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UNLOCKING THE POWER OF PHYTOCHEMICALS IN PARKINSON'S DISEASE: BRIDGING CURRENT INSIGHT TO FUTURE THERAPEUTICS INNOVATIONS

Vandana S. Nade, Vaishnavi A. Ahire*, Vaishnavi B. Nikam, Laxman A. Kawale, Pooja V. Bombale, Divya A. Patil and Priyanka J. Hemake

Department of Pharmacology, M.V.P. Samaj's College of Pharmacy, Gangapur Road, Nashik, Maharashtra-422002, India.

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***Corresponding Author**
Vaishnavi A. Ahire
Department of Pharmacology, M.V.P. Samaj's College of Pharmacy, Gangapur Road, Nashik, Maharashtra-422002, India.

ABSTRACT

Phytochemicals have emerged as promising candidates in neurodegenerative disorder therapeutics, particularly parkinson's disease (PD). PD is characterized by the progressive degeneration of dopaminergic neurons and the aggregation of α-synuclein, leading to motor and non-motor symptoms. Current treatments like Levodopa, primarily address symptoms without halting disease progression or neuronal degeneration. This review highlights the neuroprotective potential of various naturally occurring phytochemicals, such as chrysin, daphnetin and theaflavin, etc. These compounds exhibit antioxidant, anti-inflammatory, and signaling modulation properties, targeting pathways like Nrf2, NF-κB, and PI3K/Akt. The mechanisms of action, such as oxidative stress mitigation, mitochondrial function enhancement and autophagy regulation, offer a multi-faceted approach to combating PD. Furthermore, by investigating numerous experimental models that assess the potential neuroprotective efficiency of antioxidant phytochemical derivatives in terms of their inhibitory effects on oxidative stress and neuroinflammation in the brain. Naturally derived antioxidant phytochemicals may be considered prospective pharmaceutical therapeutic options to alleviate symptoms or reduce the progression of parkinson's disease. However, additional well-designed clinical trials are needed to assess the preventive and therapeutic advantages of phytochemicals as prospective medications in the treatment of Parkinson's

disease. By bridging existing knowledge with therapeutic innovation, this study underscores the role of phytochemicals in developing future interventions for PD.

KEYWORDS: Parkinson's Disease, Phytochemicals, Neurodegeneration, Neuroprotection, α-synuclein.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive, chronic neurodegenerative movement disorder, with prevalence increasing with age. In the Western world, PD affects approximately 315 per 100,000 people of all ages, and this prevalence is projected to double by 2030, significantly contributing to global mortality, morbidity, and socioeconomic burden.[1] The clinical symptoms commonly associated with PD include bradykinesia, resting tremor, postural instability, rigidity, depression, and anxiety. A key hallmark of PD is the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to dopamine (DA) depletion in the striatum (ST)—a major factor underlying the motor impairments characteristic of the disease.[2] Beyond the dopaminergic system, other neuropathological processes involve nondopaminergic systems with some overlapping with Alzheimer's disease (AD) pathology. These include cholinergic dysfunction and disruptions in serotonergic, glutamatergic, and noradrenergic pathways, all contributing to dopaminergic neuronal death and/or DA system dysfunction. PD is also associated with a range of nonmotor symptoms, such as sleep disturbances, cognitive changes, autonomic dysfunction, mood alterations, depression, fatigue, and pain.[3]

Since the aggregation of misfolded α-synuclein is a key component of Lewy bodies, a significant clinical characteristic of Parkinson's disease, PD is referred to as a synucleinopathy. Furthermore, α-synuclein has a special role in the etiology of Parkinson's disease and seems to be connected to both familial and sporadic forms of the illness.[4] Remarkably, a number of neurotoxin pathways, such as posttranslational modifications, neuroinflammation, oxidative stress, mitochondrial dysfunction, altered mitochondrial morphology, synaptic dysfunction, phospholipids, induced endoplasmic reticulum (ER) stress and metal ions, have been broadly associated with α-synuclein accumulation. Misfolded α-synuclein may be responsible for the aging process in Parkinson's disease. Age-related failure of the antioxidant defense system and excessive production of ROS worsen oxidative stress in the brain.[5]

