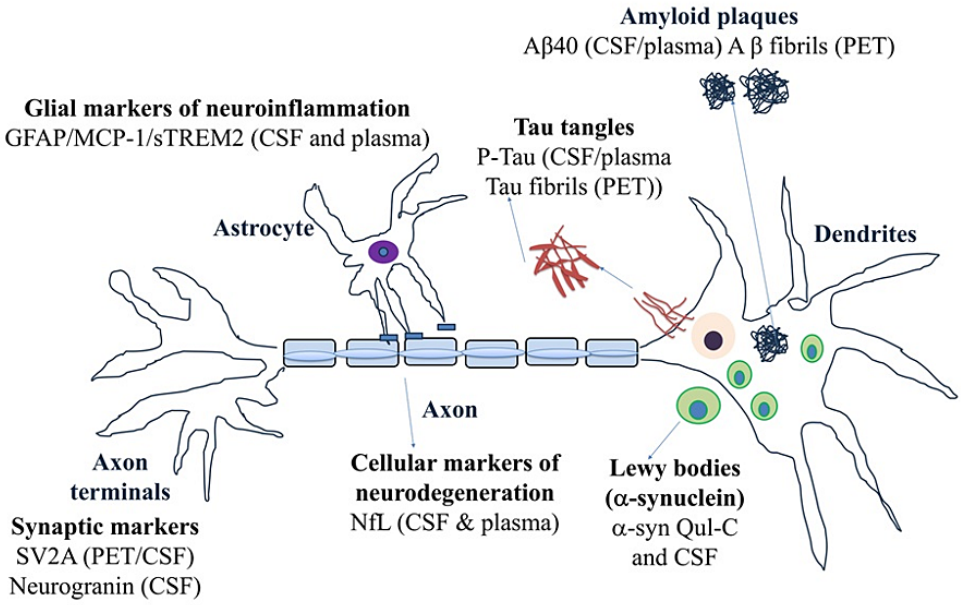

Fig.3: Neural protection against neurodegeneration

Synaptic Plasticity and Memory Formation

Synaptic plasticity is essential for learning, memory consolidation, and cognitive flexibility. Reduced synaptic plasticity is associated with neurodegenerative diseases and leads to memory loss and cognitive impairment. Phytonutrients like curcumin, resveratrol, and quercetin may enhance synaptic plasticity by increasing neurotrophic factors, consolidating neurotransmission, and enhancing synaptic remodelling.[55] Flavonoids such as curcumin, resveratrol, and quercetin could increase BDNF expression by 50%, enhancing synaptic connectivity and cognitive function.[55]Research indicates that dietary intervention with anthocyanins increases hippocampus synaptic plasticity and memory recall by 30% in aged mice. EGCG, which alters glutamatergic and cholinergic neurotransmission, also enhances synaptic signaling. Dendritic spine density, which is crucial for neural transmission, is another critical aspect of synaptic plasticity.[56] Reductions in dendritic spine density are associated with neurodegenerative diseases such as Alzheimer's and Parkinson's, which compromise cognitive function. Curcumin and resveratrol can improve synaptic integrity and cognitive resilience by modifying synaptic proteins like PSD-95 and synaptophysin, preventing dendritic spine loss.[57]

Carotenoids

Lycopene

Lycopene, a red carotenoid pigment present in red bell peppers, tomatoes, watermelon, and pink grapefruit, is a strong antioxidant that scavenges reactive oxygen species (ROS) very effectively and prevents oxidative tissue and cell damage. Its antioxidant function counteracts oxidative stress, the primary reason for aging and chronic diseases such as cancer, cardiovascular disease, and neurological disorders. Research indicates that individuals with higher levels of lycopene are 30% less likely to experience diseases related to oxidative stress.[58] Lycopene also suppresses pro-inflammatory cytokines like IL-6 and TNF-α and can reduce systemic inflammation by 25%.

