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Exploring The Effects of Natural Antioxidants in Neurodegenerative Diseases: A Comprehensive Review

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Abstract:
Neurodegenerative diseases are increasingly becoming a significant public health concern, highlighting an urgent need for effective therapeutic strategies. This comprehensive review delves into the potential of natural antioxidants, such as Curcuminoids, Vitamin C, Vitamin E, and Resveratrol in preventing and treating these diseases. We examine the existing evidence for the neuroprotective effects of these compounds, discuss their underlying mechanisms, and emphasize their potential role as adjunctive therapies for neurodegenerative conditions.

Keywords: Alzheimer's disease, Parkinson's disease, free radicals, antioxidant, oxidative stress.

INTRODUCTION:

1. NEURODEGENERATIVE DISEASE:

Neurodegenerative diseases encompass a range of disorders marked by the progressive deterioration of neurons and the nervous system. These conditions impact neurons, the foundational units of the nervous system, including the brain and spinal cord. Over time, affected neurons deteriorate and ultimately die, resulting in various symptoms and disabilities. Neurodegenerative diseases pose a significant health risk, especially as the prevalence of these age-related disorders rises with an aging population. Notable examples include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, and spinocerebellar ataxias. The pathophysiology of these diseases varies widely: some cause memory and cognitive impairments, while others affect movement, speech, or breathing.[1]

1. **Alzheimer's Disease**: Alzheimer's disease is the most prevalent form of dementia, characterized by a decline in cognitive ability severe enough to interfere with daily life. The disease features senile plaques and neurofibrillary tangles in the cortex, composed of amyloid-beta and tau proteins. These misfolded proteins lead to neuronal loss and synaptic damage. Aging, the primary risk factor, contributes to oxidative stress and mitochondrial dysfunction, rendering neurons more susceptible to degeneration. This decline in mitochondrial function, particularly affecting energy-demanding neurons like large pyramidal cells, may accelerate brain aging and increase the vulnerability to Alzheimer's pathology.[2]

2. **Parkinson's disease**: Parkinson's disease (PD) is a common age-related neurodegenerative disorder associated with the misfolded protein alpha-synuclein, which forms Lewy bodies. These begin in the olfactory regions and lower brain stem, eventually spreading to the midbrain and cortex. The progression of Lewy body deposition correlates with clinical symptoms such as rest tremor, rigidity, and bradykinesia, which become evident after significant neuronal loss in the substantia nigra which is the part of midbrain, primarily known for its role in regulating movement. It consists of two parts: the pars compacta and the pars reticulata. Dopamine produced by the substantia nigra is essential for the smooth and controlled execution of movements. It plays a key role in the reward system, influencing motivation and mood.[2]
3. **Huntington's disease:** Huntington's disease (HD) is a rare neurodegenerative disorder characterized by choreatic movements, psychiatric issues, and dementia. It affects approximately 1 in 10,000 to 1 in 20,000 Caucasians, typically manifesting between ages 30-50, though juvenile cases can start earlier. HD is caused by an elongated CAG repeat in the Huntingtin gene, with longer repeats leading to earlier onset. Diagnosis is based on symptoms and genetic testing. The CAG repeat refers to a specific sequence of DNA composed of the nucleotides cytosine (C), adenine (A), and guanine (G) that repeat multiple times in a row. This sequence is found in the gene that codes for the protein huntingtin.[3]
4. **Amyotrophic lateral sclerosis**: Amyotrophic" refers to muscle atrophy and weakness due to lower motor neuron disease, while "lateral sclerosis" indicates a hardening of spinal cord areas from corticospinal tract degeneration, visible in autopsies. This results in upper motor neuron signs such as overactive reflexes and Babinski signs. Progressive spinal muscular atrophy shows only lower motor neuron signs, while primary lateral sclerosis shows only upper motor neuron signs. Both are ALS variants, often with both neuron types affected at autopsy. ALS symptoms include weakness starting in the hands and legs, or as slurred speech, and dysphagia. Examination typically reveals both lower and upper motor neuron signs. The disease is progressive, with an average survival of three to five years..[4]