Although, levodopa (L-dopa) is the most effective treatment for PD's early-stage motor symptoms, it is not thought to be a cure for the disease. Tremor might only be marginally lessened, although bradykinesia and stiffness react the best. Balance issues and other symptoms could not get any better. L-dopa, however, is ineffective in treating Lewy pathology, nonmotor symptoms, or neuronal loss. Patients eventually need larger dosages of L-dopa, which are linked to more adverse effects such dyskinesia.[6,7] By effectively scavenging oxygen free radicals and enhancing the cellular antioxidant defense system and associated molecules, plant products and their bioactive phytochemicals can shield cells from oxidative damage. These antioxidant phytochemicals have been shown in multiple studies to have neuritogenic potential, reestablishing synaptic connectivity by reversing the loss of neuronal processes. By focusing on many mechanisms beyond those previously described, a variety of antioxidant phytochemicals have demonstrated potentially neuroprotective qualities. Biologically active substances known as phytochemicals typically match secondary metabolites found in plants, such as terpenoids, flavonoids, and alkaloids.[8]

Moreover, phytochemicals inhibit nuclear factor kappa B (NF-κB) pathways and aid in the activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and extracellular signal-regulated kinase (ERK) pathways.[9] This study provides information about the neuroprotective properties and mechanisms of action which recently identified naturally occurring phytochemicals that alter the course of Parkinson's disease at the cellular and molecular level to combat oxidative stress and neurodegeneration. Therefore, we explored the pharmacological innovative targets of various phytochemicals involved in neurodegeneration of parkinsons disease.[10,11]

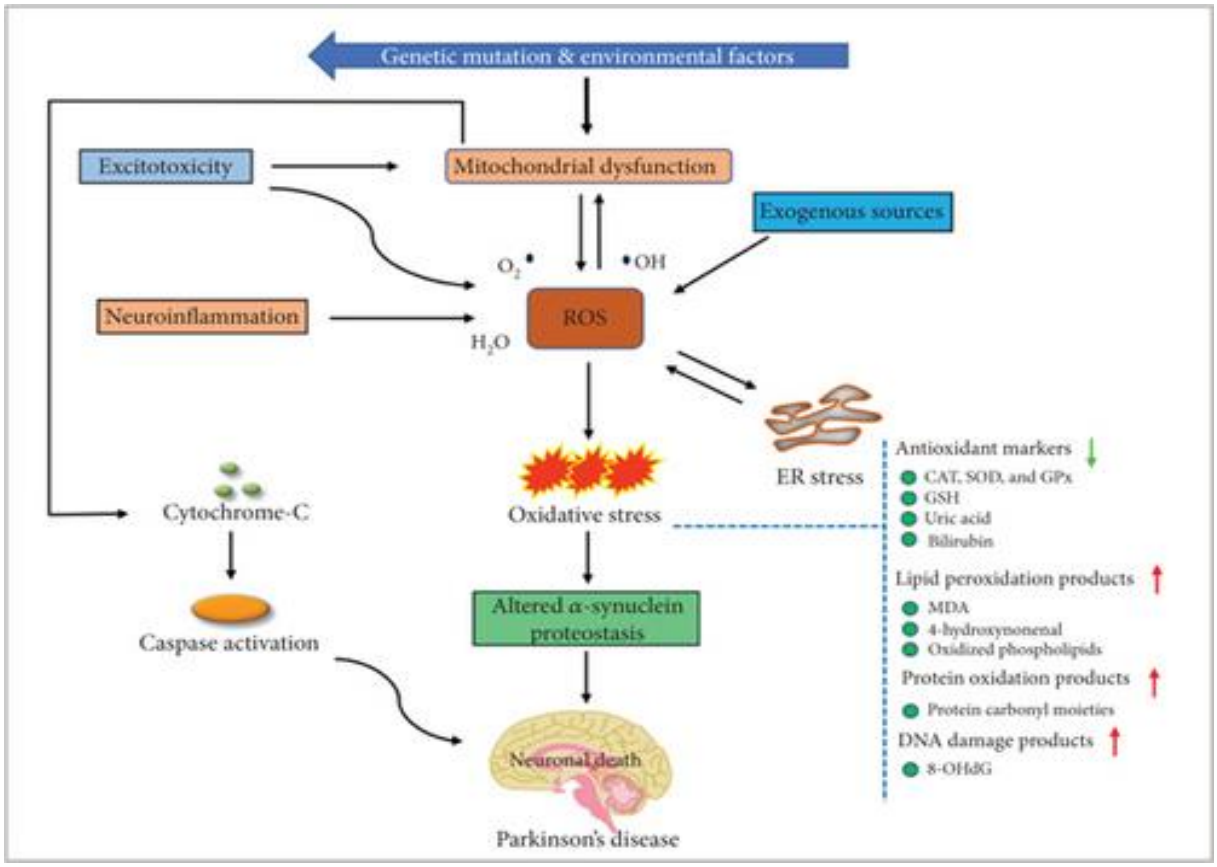

Figure 1: The pathogenesis of parkinson's disease.