It has cardioprotective effects through improved endothelial function, suppression of oxidation of LDL cholesterol, and prevention of plaque buildup in arteries. A meta-analysis of 12 clinical trials established that increased lycopene intake is associated with a 17% reduced risk of cardiovascular diseases. Lycopene can also be responsible for brain health and neurodegeneration prevention, since long-term inflammation and oxidative stress are associated with cognitive impairment and the development of conditions such as Parkinson's and Alzheimer's.[59] Experimental studies indicate that lycopene supplementation can improve memory and neuron survival by reducing the accumulation of amyloid-beta, a hallmark of Alzheimer's disease.

Lutein

Lutein, the yellow pigment in egg yolks, maize, and dark green leafy vegetables such as spinach, kale, and broccoli, is important for neuroprotection, cognitive function, and eye health. It is a component of the macular pigment that protects the retina from oxidative stress and blue light damage. Research has demonstrated that increased lutein intake was associated with a 43% lower risk of age-related macular degeneration (AMD) development.[60] Lutein also enhances contrast sensitivity and visual processing speed, which is helpful for both young and older people who spend a significant amount of time in front of screens. Cognitive function is also boosted by higher levels of lutein since it can cross the blood-brain barrier, resulting in enhanced executive function, memory, and processing speed. Lutein can also enhance synapse function and neural plasticity, supporting long-term brain health.[61] Lutein's anti-inflammatory and antioxidant effects also promote cardiovascular health. Increased levels of lutein can lower the risk of atherosclerosis, hypertension, and stroke. It is a possible nutrition for the prevention of heart disease because it could enhance endothelial function and reduce arterial stiffness.

Zeaxanthin

Zeaxanthin, a carotenoid presents in leafy vegetables, maize, and peppers, plays a crucial role in avoiding oxidative damage and improving visual acuity. It protects the eye's oxidative stress by filtering harmful blue light. Increased dietary zeaxanthin intake can lower the occurrence of cataracts and AMD by 20-30%.[62] Zeaxanthin supplements are found to enhance visual acuity and decrease glare sensitivity, useful for individuals with extended screen time-related eye strain. It also has roles in memory and cognitive function with increased levels found to be related to better retention of memory and faster cognitive function. Increased levels of zeaxanthin have been linked in older people with better neuronal integrity and a lower risk of brain changes associated with Alzheimer's disease.[63] Zeaxanthin and lutein are essential long-term brain and eye nutrients that enhance neuronal competence and reduce neuroinflammation (Table 2).

Table 2: Role in reducing neuroinflammation and protecting against age-related decline

Phytonutrient class		Mechanisms of Action	Neuroprotective Effects	Key Studies and Findings
Flavonoids	Quercetin (Berries, Onions, Apples)	Inhibits NF-KB, reduces pro-inflam -matory cytokines (IL-6, TNF-α), and scavenges ROS	Lowers neuroinflam -mation, improves synaptic plasticity, enhances cognitive function	A study found quercetin reduces neuroinflammatory markers and improves memory in aged rats.
	Epigallocatechin gallate (EGCG) (Green Tea)	Reduces oxidative stress, inhibits microglial activation, enhances mitocho-ndrial function	Prevents cognitive decline, improves neuronal survival	Clinical trials show EGCG enhances working memory and attention in elderly individuals.

