Role of Polyphenols in the prevention of neurodegeneration

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ABSTRACT

Polyphenols are common secondary metabolites in the plant kingdom; this diverse family of chemical compounds has been extensively studied in pharmacology due to its high biomedical potential and abundance in vegetables and fruits. Within the last years, a rapidly growing number of polyphenolic compounds with neuroprotective effects have been described. Many efforts have been made to explore the mechanisms behind the neuroprotective action of polyphenols. However, many pathways and mechanisms considered for mediating these effects are rather general than specific. Moreover, despite the beneficial effects of polyphenols in experimental treatment of neurodegeneration, little has been achieved in bringing them into routine clinical applications. Among the pharmacological activities attributed to natural polyphenols are antioxidant, anti-inflammatory, antibacterial, anthelmintic, antidiabetic, antiaging and neuroprotective. Interestingly, recent clinical trials have confirmed, some of the overwhelming in vitro pharmacological studies, especially those describing orally administered polyphenols with protective effect against metabolic and neurological diseases. Future studies on this latter area are the next frontier towards expanding the current knowledge on the mode of action of plant-derived compounds, and their metabolites, on human health.

Keywords: Neurodegeneration, polyphenols, antioxidant, neuroprotection

I. INTRODUCTION

Neurodegenerative diseases (ND) include Alzheimer's (AD) and Parkinson's disease (PD) and multiple sclerosis (MS) which primarily affect the neurons in the human brain and are characterized by deterioration of neurons or myelin sheath, sensory information transmission disruption, movement control, and more [1]. The greatest risk factor for ND is aging, which carries mitochondrial dysfunction, chronic immune-inflammatory response, and oxidative stress, the major causes of neuronal damage and death [2]. Nowadays, ND are chronic and incurable conditions whose disabling effects may continue for years or even decades representing an enormous disease load, regarding human suffering and economic cost. Dietary genetic, and molecular factors are important determinants in progression and intervention of neurodegenerative diseases [3]. The ND are more common and have a disproportionate impact on countries with longer life expectancies and represent the fourth highest source of overall disease burden in the high-income countries. Plant secondary metabolites are one of the most important sources of therapeutic drugs and in fact many drugs currently in use are derived from plants. Recently, a number of natural

medicinal plants have been tested for their therapeutic properties, showing that the raw extracts or isolated pure compounds from them have more effective properties than the whole plant as an alternative for the treatment of ND [4]. These properties are due mainly to the presence of polyphenols alkaloids, and terpenes, among others, that are micronutrients produced by plants as secondary metabolites. There is substantial evidence (epidemiological studies, animal studies, and human clinical trials) that indicates that polyphenols reduce a wide range of pathologies [5].

II. POLYPHENOLS

Natural polyphenols are most commonly found chemical compounds in consumed herbal beverage and food. They constitute a large group of phytochemicals with more than 8000 identified compounds [6]. The primary function of these compounds is protection of plants against reactive oxygen species (ROS), produced during photosynthesis, and consumption by herbivores. Within the previous decades, most of the studies on polyphenols have been focused on anti-oxidant properties. Along with introducing resveratrol, as a potential anti-aging agent, much focus has been placed on protective effects of various polyphenols against aging and related neurodegenerative disease. Increase in life span by polyphenols can be associated with increased or improved brain function. For instance, epigallocatechin gallate (EGCG) postponed the onset of neurological symptoms and prolonged life span in a mice model of amyotrophic lateral sclerosis (ALS) [7]. Long term treatment with epigallocatechin gallate increased the life span and enhanced movement abilities in a transgenic Drosophila melanogaster model of Parkinson's disease (PD) [8]. Despite the prominent evidence of neuroprotective effects of polyphenols from in vitro and preclinical models, overall success in bringing these compounds into routine clinical application has been limited. Polyphenols exhibit strong potential to address the etiology of neurological disorders as they, attenuate their complex physiology by modulating several therapeutic targets at once [9]. In particular, signaling pathways like PPAR, Nrf2, STAT, HIF, and MAPK along with modulation of immune response by polyphenols are evaluated by various studies[10].Although current polyphenol researches have limited impact on clinical practice, they have strong evidence and testable hypothesis to contribute clinical advances and drug discovery towards age-related neurological disorders.