Brain cells are susceptible to oxidative stress when ROS creation out spaces intracellular antioxidant defenses. In addition, earlier studies have demonstrated that increased ROS production causes significant and simultaneous dysregulation of several signaling pathways, such as RAS-MEK-ERK1/2,[12] PI3K/AKT/GSK3β,[13] Keap1-Nrf2-ARE,[14]NF-κB.[15]

In recent decades, a number of scientific findings have shown that Nrf2 is extensively involved in the regulation of various physiological functions through its antioxidant, anti-inflammatory, autophagic, detoxifying, and proteasomal actions.[16] Normally, these targets are thought of as antioxidant genes.[17]

2. TARGETS OF PHYTOCHEMICALS IN PARKINSONS DISEASE

1) Chrysin

Chrysin is a naturally occurring polyphenolic substance called a flavonoid; flavonoids are found in a wide variety of foods, including fruits, vegetables, blue passion flowers, mushrooms, plants, and honey.[11] Chrysin's neuroprotective effects, which stem from its anti-inflammatory, antioxidant, and other pharmacological characteristics, have been investigated.[12] Chrysin's neuroprotective properties demonstrate that dopaminergic neuronal

death is inversely correlated with increases in dopamine (DA) levels in both in vitro and in vivo investigations.[13,14] Additionally, as assessed by the Barnes maze, beam walk, horizontal and vertical grid, rotating behavior, and passive avoidance tests, chrysin treatment greatly reduced the animals' motor impairment and cognitive dysfunction. Chrysin thus shows promise as a disease-modifying substance that could also help in alleviate Parkinson's disease symptoms.[15] Krishnamoorthy et.al. studied the effect of chrysin on mice which indicated the reduced dopaminergic neuronal loss in the SN area in an MPTP-based experimental paradigm. Chrysin protected against dopaminergic neurodegeneration and enhanced locomotor activity in MPTP-injected PD animal models, according to a fairly recent study.[16] Krishnamoorthy et.al. and Del Fabbro et.al. investigated that there is an increase DA levels in MPP+ and MPTP-treated CGN cells as well as mice models of parkinson's disease by functioning as an inhibitor of Monoamine Oxidase B (MAO-B). Chrysin also raised the levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), according to a number of neurotoxin-induced in vivo tests.[17] By suppressing proapoptotic proteins like caspase-3, caspase-9, and Bax and increasing the expression of the antiapoptotic protein Bcl-2 against MPP+ neurotoxicity, Guo B et.al. showed the neuroprotective effect at the molecular level. Furthermore, in 6-OHDA- and MPTP-induced PD mice models, chrysin therapy produced neuroprotectivity by controlling or reestablishing BDNF and glial cell-derived neurotrophic factor (GDNF) levels in the ST area.[18] Therefore, chrysin's many protective functions in parkinson's disease, including neuroprotective and symptom-relieving, are very valuable and could lead to new avenues for innovative therapeutic management of PD; more clinical research to be required. Chrysin has antiviral and antibacterial properties in addition to parkinson's disease.[19]

2) Daphnetin

Among the coumarins included in daphne are daphnetin, DAP-8-glucoside, daphnin, esculin, umbelliferone, and acetil-umbelliferon. Although Daphne species also had trimeric coumarin metabolites such triumbellin and daphneretusin B, dimeric coumarins include rutarensin, daphnoretin, daphneretusin-A, and dimethyl-daphnoretin-7-O-glucoside.[20] Fan X et.al. showed the nephroprotective effect against cisplatin-induced nephrotoxicity by activating the Nrf2 pathway and suppressing the NF-kB signaling pathway.[21] Reactive oxygen species (ROS) and inflammatory signaling molecules such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) are the primary causes of neurodegenerative disorders. It also inhibits JAK/STAT activation, which decreases levels of COX-2 and inducible nitric oxide synthase