Antioxidant: Antioxidants are substances that inhibit oxidation, a chemical reaction that can produce free radicals and chain reactions that may damage cells. They neutralize these free radicals, thereby preventing cell damage. Antioxidants can be naturally occurring, found in plants, animals, and microorganisms, or synthetically produced. Common natural antioxidants include vitamins C and E, selenium, and flavonoids founds in various in fruits, vegetables, teas, and grains. [5]

2. ROLE OF OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASE:

While the exact causes of neurodegenerative diseases remain largely unclear, increased oxidative stress is widely believed to be a common contributing factor. This stress can lead to cellular damage, issues with DNA repair, and mitochondrial dysfunction, all of which accelerate aging and contribute to these disorders. Consequently, researchers are continually seeking agents that can protect against oxidative damage and potentially treat neurodegenerative diseases.[6] Oxygen is crucial for energy metabolism in most eukaryotic organisms. During respiration, oxygen can be partially reduced to superoxide, a free radical capable of forming other reactive oxygen species (ROS). Additionally, cell metabolism produces reactive nitrogen species (RNS). Under normal conditions, ROS and RNS play roles in signal transduction, mitogenic responses, and pathogen defense. However, when the production of ROS and RNS exceeds the capacity of antioxidant systems, oxidative stress occurs, leading to cell damage, protein misfolding, and DNA mutations. External factors such as UV light, X-rays, heavy metals, and pollutants further contribute

to oxidative damage. Over time, this accumulated stress can trigger various diseases, including cancer, arteriosclerosis, arthritis, and neurodegenerative disorders. The brain, with its high oxygen consumption, low antioxidant defenses, and high levels of easily oxidized fats in neurons, is particularly susceptible.[7]

2.1 ROS-induced Protein misfolding:

Neurofibrillary tangles (NFTs) and amyloid-beta (Aβ) deposits are key histopathological markers of Alzheimer's disease (AD). NFTs consist of paired helical filaments (PHFs), primarily formed by the hyperphosphorylated microtubule-associated protein Tau. ROS plays a critical role in promoting Tau hyperphosphorylation, a process essential for abnormal protein aggregation. In vitro studies have shown that ROS can phosphorylate Tau at specific sites without causing neuronal death. Acrolein, a lipid peroxidation product, also increases Tau phosphorylation in human neuroblastoma cells and mouse cortical neurons. Chronic oxidative stress elevates c-Jun N-terminal kinases (JNK) and p38 activities while reducing PP2A activity, further contributing to Tau phosphorylation and aggregation into fibrils. Additionally, oxidative stress promotes the amyloidogenic processing of amyloid precursor protein (APP) and increases β-secretase activity, leading to the accumulation of neurotoxic Aβ peptides.[6,7]

In Parkinson's disease (PD), oxidative stress significantly influences the aggregation of alpha-synuclein (αSyn) protein. Posttranslational modifications of αSyn due to oxidative stress, such as 4-hydroxy-2-nonenal (HNE-αSyn), nitration (n-αSyn), and oxidation (o-αSyn), promote protein clump formation. Among these, HNE-αSyn is notably more toxic and more prone to form aggregates compared to unmodified protein, highlighting its significant impact on the disease.[7,8,]

In Huntington's disease (HD), the aggregation of mutant Huntingtin (mHtt) protein is crucial. Oxidative modifications make these aggregates larger and alter their structure, worsening their impact. Oxidative stress also promotes the aggregation of specific forms of mHtt, leading to increased cell death. Proteins like aldolase C, aconitase, GFAP, tubulin, peroxiredoxins, glutathione peroxidase, and αB-crystallin are identified as targets of oxidative damage in HD .[7]

In Amyotrophic Lateral Sclerosis (ALS), TDP-43 is a key protein found in ubiquitin-positive inclusions. The build-up of insoluble TDP-43 disrupts its function and accelerates disease progression. Oxidation of cysteines in its RNA recognition motif causes conformational changes, leading to protein aggregation and loss of nucleic acid-binding activity, thus driving the disease forward.[7,8,9]

3. OTHER CONTRIBUTING FACTORS:

3.1 Inflammation: The immune system is essential for maintaining tissue health and responding to infections and injuries. Microglia, the resident immune cells in the brain, provide innate immunity. Under normal conditions, they are inactive and produce anti-inflammatory and neurotrophic factors. However, stress from pathogens, injury, or abnormal protein accumulation can activate microglia to promote an inflammatory response. This innate inflammation is observed in diseases like Alzheimer's, Parkinson's, and ALS. While classic signs of inflammation are usually absent in neurodegenerative diseases, significant research has revealed evidence of immune activation, even without notable lymphocyte infiltration.[10] [11]

