REVIEW ARTICLE

Natural polyphenols in central nervous system disorders – A review

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Abstract

Polyphenols are widespread constituent present in plants that provide a shield against various stress-causing factors. They are naturally present in our diet and their consumption is inversely associated with harmful central nervous system-related variables due to stress. The rich source of polyphenol is tea, coffee, vegetables, cocoa, etc. Cocoa is also a very rich source of polyphenol origin. Flavon-3-ols, cocoa reduces of the risk of stroke, myocardial infarction, diabetics, as well as healthier systematic inflammation in endothelial lipid dependent on blood flow and the insulin immune to blood pressure. The cardiometabolic safety was also linked to flavonoids quercetin and stilbene resveratrol. Flavonoids and other polyphenols are all-encompassing plant chemicals that perform a number of bionomic functions for their home plant. Polyphenol dietary consumption is known for decreased oxidative stress. Intake of polyphenols in the form of diet well known for reduced oxidative stress. Reduced oxidative stress causes the suppression of the risk of associated neurodegenerative diseases, such as, Alzheimer's disease (AD), stroke, multiple sclerosis (MS), Parkinson's disease (PD) and Huntington's disease (HD). Consequently, the analysis indicates that polyphenol beneficial effects on human brain activity and this review describe these implications by discussing the latest mechanistic hypothesis.

Key words: Neurodegeneration, Polyphenols, Oxidative stress, Flavonoids, Neuroprotection, Cognition

INTRODUCTION

The World Health Organization (WHO) estimated that 52% of early death cases in 2012 contributed to non-communicable diseases (NCD), with even more than 75% diagnosed with heart diseases, obesity, diabetes, and chronic diseases.[1] Recommendation from the WHO to blast the intake of fruits, vegetables, and fibers is a method for the improvement to reduce the risk of such NCD's.[2] In addition to nutrients present in fresh fruits and green vegetables such as important nutrients.[3] There is an appropriate product division that can contribute to health, including, for example, fiber, carbenoids, and phytosterols. The "phenolics" represent a wide group of present phytochemicals, which inevitably have greater or lesser one phenyl with greater or lesser one hydroxyl group attached.[4] Neurodegenerative disorders such as Alzheimer's disease (AD), stroke, and Parkinson's disease (PD) cause leading of clinical problem in the developed countries and they are an economic burden for the health care system.[5,6] AD is the most common cause of dementia and impermanence in the world.[7] Multiple sclerosis (MS) is distinguished from symptoms such as mood disorder, fatigue, vision, change muscle weakness, and motor change.[8] Stroke is aforesaid to MS or cerebral ischemia is a pathological state attended with inflammation and immune system diseases.[9] PD is an enlightened neurodegenerative disease; its genetic forms are distinguished by mutation of six genes involve clinically important ATP13A3, phenomenon in cognitive impairment, and depression.[10] Huntington's disease (HD) is some other neurological disorder causing cognitive impairment attended by oxidative stress and mitochondrial dysfunction. There are few clinically applicable medicines and therapies available of AD, MS, PD, HD, and stroke. Intake of polyphenols in the form of diet well known for reduced oxidative stress and the suppression of the risk of associated neurodegenerative diseases such as AD, Stroke,

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MS, PD, and HD.[11] Consequently, the analysis indicates that polyphenol shows beneficial effects on human brain activity and this review describes these implications by discussing the latest mechanistic hypothesis.

THE HEALTH ASSETS OF POLYPHENOLS

It was originally thought that the primary action of polyphenols consists though the direct antioxidants effect. Similarly, aforesaid effects are no prolonged examined as related to *in-vivo* research, as in many other tissues, these substances did not attain concentrations which are high to have important consequences in terms of free radical scavenging.[12-15] Consequently, it is always initially thought that flavonoids also have a beneficial effect on sugar consumption. A second area is when the potential impacts were asserted at stages involving an increase in energy production which can be condoned inside defined limits (e.g., tree apples instead of two). A third area is when the volume desired provides concentrations of consumption attainable through nutritional supplements or physiological strategies[16-18] [Table 1].