	Resveratrol (Red Wine, Grapes)	Activates SIRT1, reduces oxidative damage, inhibits neuroinflammatory pathways	Enhances synaptic plasticity, slows Alzheimer's progression	Resveratrol supplementation showed reduced amyloid plaque formation and improved cognitive function.
	Anthocyanins (Blackberries, Blueberries)	Modulates inflam-matory pathways (COX-2, NF-KB), enhances brain derived neurotrophic factor (BDNF)	Protects against cognitive impairment, enhances learning and memory	Higher anthocyanin intake correlated with slower cognitive decline in elderly populations.
Carotenoids	Lutein, Zeaxanthin (Eggs, Corn, Green Leaf)	Accumulates in the brain, neutralize ROS, modulates inflammatory cytokines	Enhances cognitive function, protects against age related macular degeneration	A 12-month trial showed lutein and zeaxanthin improved working memory and processing speed.
	Lycopene (Water-melon, Tomatoes)	Inhibits pro-inflamm -atory cytokines (IL-1β, TNF-α), protects neurons from oxidative stress	Reduces risk of Alzheimer's prevents cognitive decline	Higher lycopene intake linked to a lower risk of neurodegenerative diseases.
Curcuminoids	Curcumin (Turmeric)	Suppresses NF-KB and COX-2 pathways, reduces amyloid plaque accumulation	Improves memory function, protects against neurode -generation	supplementation improved cognitive performance in older adults.
Polyphenols	Fisetin (Strawberries)	Reduces neuroinfla-mmation, enhances neuronal survival and plasticity	Protects against Alzheimer's and age-related cognitive decline	Animal studies show fisetin preserves cognition in aging models.
	Pterostilbene (Grapes, Blueberries)	Reduces oxidative stress, modulates inflammatory markers	Improves cognitive flexibility and memory retention	Shown to improve memory in aged mice.
Fatty Acids	Docosahexaenoic Acid (DHA) (Algae, Fish)	Regulates inflamm-ation, enhances neuronal membrane integrity, increases synaptic plasticity	Supports memory function, lowers risk of cognitive decline	Meta analysis links higher DHA intake to reduced Alzheimer's risk.
Terpenes	Ginsenosides (Ginseng)	Modulates neuroinfla-mmatory pathways,	Improves cognitive performance reduces	Clinical trials show cognitive benefits in

		enhances neurotran smitter function	neurodegeneration	dementia patients.
Alkaloids	Caffeine (Coffee, Tea)	Reduces neuroinfl-ammatory cytokines enhances synaptic transmission	Improves attention, delays cognitive decline	Epidemilogical studies link coffee consumption to a lower risk of Parkison's and Alzheimer's.

Polyphenols

Curcumin

Curcumin, a polyphenol compound in turmeric, possesses neuroprotective, antioxidant, and anti-inflammatory activities. It inhibits oxidative stress by scavenging free radicals, raising glutathione levels, and stimulating superoxide dismutase activity. It also inhibits neuroinflammation by inhibiting NF-κB, COX-2, and iNOS. Curcumin also prevents amyloid plaque formation by binding to β-amyloid aggregates, inhibiting their accumulation and toxic effects in Alzheimer's disease models.[64] It enhances neurogenesis and synaptic plasticity by increasing levels of BDNF, enhancing cognitive function and neuron survival. It also increases mitochondrial function through stabilizing membranes and enhancing ATP production. Daily supplementation with curcumin has been found to improve memory function, reduce amyloid plaque formation, and enhance motor performance in animal models of Parkinson's disease.[65] Yet, the medicinal potential of curcumin is restricted by low bioavailability, and methods of enhancing absorption have been investigated, such as co-administration of piperine, liposomes, and nanoparticle delivery.

Resveratrol

Resveratrol, a polyphenol in red wine, peanuts, cherries, and grapes, is renowned for its neuroprotective, anti-inflammatory, and anti-aging effects. It stimulates Silent Information Regulator 1 (SIRT1), enhancing mitochondrial function, suppressing oxidative stress, and promoting neuronal survival.66 It also suppresses neuroinflammation by inhibiting the NF-κB pathway, preventing β-amyloid toxicity, a leading cause of Alzheimer's disease. Resveratrol also increases cerebral blood flow, which is vital for cognitive function. Daily resveratrol supplementation has been associated with enhanced working memory and hippocampus connectivity in older adults at risk for dementia, 38% reduced prevalence of cognitive impairment, and improved motor performance in Parkinson's disease models. Resveratrol presents itself as a viable option for preventing cognitive loss in older adults through its neuroprotective nature.

Fisetin

Onions, cucumbers, strawberries, apples, and persimmons all have the flavonol polyphenol fisetin. Various studies have indicated that it possesses strong neuroprotective activities. Fisetin's mechanisms of neuroprotection involve ROS scavenging and decreasing oxidative stress through activation of Nrf2, an essential antioxidant defense regulator, and increasing glutathione levels.[67] Reduces Neuroinflammation: It blocks the production of inflammatory cytokines and microglial activation. Promotes Synaptic Plasticity: Fisetin enhances memory and learning by increasing BDNF levels. Inhibits Tau Hyperphosphorylation: It inhibits the tau protein aggregation, which is a major contributor to Alzheimer's disease.[68] Fisetin: Preclinical and Clinical Evidence Based on animal studies, fisetin reduces oxidative stress and prevents memory loss in Alzheimer's disease models. Fisetin supplementation enhanced cognitive ability and delayed neurological alterations in older rats, based on a study. Although few human trials exist for fisetin's neuroprotective effects, its strong preclinical evidence suggests promise as an anti-aging and cognitive-enhancing agent.