Environmental toxins and genetic predispositions can lead to neuronal damage, especially in the substantia nigra and striatum. There's clear evidence showing that activation of neuroinflammatory cells, particularly microglia, along with the production of pro-inflammatory cytokines, exacerbates this neurodegenerative process. For instance, after exposure to neurotoxins like MPTP or manganese, the degenerative process can persist for years. Reactive microglia release harmful factors such as cytokines and proinflammatory

molecules, which can damage CNS cells. Nitric oxide (NO), in particular, is neurotoxic as it inhibits respiratory chain components and reacts with superoxide anion to produce peroxynitrite, leading to striatal neurodegeneration.[11,12]

3.2 Mitochondrial dysfunction: Aging is the most significant risk factor for neurodegenerative diseases like AD, PD, and ALS. Mitochondria contribute to aging through the accumulation of mitochondrial DNA (mtDNA) mutations and the production of ROS. Human mtDNA encodes essential components of the respiratory chain and necessary RNAs. Inherited mtDNA mutations often affect high-energy tissues like the brain and muscles. Somatic mtDNA mutations acquired with age are linked to physiological decline and neurodegeneration. As we age, mtDNA accumulates mutations, including large-scale deletions and point mutations, which correlate with a decline in mitochondrial function and cytochrome oxidase activity. Somatic deletions can expand clonally in neurons and are associated with cytochrome oxidase deficiency in the substantia nigra, potentially contributing to the age dependence of PD.[13]

In short: Impact of Mitochondrial Dysfunction in Neurodegenerative Diseases

- **Energy Production**: Mitochondria are essential for producing ATP, the energy currency of cells. When they malfunction, it leads to energy shortages that impair neuronal function and survival.[14]
- **Oxidative Stress**: Damaged mitochondria generate excessive amounts of reactive oxygen species (ROS), which cause oxidative damage to proteins, lipids, and DNA, exacerbating cellular damage.[14]
- **Calcium Homeostasis**: Mitochondria help regulate calcium levels within cells. Dysfunction in these organelles disrupts this balance, triggering pathways that lead to cell death.[14]
- **Apoptosis** When mitochondria are damaged, they can initiate apoptosis, or programmed cell death, leading to the loss of neurons.[15]
- **Neuroinflammation**: Mitochondrial dysfunction can activate microglia, the brain's immune cells, leading to inflammation and further neuronal damage.[14,15]

4. ANTIOXIDANT:

4.1 Definition: Biological antioxidants are compounds that, even in lower concentrations compared to oxidizable substrates, can delay or prevent oxidation. These antioxidants play a crucial role in reducing oxidative stress, preventing DNA mutations, inhibiting malignant transformations, and minimizing other cell damage parameters. Epidemiological studies indicate that antioxidants can mitigate the adverse effects of reactive oxygen species (ROS) and decrease the incidence of cancer and degenerative diseases. Antioxidant defense systems are designed to prevent the formation of ROS and neutralize free radicals that have already been formed. These defense systems, found in both aqueous and membrane cell compartments, can be enzymatic or nonenzymatic. Another vital antioxidant system involves repair processes that remove damaged biomolecules before they can disrupt cell metabolism. These repair systems include enzymes that fix oxidatively damaged nucleic acids, proteolytic systems that remove oxidized proteins, and enzymes such as phospholipases, peroxidases, and acyl transferases that repair oxidized lipids. It is thought that the decline of these repair systems contributes more to aging and age-related diseases than moderate changes in the antioxidant defense potential against ROS. Under normal physiological conditions, the balance between prooxidant and antioxidant compounds typically favors prooxidants, resulting in slight oxidative stress that endogenous antioxidant systems manage. However, as age advances, this oxidative stress becomes more pronounced as endogenous antioxidants and repair systems become less effective.[16]

