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Neuroprotective Role of Polyphenols in Treatment of Neurological Disorders: A Review

Mudasir Maqbool [1,*] and Mehrukh Zehravi [2]

[1] Research Scholar, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India
[2] Department of Clinical Pharmacy Girls Section, Prince Sattam Bin Abdul Aziz University Alkharj, Saudia Arabia

[*] *Corresponding author*: Research Scholar, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India. Email: bhatmudasir92@gmail.com

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Abstract

The most frequent illnesses characterized by the gradual malfunctioning of brain neurons are neurodegenerative disorders (NDs). Genetic mutations and a range of biological processes can produce NDs. Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS) are all related to oxidative stress (OS). Reduced brain activity has become a greater health threat with a growing elderly population. It causes some pathophysiological alterations and is an important risk factor for a range of neurodegenerative illnesses. An increase in reactive oxygen species (ROS) can cause neuronal cell death, and it is thus essential to control ROS levels to maintain normal neuronal activity. Synthetic medicines are often used to treat neurological disorders; however, harmful effects have been reported. Multiple bodies of research have shown the effectiveness of polyphenols in the treatment of various NDs due to their negligible side effects. This review article describes the neuroprotection effects of polyphenols such as resveratrol, epigallocatechin-3-gallate, curcumin, and quercetin, as well as the signaling pathways and immune response controls through polyphenols.

Keywords: Curcumin, Parkinson's Disease, Resveratrol, Alzheimer's Disease

1. Context

Neurodegenerative disorders (NDs) are a global problem for which no effective therapy or cure is possible. Neurodegenerative disorders are the most common in the elderly. Globally, the number of elderly people with NDs has increased, leading to more deaths. The most common NDs in elders are Parkinson's disease (PD), Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). Roughly, 13.26% of the population of China is more than 60, with more than five million people suffering from Alzheimer's disease.

Several reasons complicate the evaluation of neurodegenerative diseases with atrophic changes in brain aging. Many biological factors such as oxidative stress, mitochondrial malfunction, neuronal and glial inflammation, proteins accumulation, and apoptotic pathways activation lead to pathogenesis of these disorders. Because neurodegenerative disorders advance slowly, there is no conclusive treatment option to stop the illness development of these disorders (1-5). Flavonoids were the widely used phytochemicals with distinct therapeutic characteristics in the past few decades. Polyphenols are plant-based phenolic compounds, some of which are accessible in ether or ester forms. Polyphenolic substances contain pharmaceutical flavonoids such as epigallocatechin, catechin, epigallocatechin gallate, and flavonoids such as quercetin and luteolin. Flavonoids are important metabolites found in a wide range of foodstuffs and medicinal plants. Polyphenols have anticancer, antiviral, antioxidant, and antibacterial characteristics. As a result, polyphenolic compounds are acclaimed for some conditions, including neurological issues, as natural remedies.

A variety of sources of polyphenolic compounds have been demonstrated to increase cognitive functioning and minimize brain neuropathy through a variety of mechanisms. The capacity of these components to treat brain diseases is determined not only by their ability to reach the brain and its chemical structure or direct interaction with brain cells or neurons but also by their ability balance the connection between the brain and other neurological axes. According to preclinical research, these bioactive components are protective against illnesses of the brain such as autism, Down's syndrome, neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, and psychiatric disorders such as anxiety and sadness (6-13).

