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Neuroprotective Role of Polyphenols in the Treatment of Neurological Disorders

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ABSTRACT

Neurodegenerative diseases (NDs) are most common disorders that are mostly described by progressive dysfunctioning of the neurons in the brain. Genetic mutations and various biological processes can lead to the NDs. The NDs like Alzheimer's (AD), Parkinson's (PD) and Multiple sclerosis (MS) are related to the oxidative stress (OS). Reduction of the neuronal activity with increasing the elderly population has become greater health problem and causes numerous pathophysiological alterations and it is crucial risk aspect for many of neurodegenerative diseases. Raised levels of the (ROS) reactive oxygen species can lead to the death of neuronal cell therefore, decreased levels ROS are significant to retain the normal functions of the neurons. Indeed, the synthetic drugs are widely used to treat the neurological disorders but they are shown to have the side effects. In the treatment of various NDs, benefits of using the polyphenols have been suggested by the various studies because of their minute side effects. In this review, neuroprotective effects of the polyphenols like resveratrol, epigallocatechin-3-gallate, curcumin, and quercetin in PD, AD and MS and signaling pathways as well as regulation of the immune response via polyphenols are discussed.

Keywords: Alzheimer's disease, Curcumin, Multiple sclerosis, Parkinson's disease, Resveratrol

1. INTRODUCTION

Neurodegenerative diseases (NDs) are a worldwide problem as there is no accurate treatment/cure for it. NDs are the most common between older people [1]. The rate of elder people suffering from the NDs is increasing globally which is further leading to death [2]. The most common NDs found in elderly people are Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [3]. About 13.26 % of China's population is above the age of 60 and above 5 million have the AD-related dementia. The 2 million of the PD and many other linked neurological disorders [4]. There are many factors which are tangled in the evaluation of the neurodegenerative diseases with atrophic changes in brain aging. Many biological agents like oxidative stress, impairment in mitochondria, inflammation of neurons and glials, accumulation of protein products and apoptotic

pathways activation [5]. There is no definite therapeutic intimation to terminate the progression and enhancement of disease in the patients due to the slow development of the neurodegenerative diseases. [6]. Flavonoids are extensively used phytochemicals that have distinctive therapeutic effects in the last few decades [7].

Polyphenols are plant-extracted phenolic compounds, some of which exist as their ether or ester forms. Polyphenolic compounds includes mixes of different class of phenolic aggravates that incorporate flavanoids, for example, epigallocatechin, catechin, epigallocatechin gallate, and flavonoids, for example, quercetin and luteolin, as pharmaceutically significant compounds [8]. Flavonoids are important metabolites and naturally present in fruits and medicinal plants [9]. Polyphenols have different bioactivities like antitumor, anti-inflammatory and antioxidant and antimicrobial efficacy [10]. Due to which, Polyphenolic compounds have viewed as the natural sources for treatment of various illnesses, like neurological disorders. Evidences show that polyphenolic compounds of various sources, are able to improve the cognitive functions and decrease brain neuropathology through the multiple mechanisms [11]. The capacities of these components to treat brain diseases not only depending on their ability of reaching to the brain or on their chemical structure, or directly their interaction with the brain cells or neurons, but also have ability to balance the connection among brain and gut to interfere with many branches of axis [12]. According to the Preclinical studies, these bioactive components have protective effects in brain disorders, for example, neurodevelopmental diseases like Autism spectrum disorder and Down's syndrome, neurodegenerative like PD, AD and the psychiatric disorders like anxiety and depression [13].