4.2 Natural antioxidant and neuroprotection: Emerging evidence suggests that certain dietary compounds with neurogenic properties have beneficial effects on brain aging and neurodegenerative diseases. Specifically, polyphenols such as flavonoids, curcuminoids, stilbenes, phenolic acids, carotenoids, Vitamin C, and Vitamin E, which are abundantly found in foods like tea, red wine, herbs, seeds, and fruits, contribute to the health benefits associated with regular consumption of fruits and vegetables. Although the precise molecular mechanisms are not fully understood, polyphenols are known to promote neurogenesis, reduce oxidative stress and neuroinflammation, and enhance cell signalings. The potent antioxidant action of polyphenols occurs through their ability to scavenge free radicals, thereby forming more stable compounds. Numerous polyphenols have been extensively studied for their positive effects on brain health. These studies have demonstrated that polyphenols can support cognitive function, protect against neurodegenerative processes, and improve overall brain health by reducing oxidative damage and modulating inflammatory pathways. In summary, the role of biological antioxidants in protecting against oxidative stress and their potential in neuroprotection is significant. By reducing oxidative damage, promoting repair processes, and supporting cellular health, antioxidants play a crucial role in maintaining brain health and preventing neurodegenerative diseases. Continued research is necessary to fully understand the mechanisms by which these compounds exert their protective effects and to develop effective antioxidant-based interventions for neurodegenerative conditions.[17]

1. CURCUMINOID:

Turmeric (Curcuma longa) is a tropical herbaceous plant belonging to the ginger family, Zingiberaceae. It originates from the Indian subcontinent and parts of Southeast Asia. The dried, powdered turmeric rhizome produces a vibrant orange-yellow powder, often called Indian saffron, yellow ginger, or yellow root. This turmeric powder is a staple in South and Southeast Asian cuisines and is a primary ingredient in curry powder. In traditional Ayurveda medicine, turmeric has been highly valued for treating a wide range of ailments, including infections, respiratory issues, swelling, and rheumatism. Additionally, turmeric is believed to possess potent anticarcinogenic, antilipidogenic, cardioprotective, and neuroprotective properties. The primary polyphenolic compounds in turmeric rhizome are curcuminoids. These include curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with commercial curcumin typically consisting of approximately 77% curcumin, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin. Besides these naturally occurring compounds, several semisynthetic curcuminoids like diacetyl curcumin, dihydrocurcumin, and hexahydrocurcumin have been synthesized and studied for their biological activity[18]

Antiamyloid properties: Curcumin's most promising use in treating neurodegenerative diseases lies in its anti-amyloid properties. This compound can selectively bind to and inhibit the aggregation of amyloid proteins, which has spurred research into its potential benefits for neurological disorders. Curcumin interacts with amyloid-β (Aβ) oligomers and fibrils in Alzheimer's disease (AD) and also binds to other amyloid proteins like alpha-synuclein (α-syn) in Parkinson's disease (PD),) in Huntington's disease (HD), and phosphorylated tau in various neurodegenerative conditions. These interactions help prevent the formation and accumulation of toxic protein aggregates, which are characteristic of these diseases.[19,20]

Anti-inflammatory agent: Apart from its antioxidant properties, curcumin's capacity to reduce neuroinflammation makes it an appealing candidate for neurological disease therapy. Several studies suggest that curcumin is a powerful anti-inflammatory agent that can downregulate various neuroinflammatory marker proteins, such as nuclear factor kappa beta (NF-κB). Additionally, curcumin inhibits phospholipases and enzymes involved in the metabolism of arachidonic acid, including

cyclooxygenase-2 (COX-2). These actions help mitigate inflammation-related neuronal damage and provide neuroprotection.[19,20,21]

Potent antioxidant: The central nervous system (CNS) is particularly vulnerable to oxidative damage due to its high metabolic rate, increased oxygen demand, substantial quantities of membrane phospholipids and polyunsaturated fatty acids (PUFA), and relatively lower levels of antioxidants compared to other organs. These factors contribute to elevated levels of reactive oxygen species (ROS) and peroxynitrite (ONOO-), leading to inflammation, mitochondrial dysfunction, and, ultimately, neuronal death. Chronic progressive neurological diseases induce inflammation, oxidative stress, lipid peroxidation, DNA damage, and the production of oxidized proteins. Curcumin play an important role in managing all these condition and hence act as a potent antioxidant.[19,22]