2. Polyphenols in Neurological Disorders

2.1. Alzheimer's Disease

Alzheimer's disease (AD) is a neurological condition that causes cognitive impairment and loss of memory. Prescribed AD drugs currently provide symptomatic alleviation. If used regularly, there may be substantial responses or bad effects. Natural substances are a preferred alternative to commercial AD medicines. Polyphenols are plant-based secondary antioxidant and neuroprotective metabolites. The development of polyphenols in neurological illness treatment is hindered by their complicated bioactivity and brain absorption. Polyphenol dietary intake has been developed to minimize OS, modify signaling pathways, and decrease the risk of AD through boosting cognitive capacities. Some scientific research has indicated that everyday polyphenols have favorable effects on the pathophysiology of AD. Tau protein-amyloid accumulates in AD, and tau protein-hyperphosphorylation in neurons is induced by intracellular neurofibrillary engravings (NFT). They occur mostly in the hippocampus and brain cortex, which cause neuronal degeneration (14-19). The formation of amyloid aggregated protein in the brains of AD patients causes inflammation and oxidative damage. Two further reasons for this syndrome include cholinergic neurotransmission depletion and excessive glutamatergic neurotransmission.

Curcumin is a key polyphenol present in turmeric. Turmeric powder comprises the turmeric plant's yellow-orange part. Due to its various bioactivities and absence of unwanted effects, curcumin has gained more attention during the last few decades. In ancient times, it was used in India to cure some diseases. Curcumin is a strong antioxidant, anti-cancer, and anti-inflammatory agent. Curcumin can be consistent with amyloid-beta (Aβ) by overcoming the kappa B nuclear factor (NF-$\kappa\beta$), which allows this polyphenol to halt the degenerative AD process. Curcumin is also a lipophilic substance that can easily overpass the blood-brain barrier and join plaques to limit the aggregation and dispersion of amyloid peptides. Increasing data suggest the way that PI3K/Akt/GSK-3β flags are directly influenced by Aβ and AD-brain alterations. Neurotrophins engage in the PI3K/Akt signaling pathway to ensure neuronal continuity and plasticity. Their act may be activated by neurotrophic factors coming from the brain (BDNF). According to Kim et al. (2005) review, curcumin is the most powerful antioxidant, with around 214 antioxidant compounds. Curcumin improved cognitive impairments in elderly rats (20-28).

Resveratrol is the most important non-flavonoid present in red wine, almonds, and grapes. A wide spectrum of pharmacological activity has been examined, including anti-inflammatory, antioxidant, anti-carcinogenic, and anti-mutagenic properties. Most models of AD are in vitro and in vivo. Resveratrol has proven to be neuroprotective. Besides its antioxidant and anti-inflammatory characteristics, research shows that resveratrol helps divide the non-amyloidogenic amyloid precursor protein (APP). It also helps eliminate neurotoxic amyloid-beta (Aβ) peptides that play a crucial role in the prevention and development of AD pathophysiology. Resveratrol also lowers neuronal cell loss through some additional mechanisms, the main one being NAD+-dependent histone-deacetylase enzymes known as sirtuins. Resveratrol can be used as a non-oxidant agent due to decreasing ROS formation, raising the magnitude of GSH and intracellular Ca21 in neurons, and changing the way of second messengers, calcium-dependent AMP-activated protein (cAMP), and nitric oxide (29-33). Resveratrol attaches to the plaques of Aβ and leads to the removal of the Aβ peptide, and also prevents AChE activity in in vitro cells.

Green tea includes several epigallocatechin 3-gallates, a reasonably common flavonoid of catechin. Besides, EGCG has antioxidant and some pharmacological properties and was examined in neurological diseases, atherosclerosis, and cancer. This component has gained a great deal of interest for its potential to prevent neurodegeneration in recent decades. It is noteworthy to see that NDs are negatively related to tea drinking. The administration of D-gal in AD models has a crucial role in reducing Aβ according to studies of AD models supplied with EGCG. A study indicated that EGCG administration helped avoid brain neuron death by reducing the activity of NF-$\kappa\beta$ and Extracellular Receptor Kinase (ERK) and decreasing the concentrations of β- and γ-secretases (i.e., APP cleaving enzymes) (34-39).