2. POLYPHENOLS IN NEUROLOGICAL DISORDERS

2.1. Alzheimer's Disease (AD)

AD is a neurodegenerative disease, which causes intellectual impedances and loss of memory. At present recommended drugs for the AD provide symptomatic comfort. If these are taken continuously they may causes serious reactions or side effects. For the Alzheimer's disease treatment natural products are better alternatives for the present synthetic medicines [14]. Polyphenols are normally secondary metabolites extracted from plants which have great anti-oxidant and neuroprotective properties [15]. The advancement of polyphenols in treatment of the neurological issues are prevented due to their complex nature with respect to their bioactivity and the bioavailability in the brain [16]. Dietary admission of the polyphenols has been setup to decrease the OS, regulate the signaling pathways and diminish the risks of Alzheimer's disease (AD) through increasing the intellectual functions [17]. A few scientific reports have shown that the regular use of polyphenols display positive outcomes for AD pathology [18]. AD is marked by accumulation of the extracellular proteins β-amyloid and the intracellular neurofibrillary tangles (NFT) constitute the hyper phosphorylation of tau proteins in neurons. They are mainly situated in the brain regions of hippocampus and cerebral cortex, causing to the neuronal degradation [19]. The deposition of aggregated β-amyloid protein in the brain of AD patients causes inflammation and oxidative stress. The depletion of cholinergic and high glutamatergic neurotransmission are the other reasons for the occurrences of this disease [20].

In turmeric, Curcumin (diferuloylmethane) is found which as a key polyphenol. It is the yellow, orange part of the turmeric, present in the turmeric powder [21]. In present decades, more attention is given on curcumin due to its different bioactivities without any side effects. In ancient times, it was used in Indian for the treat different disorders [22]. Curcumin can

function as a strong antioxidant, anticancer, and antiinflammatory compound. [23]. A known method of working for the curcumin in the AD is that it can cohere to amyloid beta (Aβ) by defeating nuclear factor kappa B (NF-ϰβ), granting this polyphenol the potential to less AD pathological process [24]. In addition, curcumin is mostly a lipophilic compound which can simply cross blood brain barrier, join the plaques, stops aggregation and the disaggregation model of the amyloid peptide [25]. Enhancing proofs suggests that PI3K/Akt/GSK-3β flagging way is directly affected by the Aβ showing and is change in AD brains [26]. Neurotrophins turn on the PI3K/Akt signaling pathway to check neuronal continuity and plasticity. Brain-derived neurotrophin factors (BDNF) can activate Akt [27]. A review by Kim et al. (2005) suggested that nearly 214 compounds that have anti-oxidant effects and curcumin show greatest capacity towards the Aβ. In old mice, upon directing of the curcumin, the cognitive paucity was improved [28].

Resveratrol is the most important non-flavonoids present in the red wine, nuts and grapes [29]. Resveratrol has majorly examined to have a broad spectrum of the pharmacological characteristics like anti-inflammatory, antioxidant, anti-carcinogenic, and anti-mutagenic properties [30]. Mostly *in vitro* and *in vivo* models of the AD Resveratrol has showed neuroprotective outcomes. Aside from its important antioxidant and anti-inflammatory character, evidence indicates that resveratrol also ease non-amyloidogenic division of amyloid precursor protein (APP). It facilitate removal of neurotoxic amyloid beta (Aβ) peptides, an important part in preventing and declining AD pathology [31]. Resveratrol also decrease the loss of neuronal cells through different types of extra mechanisms, most importantly the working of NAD+-dependent histone deacetylases enzymes, named sirtuins [32]. Resveratrol can work as antioxidant by extinguishing ROS production, enhancing the magnitude of GSH and intracellular Ca21 in the neurons by changing mode of the second messengers, calcium-dependent AMP-activated protein kinase (cAMP) and nitric oxide [33]. Resveratrol mostly adhere with the Aβ plaques that lead to the removal of the Aβ peptide and it also resist the activity of the AChE the in vitro cells. [34].

Epigallocatechin-3-gallate are extensively present in green tea and is very common flavonoid of the catechins [35]. EGCG has an antioxidant potential with range of the pharmacological properties and has been put through to the various studies in the neurodegenerative diseases, atherosclerosis and the cancer [36]. In the last few decades, this component has bring lot of attention due to its potential to impede the neurodegeneration. It is very interested that existence of the NDs is inversely related to the utilization of the tea [37]. In studies of AD models experiments where EGCG was given, declare that administration of the drug D-gal in the AD models have played a key role in the lowering of the Aβ [38]. A study exhibited that administration of the EGCG can leads to the deterrence of neuronal cell death by suppressing activity of the nuclear factor kappa B (NF-ϰβ) and extracellular receptor kinase (ERK) and reduced level of the β- and γ-secretases [i.e. amyloid precursor protein (APP) cleaving enzyme] [39].