The main mechanisms of polyphenols include their well-characterized antioxidant effects, inhibition of intracellular kinases activity, binding to cell surface receptors, and modifying cell membrane functions. A number of in vivo and in vitro studies have shown that polyphenol catechins from green tea extract possess a protective role in neurodegeneration [11]. Pretreatment with the flavonoid epicatechin attenuated neurotoxicity induced by oxidized low-density lipoprotein in mouse-derived striatal neurons, as evidenced by apoptotic DNA fragmentation and caspase-3 activation. Catechin conferred a similar protection to primary culture of mesencephalic neurons challenged with 6-hydroxydopamine (6-OHDA) [12].Tea catechins are powerful hydrogen-donating antioxidants and free radical scavengers of reactive oxygen and nitrogen species in a number of in vitro systems. They have also been shown to inhibit lipid peroxidation induced by iron ascorbate in homogenates of brain mitochondrial membranes and brain synaptosomes. Green tea poly- phenols have been found to be more effective antioxidants than vitamins E and C on a molar basis, as indicated by their reduction potentials. In addition to their radical scavenging action, green tea catechins possess well-established metal-chelating properties.

Furthermore, it has been shown that a number of flavonoids and phenolic antioxidants activate the expression of some stress-response genes, such as phase II drug- metabolizing enzymes, glutathione S-transferase, and heme-oxygenase 1, probably via their binding to the antioxidant regulatory element (ARE) present in the promoter of their respective genes [13]. Additionally, the transcriptional activation of these stress-response genes correlated with an increase in the activity and nuclear binding of the transcription factors Nrf1 and Nrf2 to the ARE sequences contained in their promoters via activation of the MAPK pathway.

Resveratrol, a polyphenol abundant in grapes and red wines, [14] inhibited Aβ 42 fibril formation and protected from Aβ neurotoxicity by inhibiting inducible nitric oxide synthase inhibition. Resveratrol, with possibly high bioavailability in lipid core nanocapsules, exhibited therapeutic action in AD [15]. Rutin has been found to control oxidative stress, malondialdehyde, and glutathione disulfide formation in SH-SY5Y neuroblastoma cells [16]. Rutin has also attenuated the inflammatory cascade by decreasing cytokines like TNF-α and IL-1β. Ferulic acid, a phenolic acid, has also exhibited higher neuroprotection against Aβ toxicity than quercetin [17]. Recent research findings have shown that polyphenols have therapeutic relevance in both cell and animal model studies. The ability of polyphenols to improve synaptic transmission by elevating cAMP, target multiple signaling pathways, and reduce Aβ toxicity suggests their therapeutic utility for age-related disorders like AD and dementia. Epigallocatechin-3-gallate (EGCG) exhibited neuroprotective effects by modulating neuroinflammation and attenuating neural damage. Quercetin, apple polyphenols, myricetin have also activated SIRT1, thus exhibiting potential in MS treatment [18].

Polyphenols with their ability to attenuate oxidative stress and inflammation present therapeutic option in neurodegenerative disease. Other polyphenols such as baicalein, kaempferol, caffeic acid, and EGCG have been shown to extend neuroprotection in PD studies. Similarly, polyphenolic extracts from various plants have also exhibited pharmacological role in PD studies.

III. POLYPHENOLS IN THE NEURODEGENERATION

Studies on neuroprotective effects of polyphenols can be divided into the following categories:

(1) Neuroprotective action through antioxidant pathways, (2) interaction with signaling pathways, (3) neuroprotection through modulation of neural mediators and enzymes like acetylcholine (Ach) and acetylcholinesterase (AChE), (4) inhibition of NMDA neurotoxicity and (5) anti-amyloidogenic effects. In the most prominently discussed effect of polyphenols is their antioxidant activity. (Fig a) It is now established that oxidative/nitrosative stress (OS/NS) has a pivotal role in pathophysiology of neurodegenerative diseases and many other types of human maladies. Oxidative damage to neuronal molecules, accumulation of iron ion species in the brain, and decreased cellular reserve antioxidant pool are major pathological aspects of neurodegenerative disorders, like Parkinson's disease (PD), Alzheimer's disease (AD) or Amyotrophic lateral sclerosis. It has been shown, that severe hypoxia or ischemia episodes increase the susceptibility to development of AD [19]. Hypoxia, in fact, can induce amyloid precursor protein (APP) up-regulation at both the mRNA and protein level and subsequently leads to amyloid beta (A) accumulation. Polyphenols exert their antioxidant effects through different mechanisms like interaction with the HIF-1 alpha pathway, inducing expression of protective genes against OS, regulation of reactive oxygen species by interacting with oxidative pathways and scavenging metal ions as pathogenic free radicals [20].