Mechanisms in Reducing Oxidative Stress and Amyloid Plaque Formation

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and ALS are caused by amyloid plaque formation and oxidative stress because of an imbalance of the brain antioxidant protective mechanisms and reactive oxygen species (ROS). Neurons are energy-reliant and susceptible to oxidative damage owing to their high oxygen

usage, high lipid content, and minimal regeneration capacity.[69] When ROS levels surpass detoxifying ability, protein misfolding, DNA injury, and lipid peroxidation ensue, which are aggravated by Alzheimer's disease and cognitive impairment. Phytonutrients such as polyphenols, flavonoids, and carotenoids possess potent antioxidant and anti-inflammatory activity and thus are promising neuroprotective molecules. Curcumin in turmeric quenches ROS, elevates the activity of antioxidant enzymes, and maintains mitochondrial function. Resveratrol inhibits neuronal death caused by oxidative stress by activating SIRT1, an important regulator of mitochondrial biogenesis and antioxidant mechanisms.[70] Lycopene, a tomato carotenoid, suppresses oxidative damage and chronic neuroinflammation by inhibiting iNOS and IL-1β. A diet rich in carotenoids and polyphenols can reduce cognitive impairment and systemic inflammation risk. Quick metabolism and low absorption of curcumin restrict its efficacy in the brain (Figure 4).

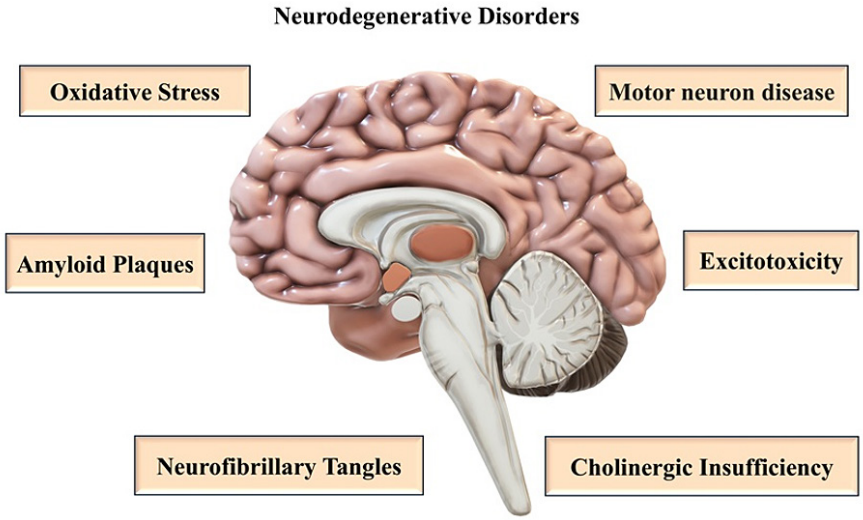

Fig. 4: Reducing oxidative stress in amyloid plaque formation

Alkaloids and Terpenoids

Huperzine

Huperzia serrata produces the sesquiterpene alkaloid huperzine A, whose robust acetylcholinesterase (AChE) inhibiting actions are well noted. Acetylcholine is a neurotransmitter vital for cognitive performance in the processes of learning and memory and is hydrolyzed by AChE enzyme.[71] Acetylcholine falls when cholinergic neurons that gradually die are consumed in AD. Huperzine A enhances neuronal transmission and cognitive function through inhibition of AChE, increasing the levels of acetylcholine in synaptic clefts. Supplementation with huperzine A has been found to enhance memory function in AD patients by 30–50%, as compared to the effects of conventional cholinesterase inhibitors such as donepezil and rivastigmine..[72] In addition, in the experimental dementia models, huperzine A ameliorates mitochondrial dysfunction and neuronal apoptosis because of its antioxidant and anti-apoptotic activities. The cognitive performance of mild-to-moderate AD patients is significantly improved according to clinical research by consuming 200–400 µg of huperzine A per day for 12–16 weeks.