2.2. Parkinson's Disease

Parkinson's disease is the most frequent human neurodegenerative disorder after AD. The dopaminergic neurons in the substantial pars compacta (SNpc) degrade because of a breakdown in motor and cognitive abilities, leading to PD. The aggregation in the cytoplasm of a selected neuron of protein inclusions containing alpha-synuclein and ubiquitin leads to the creation of marked lesions known as Lewy structures, which causes neuronal death. Medications used to treat AD and PD nowadays do not stop neurodegenerative processes but just reduce the symptoms. A neurodegenerative disease characterized by neurocyte loss in hippocampal tissues and cognitive impairment is a clinically complex neurodegenerative disease. Hippocampal brain loss inhibition is a promising strategy for PD treatment. When compared to Caucasians, the use of turmeric/curcumin is hypothesized as an explanation for India's low prevalence of AD and PD (40-45). The findings show that Indian brains have about 40% fewer melanized nigral neurons than Caucasian brains. The decreasing prevalence of PD in India is therefore associated

with dietary choices. Turmeric intake protects against diseases such as diabetes and cancer. Recent research has shown that curcumin has a neuroprotective impact in lowering the cytotoxicity caused by cadmium. Curcumin has proven to be an efficient treatment for PD induced by homocysteine in rats. Curcumin was reported to assist neuronal regeneration in a PD model by activating the signaling pathways of Trk/PI3K, which elevates the BDNF level. The main biological function of curcumin is its antioxidant impact. The antioxidant impact of curcumin raises the levels of striatal dopamine, protects neurons, and chelates SN and Fe^{2+} in the 6-hydroxy dopamine (6-OHDA) PD rat model. Phenolic rings and diketone groups of curcumin limit the formation of OH^{-}, H_2O^{2-}, and superoxides (46-50). Curcumin has been effectively investigated in various models of PD. Curcumin therapy promotes mitochondrial protection with direct impacts on therapy in a range of PD models. Curcumin therapy enhances Cu/Zn SOD, rescues mitochondrial membrane potential, and restores cell survival in MES 23.5-treated cells with 6-hydroxy dopamine (6-OHDA). The density of dopaminergic neurons may be increased by curcumin therapy in SN. According to prior research, curcumin's neuroprotective activity was linked to neurogenesis. Resveratrol was found to have protective effects in a PD rat model generated by 6-OHDA. Chronic inflammation, oxidative stress, mitochondrial malfunction, and dopaminergic loss of the neuron are all expected to occur in the substantial nigra. Resveratrol promotes a reduction in cyclooxygenase (COX-2) and tumor necrosis factor mRNA concentrations. The expression of the COX-2 protein in substantial nigra is also diminished. Resveratrol can inhibit the expression of pro-inflammatory enzymes (COX-2) and cytokines (TNF-α) that interfere with the synthesis of prostaglandins (e.g. COX-2) (51-55). Substantial nigra injection of 6-OHDA induces the death of dopamine neurons that may imitate the early stages of PD. Besides, COX-2 and TNF-α mRNA over-expression is a cause of PD. Following resveratrol administration, the levels of COX-2, TNF-α mRNA, and protein lowered in a rat model of PD. Therefore, it is notable that resveratrol has positive effects on PD generated by 6-OHDA in rats. These effects can be produced by a reduction in the expression of COX-2, TNF-α mRNA, and protein. More research is needed to employ resveratrol for the treatment of PD. The stimulation of microglia is decreased when quercetin is administered by 1-methyl-4-phenylpyridinium (MMP; a forerunner to PD pathogenesis). In PD, the model cell quercetin destroys the cell, but such metabolites do not influence cell survival due to their restricted absorption (54, 56-60).