One strategy of neuroprotection is activation of hypoxia signal transduction pathways through which the hypoxic condition is sensed and appropriate genes are activated and expressed in order to mediate compensatory survival conditions for the cells. Consequently, stabilizing HIF-1 would be a strategy to promote further cytoprotective events. Some natural polyphenols induce HIF-1 protein and lead to a further increase in mRNA levels of HIF-1 target genes [21]. Catechins, like EGCG, are a group of polyphenols which exert their neuroprotective effects through induction of the HIF-1 pathway. Resveratrol is another non-flavonoid polyphenol with significant antioxidant activity, activating the HIF-1 pathway. However, there is also evidence of definite links between hypoxia, HIF-1 activation and APP/A production. The precise role of HIF-1 alpha pathway in neurodegeneration, albeit positive or negative, is infact a matter of debate. HIF-1 acts like a double-edged sword that can be both beneficial and detrimental to neural cell survival. On the other hand, there are contradictory reports on effects of the same polyphenol on HIF-1 expression and activity. For example, in one study EGCG has been shown to exert antioxidant effects through HIF-1 pathway activation, while in another study an inhibitory effect on the same pathway has been reported. Similarly, other polyphenols have been reported to exert antioxidant effects through inhibition rather than activation of the HIF-1 pathway [22]. Therefore, claiming neuroprotective effects for polyphenols based on HIF-1 pathway modulation in vitro is still a matter.

Free oxygen radicals can damage cellular micro-organelles directly and in this regard mitochondrial damage is of great importance to neurodegenerative diseases. Oxygen radicals can also reduce free metal ions to active radicals, like superoxide anions, which are responsible for reduction of ferric (Fe3+) to ferrous (Fe2+) through the Fenton reaction. Polyphenols scavenge superoxide and hydroxyl radicals, as well as the 1, 1-diphenyl-3-picrylhydrazyl radical, peroxyl radicals, nitric oxide, carbon-center free radicals, singlet oxygen and lipid free radicals, and peroxynitrite. Amongst different polyphenols, EGCG has shown to be the most efficient radical scavenger, even among its other counterparts like ECG, EC and EGC [23]. Strong scavenging properties of EGCG are due to several hydroxyl groups at the side rings of the chemical Core. Hydroxyl groups are especially important in biological chemistry because of their tendency to form hydrogen Bonds both as donor and acceptor. Infact, polyphenols with hydroxyl groups can act as strong reducing agents and vice versa. Another important feature of some polyphenols is modulating the activity of enzymes involved in oxidative stress. In this regard, previous studies have shown that EGCG can increase the activity of superoxide dismutase (SOD) and catalase, two important. antioxidant enzymes in the mouse striatum.

Polyphenols also possess anti-acetycholinesterase activity [24]. The concept of cholinergic system deficit in neurodegeneration and its important role in cognition was proposed nearly 30 years. Loss of cholinergic activity is one the notable findings in different neurodegenerative diseases, like Alzheimer's and Parkinson's diseases Cholinergic dysfunction in neurodegenerative diseases can be the result of reduction in Ach synthesis due to reduced choline acetyltransferase (ChAT) or choline uptake, cholinergic neuronal and axonal abnormalities, and degeneration of cholinergic neurons. Accordingly, using acetylcholinesterase inhibitors, which exert their efficacy through stimulation of both muscarinic and nicotinic acetylcholine receptors (mAChR and nAChR), has been a proper therapeutic approach. To alleviate the cognitive symptoms of neurodegenerative disease. Several natural polyphenols have shown cholinesterase inhibitory Effect. In most in vivo studies, the anticholinergic activity