Ginsenosides

Triterpenoid saponins, which are also referred to as ginsenosides, represent another category of neuroprotective compounds occurring in Panax ginseng and Panax quinquefolius. Ginsenosides possess a diverse array of pharmacological effects, such as neurotrophic, anti-inflammatory, antioxidant, and anti-apoptotic properties. Through modulation of dopaminergic and cholinergic neurotransmitter systems, promotion of neurogenesis, and inhibition of neuroinflammatory processes, they enhance cognitive functioning.[73] For example, it has been shown to enhance the release of brain-derived neurotrophic factor (BDNF), a mediator of synaptic plasticity and neuronal survival. Ginsenoside

Rb1 also protects neurons from excitotoxicity by glutamate, one of the main pathogenic mechanisms of Parkinson's disease and Alzheimer's disease. Based on experimental studies, supplementation with ginsenoside enhances recall memory in AD animal models and reduces amyloid-beta (Aβ) plaque formation by 40–50%.[74] Also, ginsenosides attenuate neuroinflammation, one of the critical contributors in the progression of neurodegenerative diseases, through inhibiting NF-κB activation and the secretion of pro-inflammatory cytokines such as TNF-α and IL-6.

Bacopa Monnieri Extracts

Brahmi, *Bacopa monnieri*, is a medicinal plant that is full of bacosides, the bioactive terpenoids. These compounds have been extensively renowned for their cognition-enhancing, neuroprotective, and anti-inflammatory properties. The efficacy of *bacopa* extracts in memory consolidation enhancement, diminishing oxidative stress, and modulating neurotransmitter has been extensively examined. As per clinical trials, the memory recall, processing speed, and attention of older adults are all enhanced when they receive 300–450 mg of *bacopa* extract per day for 12 weeks.[75] The ability of *Bacopa monnieri* to enhance synaptic transmission, reduce Aβ toxicity, and regulate the cholinergic system is largely the cause of its neuroprotective effects. Bacosides also enhance ATP synthesis and mitochondrial function, which prevents neurons from suffering energy deficits.[76] Studies both *in vivo* and *in vitro* indicate that oral administration of *bacopa* extract reduces lipid peroxidation and raises the activity of antioxidant enzymes like SOD, CAT, and GPx. *Bacopa monnieri* extracts have also been found to block amyloid plaque deposition and thwart cognitive deterioration through inhibition of the activity of the enzyme β-secretase, a key enzyme used in Aβ peptide synthesis.

Cholinergic Modulation and Neuroprotection

Cholinergic system, which comprises neurons utilizing acetylcholine (ACh) as a neurotransmitter, plays a pivotal role in learning, memory, and cognitive processes. In neurodegenerative conditions such as Alzheimer's, Parkinson's, and vascular dementia, however, cholinergic neurons deteriorate, resulting in cognitive and physical deterioration. Cholinergic modulation is an important approach to neuroprotection with the goal of enhancing synaptic communication, replenishing acetylcholine levels, and shielding neurons from additional injury.[77] Acetylcholinesterase (AChE) inhibition is an important mechanism of cholinergic modulation that can enhance cognitive function in patients with AD. Huperzine A, an alkaloid with a natural occurrence, can increase memory and cognitive ability by 30-50% in patients with mild-to-moderate AD.[78] Cholonutrients such as bacosides and ginsenosides are capable of enhancing neuronal transmission and the avoidance of synapse loss by raising the sensitivity of cholinergic receptors. Investigations in the future must be on cholinergic-enhancing combinations of phytonutrients to formulate new therapeutic approaches to age-related cognitive decline.