2.3. Ischemic Stroke

Stroke is the world's third-biggest cause of mortality. By changing our diet to contain more polyphenols, we can lessen the likelihood and severity of stroke. Several models were employed to detect whether various polyphenols have excellent advantages. Green tea is a major polyphenol source. Hypoxia generates ischemic damage, which promotes inflammation and neuronal damage. Green tea polyphenol, EGCG, has shown neuroprotective effects in the brain ischemia mouse model via reducing metalloproteinase (MMP) matrices. Green tea polyphenols are found to protect neurons against the damage caused by hypoxia, modulating the inflammatory cascade and limiting the potential for trans-membrane degeneration. Quercetin plays a vital role in avoiding ischemic injury by lowering lipid peroxidation and ion channel acid sensing, both contributing to the dysregulation of the ion channel. With the same antioxidant analyses as green tea polyphenols, quercetin condenses the amount of MMP-9 in tests for cerebral ischemia (CI) and lowered blood-brain interference (61-65). Rutin inhibits p53, a protein that promotes stroke necrosis and thus limits neuronal damage in cerebral ischemia. Glutathione peroxidase and glutathione reductase reduce inflammatory cytokines in ischemic stroke model rats. Baicalin, a type of flavonoid, has been demonstrated to diminish ischemic stroke damage, p38 mitogen-activated protein kinase (MAPK), oxidative stress, caspase-3, and the toll-like receptor (TLR2/4) pathway by inhibiting these pathways (66-69).

2.4. Multiple Sclerosis

Multiple Sclerosis (MS) is a highly threatening and disabling disease that destroys the nerve sheath of myelin, causing lifelong nerve damage. It has an effect on how the body functions, especially the limbs and extremities. Multiple sclerosis is the most common non-traumatic disabling disorder that affects young individuals. Multiple sclerosis is becoming more widespread over the world, as is its economic impact. Despite that complex gene-environment interactions are likely to play a significant role, the underlying etiology of MS and the mechanisms driving an increase in patients are unknown. According to MS epidemiology, low blood vitamin D levels, smoking, childhood obesity, and infection with the Epstein–Barr virus all have a part in the disease's progression. Thanks to breakthroughs in diagnostic techniques and criteria, people with MS can now be detected earlier in their illness courses. In addition, the number, efficacy, and risk of MS treatments have all increased dramatically. A diagnosis of 'pre-symptomatic MS' is now possible, which could lead to the exploration of new preventive medicines (70, 71).

3. Multiple Sclerosis Therapies

Symptoms can be decreased, and the immune system can be improved with a doctor and a complete and effective treatment. Polyphenols are one of the therapeutically helpful chemicals for MS treatment. Resveratrol,

quercetin, epigallocatechin-3-gallate, and myricetin are some of the polyphenols utilized for MS treatment due to their advantages and efficacy. Polyphenols are examined according to many models for MS treatment by reducing inflammation and breaking the immune system. Polyphenols demonstrated to be able to reduce inflammation by modifying the cytokine pathways in various studies (for example, IL-β and TNF-α). In this method, brain demyelination is reduced, and normal limb function is restored. Polyphenols can be utilized in age-related MS and amyotrophic lateral sclerosis as prophylactics, keeping their effectiveness in mind (72-74).

4. Conclusion

Polyphenols are highly effective in both therapeutic and pharmacological settings. They can be found in a wide range of fruits and dietary meals. Various polyphenols have been studied for their impact on neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Neurodegenerative diseases are driven by inflammation, oxidative stress, and abnormal mitochondrial function, according to new research. For the treatment and prevention of many disorders, new therapeutic approaches that target specific genes and proteins are required. Inflammation, ion channels, reactive oxygen species (ROS), and neurotransmitters are all controlled and regulated by polyphenols. Antioxidant capabilities are found in polyphenols. Neuroprotective effects are found in polyphenols, including EGCG, resveratrol, and quercetin. Polyphenols have been shown to activate antioxidant pathways such as Nrf2 in numerous studies. Polyphenols can also block the NFB and STAT signaling pathways. Polyphenols control the immune response by inhibiting proinflammatory cytokines, including TNF-α and IFN-γ. Polyphenols do, in fact, provide neuronal damage prevention.

Footnotes

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