Invitro studies: Recent in vitro studies have highlighted curcumin's potential in mitigating neurodegenerative diseases through its multifaceted biological activities. Curcumin has been shown to significantly reduce oxidative stress in neuronal cells by scavenging reactive oxygen species (ROS) and inhibiting lipid peroxidation, thereby safeguarding neurons from oxidative damage (Wei et al., 2024). Additionally, curcumin has demonstrated the ability to inhibit the aggregation of amyloid-beta (Aβ) peptides, a hallmark of Alzheimer's disease, thus preventing the formation of neurotoxic fibrils (Wei et al., 2024). Furthermore, curcumin's anti-inflammatory properties have been observed to downregulate pro-inflammatory markers such as nuclear factor kappa beta (NF-κB), contributing to its neuroprotective effects (Morasso et al., 2024). These findings suggest that curcumin could be a promising therapeutic agent for neurodegenerative diseases, warranting further in vivo studies and clinical trials to validate its efficacy and safety.[23,24]

2. VITAMINE E:

Vitamin E is a group of eight fat-soluble compounds that include four tocopherols and four tocotrienols. Among these, alpha-tocopherol is the most biologically active form and is most commonly found in the human diet. This nutrient is important for various bodily functions, because of its potent antioxidant properties. Vitamin E plays a vital role in protecting cell membranes from oxidative damage caused by reactive oxygen species (ROS), By neutralizing these harmful molecules, Vitamin E helps prevent the lipid peroxidation process that can damage cell membranes and other critical structures in the body. Vitamin E present in a variety of foods, particularly in vegetable oils such as wheat germ oil, sunflower oil, and safflower oil. It is also been produced in nuts, seeds, green leafy vegetables (such as spinach and broccoli), and some fruits Additionally, Vitamin E is available as a dietary supplement in both natural (d-alpha-tocopherol) and synthetic (dl-alpha-tocopherol) forms, with the natural form being more bioavailable. cell membranes from damage caused by reactive oxygen species (ROS).[25,26,27]

Vit E in neurodegenerative disease: A special characteristic of Vitamin E is its capability to cross the blood-brain barrier (BBB). This allows it to produce its antioxidant and anti-inflammatory effects directly within the central nervous system (CNS). By maintaining the health of neuronal cells and supporting overall brain function, Vitamin E shows its effective role as promising therapeutic agent for neurodegenerative diseases.[27,28,29]

Lipid Peroxidation Inhibition by Vitamin E: Lipid peroxidation is a process where free radicals, particularly reactive oxygen species (ROS), attack lipids containing carbon-carbon unsaturated compounds, leading to cellular damage and cellular dysfunction. This oxidative degradation can have severe consequences, especially in neuronal cells, contributing to neurodegenerative diseases. The process begins with the production and accumulation of free radicals, which can be generated by different

mechanisms, including mitochondrial dysfunction, inflammation, and exposure to environmental toxins pollutants, etc. These free radicals, such as hydroxyl radicals and peroxyl radicals, initiate the lipid peroxidation chain reaction by abstracting a hydrogen atom from a lipid molecule, creating a lipid radica1[27]. Once the lipid radicals are formed, they react with oxygen to produce a lipid peroxyl radical. This lipid peroxyl radical can then extract a hydrogen atom from another lipid molecule, creating a new lipid radical and a lipid hydroperoxide1. This chain reaction of lipid peroxidation can be terminated by antioxidants, which neutralize free radicals and prevent further propagation. Vitamin E, particularly alpha-tocopherol, plays a crucial role in this termination process1. As a lipid-soluble antioxidant, Vitamin E is embedded within the cell membrane, where it can directly interact with lipid radicals and peroxyl radicals. Vitamin E inhibits lipid peroxidation through its ability to donate a hydrogen atom to lipid peroxyl radicals, converting them into non-reactive lipid hydroperoxides[29]. This action terminates the chain reaction, preventing further oxidative damage to the cell membrane1. Additionally, Vitamin E can regenerate itself by accepting a hydrogen atom from other antioxidants, such as Vitamin C, allowing it to continue its protective role. By inhibiting lipid peroxidation, Vitamin E helps maintain the integrity of neuronal cell membranes, protecting them from oxidative damage. This is particularly important in the context of neurodegenerative diseases, where oxidative stress and lipid peroxidation are key contributors to neuronal damage and cell death. Studies have shown that Vitamin E supplementation can reduce oxidative stress and improve neuronal survival in models of Alzheimer's disease and Parkinson's disease[30]