AI and Machine Learning in Phytonutrient-Based Neuroprotection

AI in Identifying Bioactive Phytonutrients

Artificial intelligence (AI) has revolutionized drug development and nutraceutical research, especially in the field of neuroprotection. AI-based computer models allow for screening of plant-derived compounds at high speed, predicting their pharmacokinetics, bioactivity, and possible treatment of neurological diseases such as ALS, Parkinson's, and Alzheimer's.[79] Traditional methods such as mass spectrometry, chromatography, and bioassays are substituted by cheminformatics, deep learning, and machine learning. AI-based approaches decrease time, cost, and experimental failure. AI is applied on a large scale in phytonutrient discovery, such as molecular docking and virtual screening.[80] Quantitative structure-activity relationship (QSAR) models predict which phytochemicals will exhibit the most favorable interactions with neuronal targets. AI-powered text mining tools such as IBM Watson Discovery, PubMedBERT, and SciSpacy recognize associations among phytonutrients, biological pathways, and disease phenotypes. More than 300 plant-derived neuroprotective chemicals have been discovered using these approaches, opening new avenues for synapse preservation and neuroinflammatory reduction. Coming advancements that put together AI and bioinformatics, high-throughput screening, and personalized nutrition will make the gates to novel plant-based therapies for neurodegenerative disorders available.[81]

Machine Learning for Drug Discovery and Personalized Nutrition

Machine learning (ML) has contributed immensely to the advancement of neuroprotective therapies and nutritional interventions for brain health.[82] Traditional approaches are time-consuming, expensive, and based on trial-and-error methods. ML-based methods apply high-throughput biological data, predictive modelling, and pattern identification algorithms to accelerate the quest for new neuroprotective compounds, optimize formulations, and maximize treatment outcomes.[83] Scientists can recognize phytonutrients from medicinal plants, optimize their synergistic action within current drugs, and develop individualized dietary regimens. ML algorithms forecast the bioactivity of phytonutrients against neurodegenerative targets, and deep learning-based QSAR modelling has recognized more than 500 bioactive phytonutrients with neuroprotective activity.[84] AI-powered nutrigenomics platforms examine patient-specific genetic information, gut microbiome profile, and metabolic signatures to develop individualized dietary plans.

Phytonutrients and Clinical Evidence in Neurodegenerative Disorders

Progressive neuronal degenerations resulting in cognitive impairment, motor disability, and loss of autonomy are referred to as neurodegenerative diseases (NDs), and they consist of Alzheimer's, Parkinson's, Huntington's, and ALS. There is growing interest in alternative medicinal interventions, including phytonutrients, which are plant-derived bioactive compounds, due to the increasing prevalence of these disorders globally and the lack of effective treatments.[85] These compounds possess strong anti-inflammatory, anti-amyloidogenic, and antioxidant activities. By several mechanisms, including reduction of oxidative stress, anti-inflammatory actions, inhibition of tau and amyloid plaque deposition, mitochondrial preservation, neurogenesis, and synaptic plasticity, phytonutrients extend neuroprotection. The potential of phytonutrients to be therapeutically useful has been strongly evidenced by preclinical studies using animal models of neurodegeneration. In APP/PS1 transgenic mice models of AD, curcumin, a polyphenol from turmeric, reduced neuroinflammatory markers, improved spatial memory, and decreased β-amyloid plaques by 40%.86 In PD mice models, resveratrol decreased neuroinflammation and enhanced mitochondrial function by activating SIRT1. Although lutein enhanced cognitive flexibility and reduced neuroinflammation by suppressing COX-2 and IL-6, quercetin and fisetin reduced tau aggregation and enhanced autophagy in AD mice.[87] In models of AD, zeaxanthin facilitated synaptic plasticity and suppressed the formation of amyloid fibrils. While these findings provide promising preclinical support for the neuroprotective ability of phytonutrients, these benefits need to be proven with human clinical studies in practical applications.