(iNOS) and increases pro-inflammatory cytokines and enzymes. It significantly enhances Nrf-2 expression was noted by Vinayagam R et.al.[22] According to the in vitro investigation on neuronal-like rat pheochromocytoma PC12, DAP increases heat shock protein (HSP)-70 by molecularly downregulating the expression of NF-kB and mitogen-activated protein kinase (MAPK). By modifying the phosphorylation of pro-apoptotic proteins and an anti-apoptotic protein (Bax/Bcl-2), these enzymes subsequently regulate neuronal death.[23] Fever, lumbago, cancer, rheumatoid arthritis (RA), coagulation problems, and various skin disorders have all been treated with the DAP was reported by Qi Z et.al.[24] Among its many pharmacological qualities were analgesic,[25] antipyretic,[26] anti-arthritic,[27] anti-inflammatory, antioxidant, anti-proliferative, antibacterial, and anti-inflammatory.[28]

3) Theaflavin

A class of polyphenols known as theaflavin (TF), which comprises theaflavin-3-gallate, theaflavin-3′-gallate, and theaflavin-3,3′-digallate, affects the quality and color of black tea.[29] Numerous recent scientific publications have suggested that TF may have neuroprotective properties against NDDs. TF has been shown to be equally efficient as EGCG in reducing neurotoxicity caused by β-amyloid and α-synuclein due to its potential antioxidant properties.[30] Recently, a randomized, double-blind, placebo-controlled study was carried out.[31] Luo Z et.al. investigated that the cell lines were used to investigate the mechanism of action of TF, 6-OHDA-induced SH-SY5Y. The findings revealed reduced nuclear morphology, reduced apoptosis, elevated MMPs, decreased intracellular NO levels, and lessened cell viability loss. These results demonstrated that TF protected against 6-OHDA-induced apoptosis by preventing the production of NO and ROS.[32] Grelle G et.al. studied that oxidative stress was eliminated by giving TF to the PC12 cell line treated with H2O2, which led to an increase in Bcl-2 expression and a decrease in the production of the proteins Bax and caspase-3. This finding implies that TF possesses antiapoptotic properties that provide cytoprotection as well as neuroprotection.[33] According to a different study, TF acted as a potent inhibitor of β-amyloid and α-synuclein fibrillogenesis and promoted the innocuous assembly of these proteins. These results suggest that TF may remove dangerous amyloid buildup.[34] TF increased the expression of DAT and VMAT-2 in the PD animal model and decreased the effects of oxidative stress in MPTP-induced neurotoxicity in mice. Additionally, TF has been shown to ameliorate dopaminergic neuronal degeneration and behavioral deficits.[35] Anandhan A et.al. investigated those mice treated with MPTP/p, TF increased nigral TH and DAT expression and decreased caspase-3, caspase-8, and caspase-9;

these effects were linked to increases in regulated behavioral function.[36] Additionally, it was discovered that proinflammatory cytokine production and microglia activation were also brought on by cholinergic system dysfunction. The anti-inflammatory markers IL-4 and IL-10 were more abundant in MPTP-injected rats as a protective measure against neural inflammation.[37] According to a recent in vivo study, TF treatment significantly decreased neuroinflammation and apoptosis, hence reducing chronic MPTP-induced neurotoxicity in mice's SN and ST studied by the Szuster-Ciesielska A et.al. [38,39,40] Furthermore, TF therapy significantly reduced the overproduction of IL-4 and IL-10 and lessened the behavioral abnormalities brought on by MPTP injection, such as catalepsy and akinesia. Anti-inflammatory, anti-influenza, cardioprotective, and anti-cancer capabilities are among the other biological actions that have been discovered.[41,42]

4) Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG), a polyphenol found in green tea, has been demonstrated to have a variety of physiologically beneficial effects on cancer, non-communicable illnesses, and inflammatory disorders in humans.[43–45] By altering several transcription factors, proteins, and other important growth factors, EGCG has been connected to a variety of pharmacological properties, including anti-inflammatory, antioxidant, metal-chelating, radical-scavenging, antiapoptotic, and anticarcinogenic properties.[46, 47] EGCG has many potential advantages for supporting healthy aging since it promotes the morphologic and functional changes that occur naturally in an aging brain. These alterations include improving learning and memory, lessening brain oxidative damage, and preventing cognitive dysfunction.[48–50] Green tea consumption and cognitive impairments in parkinson's disease disorders have been linked in a number of human studies to an inverse dose-response association.[51,52] EGCG therapy enhanced mitochondrial function, increased succinate dehydrogenase (SDH) activity, decreased lipid peroxidation production and NO levels, and elevated ATPase and ST catecholamine levels in rotenone-induced rat PD models. Furthermore, EGCG administration enhanced motor function and reduced the levels of apoptotic markers and neuroinflammatory cytokines.[53] When EGCG was given to MPTP-induced animals, the neurotoxin-induced decrease in the ST antioxidant enzymes SOD and CAT was stopped, and the overall brain activity of both enzymes was elevated.[54] Additionally, in SH-SY5Y cells, EGCG administration completely inhibited STAT3 activity and promoted the growth of neuronal cells triggered by 6-OHDA.[55] According to the most current research, EGCG's neurorescue action inhibited functional and neurochemical deficits

in MPTP-induced PD rats, decreased oxidative stress, and controlled the iron-export protein ferroprotein in the SN.[56] Levites Y et.al. found that EGCG preserved TH-positive cells in the SN area and restored movement behavior in the MPTP-injected animal model. EGCG administration increased the ratio of $CD3^+CD4^+$ to $CD3^+CD8^+$ T-cell lymphocytes in the peripheral blood and decreased the expression of inflammatory markers such TNF-α and IL-6 in the serum, according to flow cytometric analysis.[57] Wang L et.al, indicated that the additionally, effect in PQ-induced PC12 cell models, EGCG demonstrated antiapoptotic actions by maintaining MMP and preventing the elevation of caspase-3 activity and the downregulation of the proapoptotic SMAC protein in cytosol expression.[58]

It was also observed that EGCG treatment reduced TNF-*α* and NO inflammatory mediators and attenuated loss of midbrain DA levels triggered by LPS-induced neurotoxicity.[59] Hou RR et.al. conducted both in vitro and in vivo and showed that cotreatment with EGCG reduced glutamate-induced oxidative cytotoxicity in HT22 cells by inhibiting the activation of NF-κB. Furthermore, rats administered with the carbidopa and L-dopa showed less buildup of 3-O-methyldopa in their plasma and ST after receiving EGCG treatment; EGCG also had a potent therapeutic impact on PD animals' hippocampal oxidative neuronal death caused by kainic acid.[60] Many neurodegenerative disease , including parkinson's disease, have been closely associated with the process of α-synuclein and other protein deposition.[61] EGCG may interact with α-synuclein amino acid positions on peptide membranes, according to other studies. These results support the idea that EGCG may be a powerful remodeling agent of α-synuclein accumulation and a possible disease-modifying medication for the treatment of parkinson's disease. It was suggested that EGCG binds to α-synuclein via unstable hydrophobic interactions.[62,63,64]

5) Alpha and beta asarone

Alpha- (*α*-) asarone and beta- (*β*-) asarone compose an important antioxidant aromatic chemical constituent that is extracted from the rhizomes of *Acorus calamus*. Consequently, both *α*- and *β*-asarone have been reported to have one or more similar pharmacological properties that may offer beneficial effects in the therapeutic management of several diseases.[65] Importantly, the delivery of *α*- and *β*-asarone in the brain is extensive, demonstrating its ability to cross the BBB, a desirable characteristic of compounds used for the treatment of numerous neurodegenerative diseases.[66] Lu J et.al., studied the effect in PD model, *α*-asarone treatment reduced neural inflammation and suppressed IL-*β*, IL-6, and