polyphenol was accompanied by improvement of cognitive functions, like learning and memory [25]. However, the exact mechanism of interaction of polyphenols with the cholinergic system is still not clear. EGCG has shown strong anti-acetylcholinesterase activity. Resveratrol has shown in a study to block acetylcholine release from adrenal chromaffin cells. Some polyphenols such as huperzine A, quercetin, kuwanon U, E, and C, kaempferol, tri- and tetrahydroxyflavone, etc. have shown anti-butyrylcholinesterase effects in addition to their anti-cholinesterase activity, Huperzine A has shown the most promising effects in this respect Studies have shown that huperzine A is highly specific for AChE The richest natural source of huperzine A is the plant Huperzia serrata, a fascinating fungal reservoir of other AChEIs.

The role of NMDA neurotoxicity and glutamate excitotoxicity in neurodegenerative diseases like Huntington's disease (HD), [26] AD and even in cognitive impairment associated with aging has been confirmed many years ago Therefore, blocking the NMDA pathway has been a therapeutic strategy for cognitive impairment not only in neurodegenerative diseases. There is strong evidence of protective effects of several natural polyphenols against NMDA neurotoxicity. Polyphenols, act at different locations within the NMDA pathway [29].

Aβ aggregation leads to the formation of senile plaques (SP) and stimulates a series of biological signaling pathways which leads to an impairment of neuronal synapses and dendrites through oxidative stress and inflammatory responses. Polyphenols exert their effect through, modulation of α, β and ϒ secretases, inhibition of Aβoligomer formation, inhibition of Aβ induced neurotoxicity and inhibition of Aβinduced neuroinflammation. Several natural polyphenols, have effectively reduced Aβ deposition and Aβprotein concentrations in brain and serum, among which EGCG has shown the most promising anti-amyloidogenic effects [27].

Polyphenols hold pharmacological relevance, as they are associated with numerous benefits including antiaging, anti-inflammatory, and anticancer effects. Likewise, hesperidin and naringenin, abundant in citrus fruits, induced neuroprotection in rats possibly via nitric oxide synthase (NOS) inhibition. Curcumin has been shown to control Huntington aggregates and improve various transgene-dependent parameters, thereby promising therapeutic action in HD [28]. Grape and green tea polyphenols have also exhibited potential for treating/preventing HD disease pathogenesis. The overall preclinical data suggests that polyphenols extend strong neuroprotection through genetic and immunological modulation, thus promising clinical prevention or delay of neurological disorders like PD and HD [29].