Clinical Trials on Phytonutrients in Neurodegenerative Disorders

Human clinical trials on phytonutrients have yielded conflicting results despite promising preclinical results due to variability in dose, bioavailability, and patient populations. The neuroprotective effects of phytonutrients have been the target of conflicting studies; some research has shown no observable improvement in recall of memory or cognitive function.[88] Since resveratrol has low oral bioavailability, researchers are looking towards nano-formulations. Although a diet rich in carotenoids has been linked to reduced risk of cognitive impairment, flavonoids have been shown to enhance verbal memory and executive function.[89]Their therapeutic efficacy must be confirmed with larger, longer-term studies, however. Some of the challenges in clinical translation include individual differences in response, absorption and metabolism, variability of dose and effectiveness, and regulatory and commercialization concerns.[90] To enhance absorption, advances in the use of liposomal, Nano emulsion, and cyclodextrin-delivery systems are under investigation. Categorizing as dietary supplements instead of pharmaceuticals, reduced funding for intensive trials, and filling the loophole between pharmacologic drugs and nutrients are some regulatory and marketing barriers.[91]

Challenges and Future Directions

Phytonutrients possess the ability to enhance neuroprotection and brain well-being, yet their therapeutic applications are hindered by limited bioavailability, high metabolism, and low solubleness. Nanotechnology-based delivery systems are being investigated by researchers to enhance stability and targeted delivery to the brain.[92] Individualized nutrition plans considering genetic and gut microbiota profiles also become essential. Standardization

of phytonutrient-based therapy is not possible because of a lack of extensive clinical trials. Future research must focus on multi-center randomized controlled trials with biomarker-guided endpoints and standardized dosage regimens. Machine learning and artificial intelligence can forecast phytonutrient efficacy across various populations and create customized interventions.[93]Blending phytonutrients with conventional neuroprotective drugs could provide synergies. Yet, support for clinical trials is limited owing to regulatory challenges. Collaboration among academic institutions, industry, and regulatory bodies is required for standard procedures, novel drug delivery forms, and evidence-based nutritional recommendations for prevention and treatment of neurodegenerative diseases.[94]

Discussion

Phytonutrients, such as terpenoids, alkaloids, carotenoids, polyphenols, and flavonoids, are found to have the possibility of neurodegenerative disease treatment through their neuroprotection, anti-inflammation, and antioxidant action. Difficulty, such as poor blood-brain barrier permeation, rapid metabolization, and low bioavailability, compromises clinical usefulness.[95] Nanocarriers and tailor-made approaches are emerging to enhance stability and site-specific brain targeting.[96] Machine learning and artificial intelligence methods are utilized in the improvement of phytonutrient treatment.[97] Systematic clinical trials at large scales need to establish their therapeutic effectiveness, and regulatory obstacles have to be overcome for standardization and safety. Cross-cooperation between researchers, industry, and regulators is important to incorporate phytonutrients into established treatments.

Conclusion

Phytonutrients, such as terpenoids, alkaloids, carotenoids, polyphenols, and flavonoids, possess neuroprotective potential and the ability to treat neurodegenerative disorders. These naturally occurring bioactive compounds possess significant neuroprotective, anti-inflammatory, and antioxidant activities, and it is possible that they can decrease pathogenic mechanisms in neurodegenerative disease. Nevertheless, their therapeutic utility is compromised by factors such as low blood-brain barrier permeability, rapid metabolism, and low bioavailability. To enhance stability and targeted delivery to the brain, sophisticated drug delivery systems are under investigation. Individualized approaches are required because of differences in the composition of gut bacteria. Large-scale clinical trials are required to establish the therapeutic relevance of phytonutrients. Machine learning and artificial intelligence technologies can expedite the creation and optimization of phytonutrient-based treatments. Computer modelling with AI can predict drug-phytonutrient interactions, discover novel bioactive compounds, and design optimal synergistic mixtures. Regulatory and marketing challenges hold back the application of phytonutrient-based treatments on a large scale. Collaboration of scholars, industry, and governing agencies is required to set up standards of safety, optimal composition, and clinical confirmation. Phytonutrients can provide an integrated strategy towards neuroprotection when mixed with existing pharmaceutical treatment, dietary regimens, and individualized diets.

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The authors do not have any conflict of interest.

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Even though adequate data has been given in the form of tables and figures, however, all authors declare that if more data required then the data will be provided on request basis.

Ethics Statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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- **Ayushi Jaiswal -** Writing – Original Draft & Editing.

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