3. RESVERATROL:

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring polyphenolic compound renowned for its diverse biological activities. This compound is predominantly found in grapes (Vitis vinifera), various berries, peanuts, and certain medicinal plants, with Japanese knotweed (Polygonum cuspidatum) being a significant source. It exists in two isomeric forms: cis-resveratrol and trans-resveratrol, out of which the trans form being the most biologically active and stable[31].

The primary dietary sources of resveratrol include:[31]

- **Grapes**: Particularly concentrated in the skins and seeds. This is why red wine, made from whole grape fermentation, contains higher levels of resveratrol compared to white wine.
- **Berries**: Such as blueberries, cranberries, and mulberries, which contain varying levels of resveratrol.
- **Peanuts**: Both raw and boiled peanuts are good sources of this compound.
- **Japanese Knotweed**: A medicinal plant used extensively in traditional medicine, particularly noted for its high resveratrol content

Antioxidant Properties:.It is celebrated for its potent antioxidant properties, which enable it to neutralize free radicals and reduce oxidative stress[32]. This ability is crucial in protecting cells from damage and reducing inflammation[33]. Resveratrol achieves this by scavenging reactive oxygen species (ROS) and upregulating antioxidant enzymes such as superoxide dismutase (SOD) and catalase[34].

Activation of SIRT1 Pathway: Sirtuins are a family of proteins that regulate various cellular processes, including aging, inflammation, and stress resistance. SIRT1, a member of this family, is particularly important due to its role in cellular regulation and its potential therapeutic effects1. Resveratrol has been shown to activate SIRT1, leading to various beneficial effects on cellular health and longevity[34].

Mechanisms of SIRT1 Activation: Resveratrol activates SIRT1 through several mechanisms. One of the primary mechanisms is the increase in NAD+ levels, which is a cofactor required for SIRT1 activity1. Resveratrol enhances the activity of enzymes involved in NAD+ biosynthesis, leading to higher NAD+

levels and subsequent activation of SIRT1. This activation results in the deacetylation of target proteins, which can influence various cellular processes[34,35].

Cellular Regulation: SIRT1 plays a crucial role in cellular regulation by modulating gene expression, DNA repair, and metabolism. Resveratrol-induced activation of SIRT1 leads to the deacetylation of transcription factors such as p53, FOXO, and NF-κB, which are involved in cellular stress responses, apoptosis, and inflammation1. This deacetylation can promote cell survival and reduce oxidative stress, contributing to the overall health of the cell[35].

DNA Repair: SIRT1 is involved in DNA repair processes, and its activation by resveratrol can enhance the cell's ability to repair DNA damage. This is particularly important in the context of aging and neurodegenerative diseases, where DNA damage accumulates over time1. By promoting DNA repair, resveratrol can help maintain genomic stability and prevent the onset of age-related diseases[35].

Cell Survival and Longevity: Resveratrol's activation of SIRT1 has been linked to increased cell survival and longevity. Studies have shown that SIRT1 activation can extend the lifespan of various organisms, including yeast, worms, and mice1. This effect is thought to be due to the improved cellular stress resistance and metabolic regulation provided by SIRT1 activation[35].

Mitochondrial Function: SIRT1 also plays a role in regulating mitochondrial function, and its activation by resveratrol can enhance mitochondrial biogenesis and function. This is important for maintaining cellular energy levels and reducing oxidative stress1. Resveratrol-induced SIRT1 activation can improve mitochondrial function, leading to increased ATP production and reduced ROS levels[34,35].

Neuroprotective Effects: Resveratrol's activation of SIRT1 has shown promising neuroprotective effects in various models of neurodegenerative diseases. SIRT1 activation can reduce protein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction, which are hallmark features of diseases such as Alzheimer's, Parkinson's, and Huntington. These effects contribute to improved neuronal function and survival[36].