2.2. Parkinson's Disease (PD):

Parkinson's disease (PD) is most common second human neurodegenerative disorder after the Alzheimer's disease. PD is caused due to the dysfunctioning of the motor and cognitive functions that leads to the deterioration of the dopaminergic neurons in the substantia nigra pars compacta (SNpc) [40]. Trademark lesions called Lewy bodies are created due to the continuous aggregation of protein inclusions that contains α-synuclein and ubiquitin in the selected neuron's cytoplasm that cause their death [41]. The drugs that are used recently for treatment

of AD and PD are not able to stop the neurodegenerative processes but they only reduce the symptoms of these disorders [42]. PD is clinically complex neurodegenerative disease that is involved in neurocyte loss in hippocampal tissues or impairment in brain [43]. For treatment of PD, the inhibition of hippocampal cell loss in the brain is a promising strategy [44].

By comparing the Indian with Caucasians, it is suggested that the utilization of turmeric/curcumin may be the reason for low occurance of AD/PD in India [45]. It is reported by the study that there is about 40% less melanized nigral neurons in the Indian brains than Caucasian brains [46]. Therefore, in India the lower prevalence of PD is linked to dietary habits. Consumption of the turmeric gives the antioxidant defense against different diseases like diabetes and cancer [47]. It is suggested by the recent reports that the curcumin has neuroprotective role that is beneficial from decreasing of cadmium-induced cytotoxicity. Curcumin has been demonstrated to be the potent treatment for the homocystein induced PD rat model [48]. It has been observed in a PD model that, by the activation of Trk/PI3K signaling pathways, curcumin can avail in the regeneration of the neurons which increase the levels of BDNF [49]. Antioxidant activity is the most important biological activity of curcumin. In the 6-hydroxy dopamine (6-OHDA) rat model of the PD, antioxidant activity of curcumin enhance the level of striatal dopamine, preserve the SN neurons and chelates the Fe^{2+}. Curcumin stop formation of OH^-, H_2O_2, and superoxide due to having the phenolic rings and diketone groups [50]. In the different toxic models of PD, Curcumin has successfully been tested. Curcumin therapy offers the mitochondrial insurance in various PD models with the direct bearing on the treatment. In 6-hydroxy dopamine (6-OHDA) treated MES 23.5 cells, Treatment of curcumin enhance the Cu/Zn SOD, restores the membrane potential of mitochondria and it also restores the cell viability [51]. Treatment with curcumin in the SN could enhance the density of the dopaminergic neurons [52]. The earlier reports suggested that curcumin neuroprotection ability is probably due to the neurogenesis [53].

Resveratrol has been found to present the protective effects in 6-OHDA induced rat model of the PD. This model presumes the chronic inflammation, oxidative stress, mitochondrial impairment, and dopaminergic neuron loss in substantia nigra. Reduction in the level of cyclooxygenase (COX-2) and in tumor necrosis factor- α mRNA occurs due to the treatment resveratrol. It also reduces COX-2 protein expression in the substantia nigra [54]. Resveratrol has ability to decrease the expression of pro-inflammatory enzymes (COX-2) and pro-inflammatory cytokines e.g. TNF-α that intervene the production of the prostaglandins (e.g. COX-2) expression [55]. Dopamine neuron damage occurs due to the injection of 6-OHDA into the substantia nigra that can imitate the early phase of Parkinson's disease [56]. Mechanism of Parkinson's disease is due to the over expressions of the COX-2 and TNF-α mRNA. COX-2 levels, TNF-α mRNA levels and protein were decreased in the Parkinson's disease model rats after the resveratrol treatment. Therefore it is profound that resveratrol has advantageous effects on the 6-OHDA-induced Parkinson's disease in rats. These effects may be due to the lowering of the expressions of the COX-2, TNF-α mRNA and the protein. Further investigation is required for resveratrol applications in the Parkinson's disease treatment. [57].