TNF-α production in LPS-stimulated BV-2 cells. In addition, α-asarone treatment effectively inhibited the LPS-stimulated activation via regulation of NF-kB by blocking degradation of inhibitor NF-kB signaling in BV-2 microglial cells. In vivo studies also demonstrated that prophylactic administration with α-asarone inhibited microglial activation and attenuated PD-like behavioral deficits in MPTP-injected PD mice.[67] Hei X et.al. investigated the effect in the 6-OHDA-induced PD model, β-asarone improved the behavioral function of rats in the initiation time, open field, stepping time, and rotarod tests. Research has also found that β-asarone increases the levels of HVA, DOPAC, and 5-HIAA in the ST region. In addition, administration with β-asarone elevated the level of TH-positive neurons and inhibited the expression of LC3-II in SN4741 cells. Moreover, *in vivo* experimental results showed that β-asarone affected the expression of Bcl-2, Beclin-1, JNK, and p-JNK in 6-OHDA-injected PD rats. The neuroprotective effect of β-asarone occurs primarily by downregulating JNK and p-JNK expressions and then indirectly increasing Bcl-2 expression. Additionally, β-asarone may inhibit the function of Beclin-1, thereby inhibiting autophagy activation.[68] Activated autophagy is an important process that may play a defensive role through clearance of toxic aggregated α-synuclein in neurons.[69] On the other hand, dysfunction of the autophagy-lysosomal pathway has been associated with the development of PD.[70] Fang YQ et.al. showed that endoplasmic reticulum (ER) stress may induce autophagy.[71] Zhang S et.al. investigated the effect in 6-OHDA-induced PD rat models, β-asarone administration may decrease the levels of Beclin-1, CHOP, GRP78, and p-PERK while significantly increasing the level of Bcl-2. β-Asarone may increase Bcl-2 by inhibiting the p-ERK pathway, and Bcl-2 may inhibit the expression of Beclin-1. The results of the study suggested that β-asarone may regulate autophagy and ER stress via the PERK/CHOP/Bcl-2/Beclin-1 pathway.[72] Kuma A et.al. reported the β-asarone can effectively inhibit neuronal apoptosis through the CaMKII/CREB/Bcl-2 signaling pathway and regulate Bcl-2 family proteins.[73] Pan T et.al. documented that β-asarone significantly lowered the expression levels of MALAT1 and α-synuclein in the midbrain of MPTP^{-}injected PD mice. In addition, immunoprecipitation and RNA pull-down assays confirmed that MALAT1 was associated with α-synuclein, leading to the increased stability of α-synuclein and its expression in SH-SY5Y cells. β-Asarone treatment could increase the viability of cells exposed to MPP^{+}.[74] Jheng JR et.al. demonstrated that β-asarone exerted antioxidative effects on H_2O_2-stimulated PC12 cells by reducing oxidative stress via activation of the protective Nrf2/HO-1 pathway.[75] The documented other biological activities are antifungal,[76] anthelminthics,[77] for the treatment of myocardial ischemia,[76] anticancer.[77]

6) Baicalein

Baicalein (5,6,7-trihydroxyflavone; $C_{15}H_{10}O_5$) is an important flavonoid compound mainly isolated from the roots of *Scutellaria baicalensis*.[78] Ning B et.al. reported that baicalein effectively protected glutamate, amyloid-β (Aβ), 6- hydroxydopamine (6-OHDA), hydrogen peroxide (H_2O_2), 1-methyl-4-phenylpyridinium(MPP^+), 1-mehtyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine-induced neurotoxicity in cell line and animal models.[79] baicalein protects mitochondrial functions by modulating mitochondrial membrane potentials, Bcl2/Bax ratio and reducing oxidative stress.[80] In addition, baicalein can exerts its anti-inflammatory action by inhibiting glial activation as well as reducing pro-inflammatory enzymes and cytokines, including interleukin (IL)−1β.[81] IL-1β is known to be activated by caspase 1, a pro-inflammatory caspase activated during the inflammasome activation.[82] Hung KC et.al. summarized the therapeutical actions of baicalein against alzheimer's and parkinson's diseases. Baicalein effectively prevents alzheimer's and parkinson's diseases by reducing oxidative stress, inhibiting aggregation of disease-specific amyloid proteins, inhibiting excitotoxicity, stimulating neurogenesis, and anti-apoptosis as well as anti-inflammatory properties.[83] Mu X et.al. reported the neuronal cell damage or death is the most important factor for various neurodegenerative disorders. Oxidative stress, neuroinflammation, misfolding of protein and mitochondrial dysfunction are the major pathways responsible for neurodegeneration. Ju XN et.al. investigated that the several transcription factors play an important role in the pathophysiology of neuronal cell damage including nuclear factor erythroid-derived 2 (NF-E2) related factor (Nrf2), nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), cAMP-response element binding protein (CREB), Wnt, janus kinase/signal transducer and activator of transcription and TLR-4, etc.[84] In this connection, the main focus of neuroprotective agents is to protect neuronal cell damage/death for preventing the neurodegenerative diseases.[85,86] The reported other biological activities like antibacterial,[87] antiviral,[88]anti-inflammatory,[89] antitumor,[90] cardiovascular[91] and neuroprotective activities.[92]