Flavon-3-ols

A number of generally exhausted foods are huge in flavon-3-ols, including tea leaves, groundnut, cocoa butter (chocolate), grapes, and legumes.[19-21] Experimental studies have been shown that absorption of flavon-3-ols from different nutritional materials seems to have a beneficial effect on cardiometabolic outcomes, along with mitigation in the risk of obesity and respiratory consequences, that is, cholesterol levels, blood pressure, and myocardial infarction.[22-24] Anecdotal analysis of the future potential age group, situation control, or bend sectional research recommended that higher concentrations of nutritional lemonade consumption may lower the risk of stroke.[25] However, further analysis indicated that black tea consumption had a little major effect on total low-density lipoprotein or high-density lipoprotein cholesterol, indicating that the impact of flavan-3-ols on lipid variables was likely to be limited.[26]

Anthocyanins

Polyphenols are flavonoids found including in blue and red fruits and veggies, especially cherries, red grapes, and strawberries. After the consumption, the host and microbiome metabolize anthocyanins like other phytochemicals to create effective enzymes, which have anti-inflammatory characteristics and promote positive cardiac effects.[27] Anecdotal analysis of randomized clinical trials measuring the production of food items or multivitamins wealthy in polyphenol showed changes in vascular impairment, like venous stiffness.[28] While another sequential analysis showed substantial increases in triglyceride levels and massive lipoprotein cholesterol.[29]

Stilbene

Resveratrol is stilbene and it is found especially in grapes, pinot, and redcurrants.[30] The specific effective method for resveratrol was the absorption of sirtuins, which were correlated under disruption of old age.[31,32] The anecdotal analysis of randomized clinical trials suggested that resveratrol supplementation greatly reduced dieting insulin, triglycerides, C reactive protein, and systolic and diastolic blood pressure such effects were particularly marked for those with re-existing NCD's (e.g., type 2 diabetes mellitus and cardiovascular diseases).[33]

Flavanols

Quercetin is a flavanol that has been displayed to enhance endothelial functioning by inhibiting circulating concentrations of vasoactive NO product and endothelin-1 in a randomized controlled trial.[34] The huge reduction in systolic and diastolic blood pressure was found in a randomized controlled trial with quercetin supplements, especially at concentrations of around 500 mg a day.[35]

POLYPHENOLS AND PHARMACOLOGICAL ACTIVITIES

AD

Phytochemicals possess anxiolytic properties in AD and dementia, which include clinical action.[36] Herbal tea phytochemicals prevent main rat hippocampal neurons from cytotoxicity induced by Aβ Resveratrol, a polyphenol readily available in fruit and wines, stimulated the structure of Aβ-42 fibrilsand preserved toward AQ liver damage by reducing enzyme synthase of nitric oxides.[37-39]

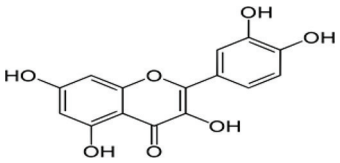
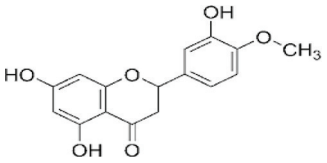
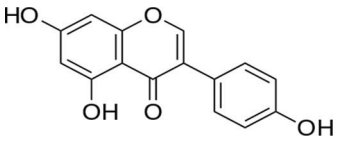
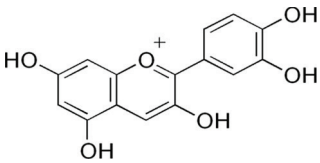
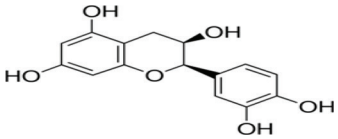
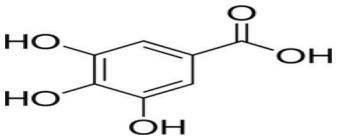
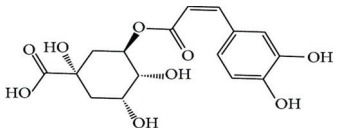
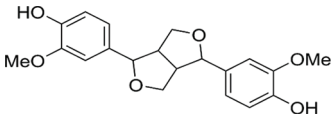
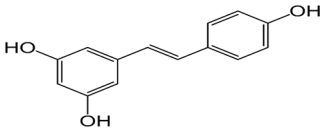
MS

MS is a neurological disease defined by the idiopathic-mediated central nervous system (CNS), endothelial dysfunction going to lead to memory loss and cognitive impairment. Polyphenols having the ability to reduce endothelial dysfunction made them future therapeutics in age-related MS and lateral amyotrophic sclerosis.[40]