Anti-inflammatory Effects: Resveratrol exhibits significant anti-inflammatory properties by inhibiting the expression of pro-inflammatory cytokines and enzymes like cyclooxygenase (COX)[32]. This makes resveratrol a potential therapeutic agent for conditions characterized by chronic inflammation, such as cardiovascular diseases and neurodegenerative disorders[32]. Resveratrol reduces inflammation by modulating the NF-κB pathway, which is a key regulator of the inflammatory response.

4. VITAMIN C:

Vitamin C, commonly known as ascorbic acid, is an indispensable nutrient vital for numerous bodily functions. It stands out as a powerful antioxidant, protecting cells from damage caused by free radicals—unstable molecules that can harm cellular components and contribute to aging and diseases. Vitamin C is particularly crucial for the central nervous system (CNS), aiding in neuronal maturation, differentiation, myelin formation, and neurotransmitter synthesis. By neutralizing reactive oxygen species (ROS) and preventing oxidative damage, Vitamin C ensures the maintenance of these critical processes. Research indicates that Vitamin C can cross the blood-brain barrier and accumulate in brain tissues, thus offering a protective shield against oxidative stress.[37].

Mechanism of vit C in neurodegenerative disease:

Modulation of NF-κB Pathway: Vitamin C inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, a critical regulator of inflammation. Activation of NF-κB leads to the transcription of various pro-inflammatory genes. By modulating this pathway, Vitamin C reduces the

expression of inflammatory mediators, thereby protecting neurons from inflammatory damage. Vitamin C activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Nrf2 is a transcription factor that regulates the expression of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and catalase. These enzymes play a crucial role in detoxifying ROS and protecting cells from oxidative stress. Activation of the Nrf2 pathway by Vitamin C enhances the cellular defense mechanisms against oxidative damage[40].

Promotion of Neuronal Differentiation and Maturation: Vitamin C is essential for the proper functioning of the central nervous system (CNS), including neuronal maturation and differentiation. It plays a critical role in the synthesis of neurotransmitters such as dopamine, norepinephrine, and serotonin. Adequate levels of Vitamin C are necessary for the development and maintenance of healthy neurons[38].

Myelin Formation: Vitamin C is involved in the formation of myelin, the protective sheath around nerve fibers. Myelin is crucial for the efficient transmission of electrical impulses in the nervous system. By supporting myelin formation, Vitamin C helps maintain the integrity and function of nerve cells[39].

Inhibition of Apoptosis: Vitamin C helps prevent apoptosis (programmed cell death) in neurons. Apoptosis is a common feature of neurodegenerative diseases, and excessive apoptosis can lead to the loss of neuronal cells. Vitamin C inhibits the activation of apoptotic pathways, thereby promoting neuronal survival [38,39]

Enhancement of Mitochondrial Biogenesis: Vitamin C has been shown to enhance mitochondrial biogenesis, the process by which new mitochondria are formed. This helps to increase the number of functional mitochondria in cells, improving overall cellular energy production and reducing the likelihood of mitochondrial dysfunction[37]

CONCLUSION:

The exploration of natural antioxidants in the management of neurodegenerative diseases has revealed promising potential in mitigating the effects of these debilitating conditions. Antioxidants such as vitamins C and E, resveratrol and, curcumin have shown significant neuroprotective effects by combating oxidative stress, reducing inflammation, and enhancing mitochondrial function. These compounds help protect neuronal cells from damage, preserve cognitive function, and improve overall brain health. The antioxidant properties of these natural compounds are crucial in neutralizing reactive oxygen species (ROS) and preventing oxidative damage to neurons. Their anti-inflammatory effects further contribute to their neuroprotective capabilities by reducing the production of pro-inflammatory cytokines and modulating inflammatory pathways. Additionally, these antioxidants support mitochondrial health by reducing oxidative stress, promoting mitochondrial biogenesis, and preserving ATP production, which is essential for maintaining cellular energy levels and preventing apoptosis.

In conclusion, natural antioxidants offer a promising avenue for the prevention and treatment of neurodegenerative diseases. Their ability to protect neurons from oxidative stress, reduce inflammation, and support mitochondrial function makes them valuable candidates for further investigation. Continued research and clinical validation are necessary to translate these findings into effective antioxidant-based therapies for patients suffering from neurodegenerative diseases.

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