7) Betulin

The naturally occurring triterpene, betulin (lup-20(29)-ene-3β,28-diol) is mostly found in shrubs and trees and other forms of the main extractive (up to 30% of dry weight) of birch tree bark.[93] The triterpene found in nature is betulin. It is frequently separated from birch tree bark. Up to 30% of the dry weight of silver birch bark is made up of it.[94] Ju XN et.al. studied the neuroprotective roles of betulin in 6-OHDA-induced DA neuron degeneration,

food-sensing behavior defects, and life span which may be related to its antioxidant and antiapoptotic activity. It can affect pathways in parkinson's disease by upregulating the Akt/Nrf2 signaling pathway, downregulating the apoptotic pathway gene, egl-1.[95] Zhou QB et.al. reported that the effect of betulin reduced α-syn accumulation, thereby blocking its toxic effect in cells. Previous research has demonstrated that a ubiquitin-proteasome mechanism repairs cells from damage under stressful conditions.[96] Ci et al. reported that betulin has the effect on regulating AMPK/AKT/Nrf2 signaling to mitigate inflammation.[97] Zhou et. al. found that betulin can modulate immune response to alleviate liver damage from hepatitis.[98] Based on these accumulating evidence and results, presumed that DJ-1 had same merits in EBI caused by subarachnoid hemorrhage(SAH) via regulating Akt/Nrf2 signaling pathway, for kindred mechanisms play similar roles in multiple neurological diseases.[99,100] It is found that the outer bark of birch trees has various biological activities on animal and human health including the following properties like antibacterial,[111] antiparasitic,[112] antiviral,[113] antiinflammatory,[114] anticancer,[115] antivenom,[116] liver protective,[117] kidney protective,[118] lung protective,[119] anticonvulsant and a cognitive enhancer in patients with alzheimer's disease, it also improves diet-induced obesity, ameliorates the stability of atherosclerotic plaques, and can be used to treat type II diabetes.[120]

CONCLUSION

Parkinson's disease (PD) is a chronic neurological condition that largely impairs mobility. It is caused by the degeneration of dopamine-producing neurons in the substantia nigra, resulting in a lack of dopamine, a crucial neurotransmitter involved in motor function. L-dopa does not effectively treat neuronal loss, nonmotor symptoms or Lewy pathology. Patients gradually demand increasing dosages of L-dopa, which are accompanied with significant side effects such as dyskinesia.

Naturally derived phytochemicals and their derivatives have a potential neuroprotective effect due to their multifaceted ability to regulate and modulate chronic inflammation, oxidative stress, and downstream signaling of different pathways, all of which are hallmarks of parkinson's disease.

In this review, we have unlocked the power of different phytochemicals in parkinson's disease. Chrysin which acts on the dopamine transporter (DAT) pathways and increased the levels of dopamine. Daphnetin acts by downregulations of pathways like janus kinase (JAK/STAT), nuclear related factor (Nrf-2), Nf-kB, beclin-2(Bax/Bcl-2). Theaflavin,

increased the expression of dopamine transporter protein (DAT) and vesicular monoamine transportor-2(VMAT-2). Epigallocatechin-3-gallate inhibited the overexpression of STAT3, NF-kB. (*α*-) asarone and (*β*-) asarone downregulated JNK and p-JNK, PERK/CHOP/Bcl-2/Beclin-1 pathways. Baicalein suppressed the nuclear factor erythroid-derived 2 (NF-E2) related factor (Nrf2), and regulated AMPK/AKT/Nrf2 signaling to mitigate inflammation (NF-kB), mitogen-activated protein kinases (MAPKs), cAMP-response element binding protein (CREB), janus kinase/signal transducer and activator of transcription and TLR-4. Betulin causes significant effect on AMPK/AKT/Nrf2 signaling. Thus, these phytochemicals will help to act by bridging current insight to future therapeutics innovations.

Future research should focus on increasing clinical acceptance of claims derived from in vitro and in vivo preclinical investigations, as well as conducting additional clinical trial studies of numerous more possible drugs and combinations thereof, to detect and prevent any undesired side effects. The efficacy of phytochemicals in clinical research will determine their pharmacological relevance in humans and nutritional intervention programs will diminish oxidative neuroinflammatory damage and halt the progression of parkinson's disease.

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