1-methyl-4-phenylpyridinium MMP (precursor for pathogenesis of PD) stimulate microglia activation is diminished by the administration of quercetin [58]. Studies also exhibit that due to the stimulation superoxide dismutase (SOD), glutathione peroxidase (GPx), Na (+), and K (+)-ATPase, the quercetin

provides neuroprotection in mice model of PD [59]. In the PD, cell model quercetin terminates the cell while the metabolite such as quercetin-3-O-β-glucuronide didn't influence the cell viability because of its low absorption [60].

2.3. Ischemic Stroke:

Globally the third most cause of death is due to stroke. We can decrease the possibility and harshness of stroke by modifying our food which richly consists of polyphenols [61]. Several models have been studying for checking the beneficial effects of different polyphenols. One such important polyphenol is green tea. We all know that hypoxia leads to the ischemic injury and this injury causes inflammation and neuronal damage. Neuroprotective activity by down regulation of the matrix metalloproteinase (MMP) in the mice model of the cerebral ischemia has exhibited by Green tea polyphenol, EGCG [62]. Polyphenols of green tea have found to play role in the protection of neurons in contradictions of hypoxia-induced ischemic injury via a controlling the process of inflammation cascade and diminishing degeneration in trans membrane potential [63]. To attenuate ischemic injury, quercetin played a crucial role by controlling the peroxidation of lipid in neuron and acid-sensing of ion channel that led to the dysregulation [64]. Quercetin by means of the same antioxidant analysis to polyphenols of green tea has condensed the level of the MMP-9 and reduced the blood-brain barrier interference in the studies cerebral ischemia (CI) [65]. Rutin regulates the neural damage in cerebral ischemia (CI) by the process of p53 down regulation, it is a protein that lead to the stroke necrosis [66]. Glutathione peroxidase and glutathione reductase has also reduced the inflammatory cytokines in the model rodents of the ischemic stroke [67]. By targeting the multiple therapeutic targets such as MMP-9 another type of flavonoid baicalin has also revealed that to diminish the ischemic stroke damage [68], p38 mitogen-activated protein kinase (MAPK), oxidative stress, caspase-3 and by down regulating the toll-like receptor (TLR2/4) pathway [69].

2.4. Multiple Sclerosis (MS):

MS is very harmful disabling disease in which myelin sheath of nerves is affected and resulting in permanent damage of nerves. It affects the functions of body especially limb or extremities [70].

3. MULTIPLE SCLEROSIS THERAPIES

By consulting with doctor and undergoing complete and proper cure, symptoms are reduced and immune system can become better. Therapeutically multiple substances have proven effective in MS treatment, polyphenols are one of them. Different polyphenols like Resveratrol, Quercetin, Eppigallocatechin-3-gallate and myricetin are induced in MS cure for their benefiiency and effectiveness [71]. Different models are studied and they revealed that polyphenols act in therapies of MS by suppressing inflammation and breaking immune system [72]. All the studies show that polyphenols actually have the strong ability which can reduce inflammation by modulating the pathway of cytokines (for example IL-β and TNF- α). In this way, they decrease the neuronal demyelination and make limb activity normal. By keeping the effectiveness of the polyphenols in mind, it is known being suggested that they can be prophylactics in age related MS and amyotrophic lateral sclerosis (ALS) [73].

4. CONCLUSION

Polyphenols are shown to have the great therapeutic efficiencies and pharmacological effects. They are presents in the various fruits and in the dietary foods. Role of different polyphenols have been tested in multiple neurodegenerative disorders like AD, PD and MS etc. Recent studies suggests that

neurodegenerative diseases occur as a result of inflammation, oxidative stress and due to the abnormal functioning of mitochondria. For the treatment and prevention of these disorders requires new therapeutic strategies to target the multiple genes and proteins. Polyphenols take part an important role in control and regulation of inflammation, ion channels, ROS and neurotransmitters. Polyphenols possess antioxidant activities. Polyphenols peculiarly EGCG, resveratrol, and quercetin, have neuroprotective effects. Many experimental studies have suggested that antioxidant pathways like Nrf2 are activated by the polyphenols. In addition, polyphenols have ability to downregulate the NFκB, and STAT pathways. By inhibiting proinflammatory markers e.g. TNF- α, IFN-γ polyphenols regulate the immune response. Polyphenols verily gives protection against the neuronal damage.

5. ACKNOWLEDGEMENT

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6. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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