Stroke

Multiple observational studies indicate that high intakes in phytochemicals may reduce neuroprotective properties as well as reduce the chances and extent of heart attack, which is also the main cause of death.[41] Herbal tea dietary fibers were also observed to protect nerve cells from hypoxia-induced hemorrhagic concussion through monitoring its cascade of swelling and eliminating the capability for transmembrane.[42]

Table 1: Chemical structure and food source of common polyphenolic compounds[1]

S. No.	Class of polyphenol	Name of compound	Chemical structure of compound	Food sources
1	Flavonols	Quercetin		Black tea, green tea, walnuts, almonds, apple with peel, blueberries, oranges, red wine, white wine
2	Flavonones	Hesperetin		Citrus fruits and juices, tomatoes and tomato-derived products
3	Isoflavones	Genistein		Soy, tofu, legumes
4	Anthocyanins	Cyanidin		Red wine, blueberries, pomegranate, blue corn
5	Flavan-3-ols	(−)-Epicatechin		Black tea, green tea, red wine, almonds, apple with peel, blueberries
6	Phenolic acids	Gallic acid		Berries, spices, cereals, tea
7	Hydroxycinnamates	Chlorogenic acid		Coffee, yerba mate, red wine, red fruits, vegetables, whole grains
8	Lignans	Pinoresinol		Whole bran cereals, flaxseed
9	Stilbenes	Resveratrol		Red wine, grapes

PD

PD is a neurological disease characterized by swelling and cell death, which leads in the substantia nigra failure of neurotransmitter neurons.[43] Phytochemicals introduce a pharmacological alternative in neurological disease to the capacity to demodulate oxidation and inflammation. Resveratrol has been shown to stimulate neurotransmitter neuron failure in rat prototype PD.[44]

HD

HD based CAG triple nucleotide upgrades and extended huntingtin protein area polyglutamine.[45] Phytochemicals have physiological significance as they can be involved with numerous advantages, such as pro-aging and pro-inflammatory.[46] Grapes and herbal tea phytochemicals also showed promise to categorize/eliminate the pathogenesis of HD disease[47] [Figure 1].

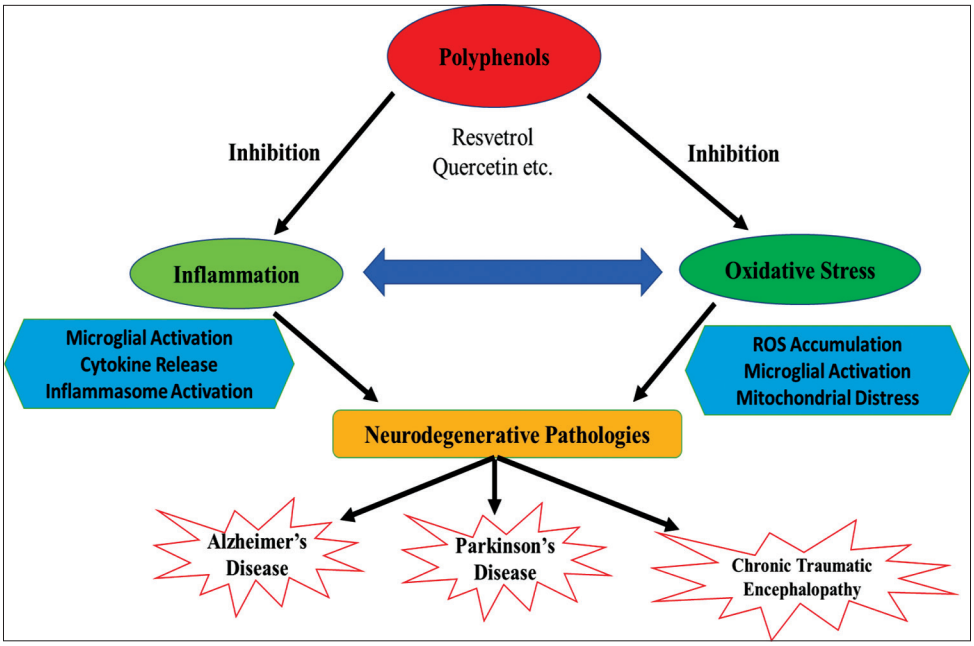


Figure 1: Polyphenols in various central nervous system disorders

EFFECT OF POLYPHENOLS ON COGNITION

In comparison to phytochemicals influencing metabolic syndrome safety, polyphenol is also assumed to have a therapeutic reaction on mental function.[48] An expected study developed in mid-life research creates a significant connection between cumulative consumption of polyphenol and mental characteristics (i.e., vocabulary and oral fluency) approximately over 13 years. Many epidemiological researches have exhibited that the production of black and green tea leaves is linked to a reduced risk of memory loss.[49,50] Lemonade production has been found to be effective the risk of stroke separately and could have a beneficial effect on PD.[51,52]