IV. FIGURES AND TABLES

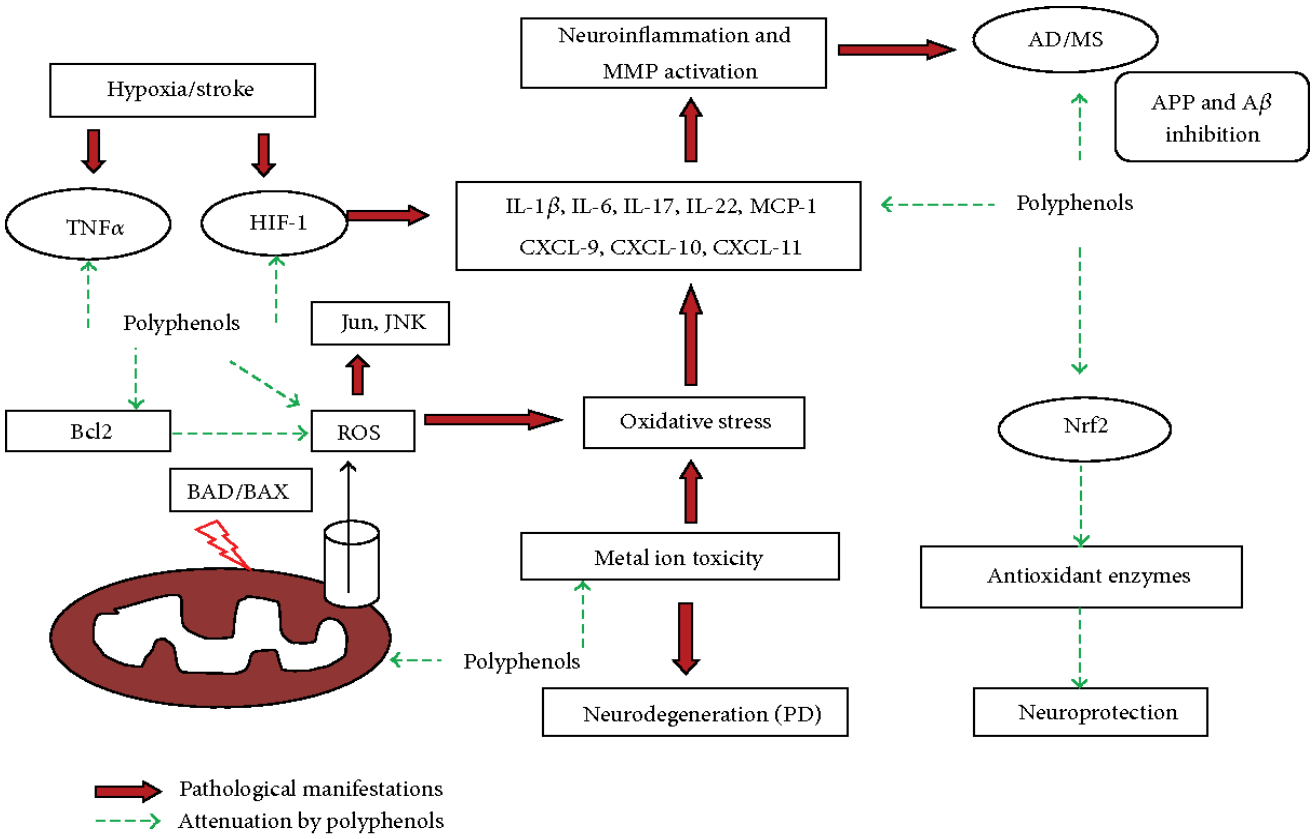

FIGURE 1: Neuroprotection by polyphenols against neurological disorders.

Adapted from Khushwant S. Bhullar, H. P. Vasantha Rupasinghe; Polyphenols: Multipotent Therapeutic Agents in Neurodegenerative Diseases, *Oxidative medicine and cellular longevity*

V. CONCLUSION

Neurodegenerative diseases (ND) are chronic and progressive conditions, characterized by neuronal loss secondary to oxidative stress and neuroinflammation. Until now they have no cure and represent high costs for the health system and patients families. Exploring alternative sources for ND therapy has led to set eyes on herbal medicine since most herbal compounds have antioxidant and anti-inflammatory properties. At present, the use of several plants in the treatment of ND is being supported by numerous scientific investigations. However, information is still missing on relevant aspects such as metabolism, pharmacokinetics, and bioavailability in the brain as well as any

changes that they may have in the CNS. Nevertheless, plant compounds or extracts remain interesting therapeutic candidates for ND management. Recent scientific evidence suggests that neurodegenerative diseases are accompanied by oxidative stress, inflammation, metal accumulation, and mitochondrial dysfunctions. Various physiological mechanisms are altered by these pathological changes which contribute to etiology of neurodegenerative diseases like stroke, MS, PD, AD, and HD. The prevention and treatment of these disorders with complex mechanisms need novel therapeutic strategies targeted for multiple genes and proteins. Polyphenols are natural plant secondary metabolites which exhibit remarkable multipotent ability to control and modulate ROS, metal toxicity, inflammation, apoptosis, signal transduction, ion channels, and neurotransmitters. Polyphenolic dietary antioxidants, particularly resveratrol, EGCG, quercetin, and other fruit polyphenols, are potent neuroprotectants. Their direct usage and dietary supplementation could act as antioxidant and neuroprotective therapy for treatment of these diseases. Most of experimental and epidemiological studies suggest that dietary polyphenols activate antioxidant pathways such as Nrf2/HO1 and downregulate NFκB, MMPs, PPAR, HIF-1, and STAT pathways. Polyphenols also modulate immune response by inhibiting proinflammatory biomarkers such as CCL17, CCL22, CCR1, CCR2, MIP1α, MIP 1β, IFN-γ, TNF-α, and IL (1β, 6, 17A, 22). These salient properties of polyphenols help to reduce two hallmarks of neurodegeneration, that is, oxidative damage and inflammation.

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