Cognitive Function

Polyphenols mainly effectively activate cellular metabolic pathways by connecting with an area of receptors in which neurotransmitters and signaling compounds attach together. It has been shown that dietary polyphenols connect with estradiol, $GABA_A$ nicotinic, opioid analgesic, and receptor tyrosine-related kinase.[53-55] In aspects of impact in signal transduction processes, polyphenols could have a protective effect mental function by disabling elements of the extracellular transmitter regulated kinase signaling cascade that leads to higher transcription factor activity, such as cAMP response component binding protein, leading to increased neurotrophy expression, such as the neurotrophic factor obtained from the brain. It can eventually lead to an increase in learning and memory and long-term potential, which pervades the restructuring of long-term memory.[56]

Cerebrovascular Function

Polyphenols transducing the "nice" NO synthase activity through eNOS tends to lead to a cerebral cortex-specific rise in regional blood circulation, angiogenesis, and neurogenesis. All these cerebrovascular functions can make a contribution to neuroprotective effects and synaptic maintenance in the face of old age and slur.[57] In particular, polyphenols related rise in vascular constriction, neurological blood circulation, and NO synthesis also involve cortical cell growth and neurogenesis, methods concerning the ability to learn, memory, and neuroprotective effects[58] [Figure 2].

POLYPHENOL: MODE OF ACTION RELATED TO HUMAN BRAIN FUNCTION

The concept that phytochemicals end up owing legitimate antioxidant effects to their positive effects on behavioral variables and disease states has been overtaken by a widespread belief that their impacts are much more plausible to be related to personal interactions with cellular signal transduction processes.[59] In general, control to the cerebellum is a component, a prerequisite for direct impacts on cognitive function, and it is noteworthy that, following dietary supplementation, polyphenols and their metabolites have been exhibited to be available in the cerebellum at small concentrations (10–300 nm). It will adequate for them all to impose pharmacological consequences on receptors and in cellular processes.[60] In comparison to personal interactions with neurotransmitter receptors, phytochemical may also actually interact with various onshore synaptic and glial protein case and lipid kinase signaling cascades along with pervasive MAPK and 3-kinase (PI3K)/protein kinase B

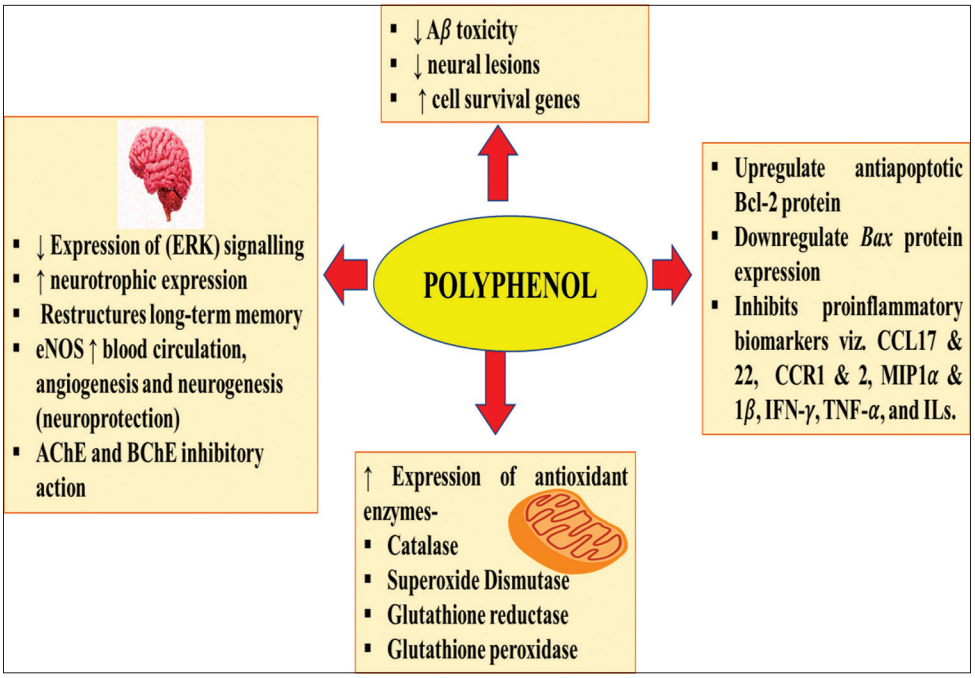


Figure 2: Polyphenols mechanism in neuroprotection

phosphatidylinositide and rapamycin signaling specified cascades.[56] The effects of phytochemicals in the brain and nervous system can be related mainly to encounters with signal transduction processes that have both a direct impact on mental function and an implicit effect by modulating provocative methods as well as improving cerebrovascular function[57,61] [Figure 3].

POLYPHENOL AND IMMUNE RESPONSE

Pro-inflammatory cytokines and genes in various neurological conditions relate to the swelling and synaptic decapitation. For drug therapy, most psychiatrists specified cytokines and other immune reactions. Polyphenols are also well recognized for their pro-inflammatory conflict and thus regulate neuroinflammation and cognitive decapitation. Epigallocatechin gallate (EGCG) has also been discovered to stimulate the phrase of chemotactic glial cell-II protein (monocyte chemoattractant protein 1 [MCP1]/C–C motif chemokine ligand 2) and interleukin-1β (IL-1β), therefore safeguarding the impartiality of the blood–brain barrier during neurological dysfunction inflammation.[62] In some other research, EGCG impeded cytokines and chemokines along with IL-1β, IL-6, MCP-1, and resveratrol have also controlled hippocampal inflammation by reducing MCP-1 mRNA levels 1β, IL-6, and MCP-levels.[63,64] A similar survey demonstrates that quercetin probably possesses neuroprotective effects in PC12 cells and zebrafish by regulating pro-inflammatory gene expression such as IL-1β and COX2.[65] Resveratrol also decreased neuroinflammation and enhanced remembrance along with cell death of IL-1β. Surveys have shown that strawberry and apple flavonoids may mitigate neuroinflammation and enhance memory loss, possibly by reducing the Interferon γ and TNF-α expression in the rat hippocampus.[66-68]

POLYPHENOL AND METAL ION CHELATION

Iron and copper play significant roles in reactive oxygen species production through redox cycling and ensuring neurodegeneration.[69] EGCG displayed iron chelating capacity in SH-SY5Y neuroblastoma cells together with stimulation of apoptotic variables such as BCL2 correlated cell death agonist (Bad), Bax, and caspase.[70] EGCG has shown better iron chelation opposed to desferrioxamine and enhanced transferrin receptor protein together with elevation in SH-SY5Y neuroblastoma cells in mRNA levels. Polyphenols are obviously active metal chelators or enhance neuroprotection against iron- and copper- oxidative damage and neurotoxicity through metal chelation, signal transduction regulation, cell proliferation, and inflammatory.[71]

POLYPHENOL AND ANTI-ACETYLCHOLINESTERASE (AChE) ACTIVITY

Neurological disease pathology like AD involves the loss of neuromediator acetylcholine, making AChE inhibitors of essential clinically appropriate drugs in AD and other dementias.[72] Black chokeberry extract, a great source of flavonoids, in balance with lemon juice impaired AChE.[73] Polyphenols derived from *Paulownia tomentosa*

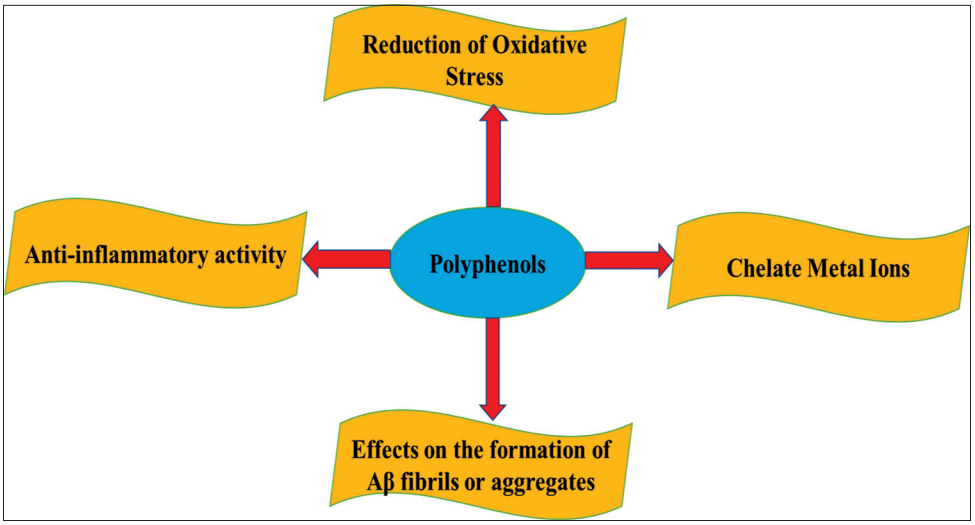


Figure 3: Polyphenols effects on brain functions

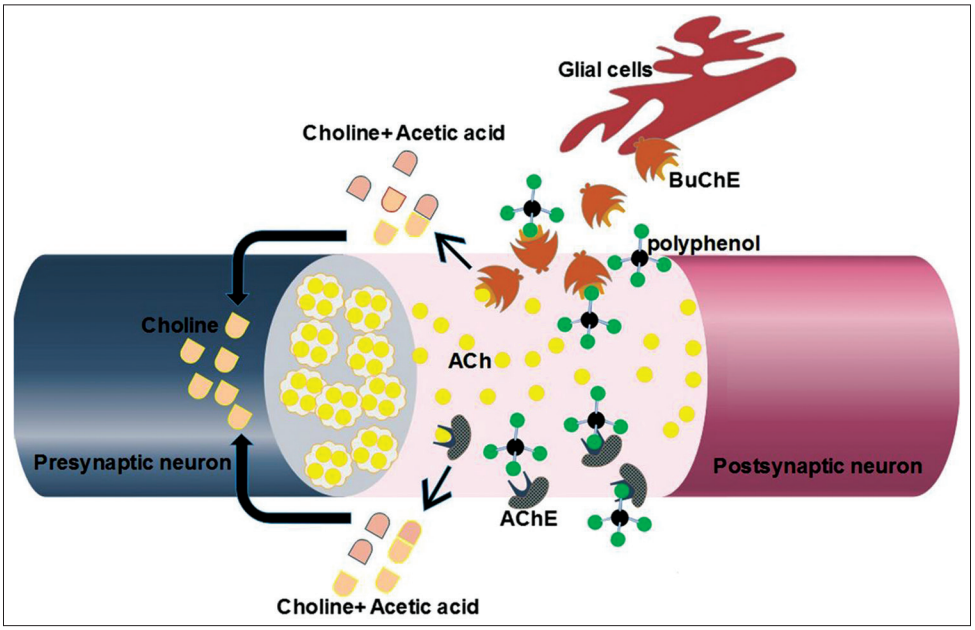


Figure 4: Polyphenols mechanism in anticholinesterase activity

fruits displayed both AChE and butyrylcholinesterase inhibitory action.[74] Quercetin has been found to enhance cognitive capacity and to possess neuroprotection against neurotoxicity triggered by trimethylation by inhibiting AChE[75] [Figure 4].

POLYPHENOLS AND AUTOPHAGY-RELATED PROTEINS

Polyphenols such as hesperetin and hesperidin prevented Aβ-induced insulin synthesis deficiency in neurons and activated autophagy with decreased AQ, culminating in enhanced mental processes.[76] Kaempferol has preserved SHSY5Yand main neuronal against rotenone toxicity by activation of autophagy. There is a wide research hole in cerebral cortex related autophagy studies, but flavonoids have the capacity to cause neuroprotective effects through protein synthesis and its related pathways.[47]

CONCLUSION

The polyphenols are the phytochemical which modulates various signal transduction pathways and shows a protective effect on CNS. Usage of plant-derived products can provide us with cheaper alternatives as compared to the synthetic ones. In recent times, their exponential increase to enhance human health by stimulating various molecular targets of neuroprotection. Also, due to the diverse availability and lack of toxicity of polyphenols, they can be aptly used clinically for neurodegenerative conditions. Future research on preclinical and clinical studies on potent polyphenols can provide their clinical acceptance along with risk assessment and unwanted

effects. This favorable outcome in the research of polyphenols will bring the resolution for their pharmacological usage in human beings.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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