Review Paper:

A Review on phytocompounds targeting Parkinson's Disease

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Abstract

Parkinson's disease is a chronic disease that has a severe impact on a person's lifestyle once it is contracted. It is the second most prevalent neurodegenerative disease. Only a few factors have been identified to signal a predisposition towards its development and no singularly known cause for the disease. This is why no cure for PD exists. Instead, the existing drugs in the market are towards the amelioration of symptoms.

This review was conducted to explore the possible phytocompounds that could be further investigated in hope to develop more efficient, potent, or readily available medication, with a focus on each of their pharmacological mechanisms. Phytochemicals derived from plants are the future of pharmaceutical drugs that are able to combine the efficacy of conventional medicine with the benefit of their organic sources. Many of the compounds have been investigated in and open new possibilities. Further investigation on efficacy of healing and protective effects of phytocompounds provides a promising medication.

Keywords: Parkinson's disease, phytocompounds, dopamine, medicinal plant, neurodegenerative disease.

Introduction

Compared to the lifestyles of our early ancestors, living in the modern world is a lot more stressful. There is a general lack of physicality and movement as more work can be done with less movement. Likewise, there is also an overall reduction of mental relaxation techniques being carried out by an average human being. Due to this increasing imbalance between work and recreation, more people are becoming inflicted with stress related disorders. Exposure to stress, especially for long periods of time, can be damaging to the brain, which acts as a crucial midpoint of regulating various systems that work in coordination to ensure a person's good health. Neurodegeneration is defined as pathological malfunctioning of neurons[47]. Neurodegenerative disease is a subset of pathological conditions that occur in the body due to the degeneration of neurons.

Parkinson's disease (PD) is the second most commonly afflicted neurodegenerative disease. Parkinson's disease is a progressive neurodegenerative motor disorder that increases chance of growing with age. Being afflicted with PD can cause disastrous changes in a person's lifestyle as general resting movement is impeded, forcing dependency upon the individual and bringing about premature mortality as well[59]. Prominent symptoms include bradykinesia, hypokinesia, akinesia, rigidity, instability of posture as well as resting tremors[22]. Other symptoms of PD that are not a direct result of loss of motor neurons include depression, psychosis, mood fluctuations, sleep disorder and cognitive impairment[18]. A study summarized that PD prevalence rate reaches up to 0.5-1% in people aged above 80[15].

Due to the vague information on what causes onset of PD, the current medication is hardly able to make a dent in healing the disease. At most, it is only able to alleviate the symptoms temporarily[12]. With the help of phytocompounds and nutraceuticals, there is a surge in the ongoing research to develop drugs with better neuroprotective abilities[61]. The use of natural characteristics of medicinal plant compounds provides greater chance for producing efficient solutions, exploring new options and optimizing preexisting drugs in the field of drug development[54].

Etiology and Pathology

There is very little information about the accurate cause of PD. There are several studies that have been conducted to discover the etiology of disease. Some studies have shown that the presence and mutation of specific genes in a person's genome make them more inclined to be afflicted with this disease later on in their lives. These genes include the Parkin gene, α-synuclein gene, leucine-rich repeat kinase 2 (LRRK2) gene and PTEN-induced putative kinase (PINK1) gene. Exposure to pesticides has also been linked to PD including those like rotenone, paraquat and dichlorodiphenyltrichloroethane (DDT)[1,46].

It has been found that inception of PD involves formation of Lewy neuritis and Lewy Bodies in the substantia nigra, pars compacta in the brain. These are cytoplasmic inclusions formed by the deposition and accumulation of alpha-synuclein. As they accumulate, they can cause death of specific dopaminergic neurons in the aforementioned part of substantia nigra which leads to an overall fall of dopaminergic neurotransmission in the striatum[7]. There are several biological side effects that occur due to buildup of Lewy Bodies, which then lead to death of the dopaminergic neuron. These include mitochondrial dysfunction, protein aggregation, oxidative stress and deregulation of ubiquitin-

proteasome pathway[9,43]. Mitochondrial dysfunction and increased oxidative stress are key in PD pathogenesis[43].

Oxidative stress and nitrative stress can result in dysfunction of mitochondria, restrict the mitochondrial respiratory chain activity and lead to the accumulation of a-synuclein proteins. Oxidative stress also prevents the functioning of the respiratory chain in the mitochondria. Simultaneously, the α-syn being excessively produced leads to increased levels of reactive oxygen species (ROS) and mitochondrial dysfunction, causing positive feedback during PD pathology[9,43].

One of the most well-known symptoms of PD is the resting tremor, also known as an involuntary shakiness. Unlike the active tremor, this kind of tremor occurs when the body is at rest and usually diminishes when motion is being carried out. Other symptoms of PD include rigidity (stiffness), movement difficulties (such as bradykinesia, hypokinesia and akinesia) and postural instability. There are also various other complications that can occur as a result of diminishing movement. These include sleep disorders, depression, dementia, mood fluctuations, cognitive impairment and psychoses[20]. The etiology of all these symptoms is still unknown, however it has been speculated that stress and inadequately functioning mitochondria are major contributors to these symptoms[24].

As a result, medication developed for patients diagnosed with PD provides at best relief from the symptoms and does not affect the actual progression of onset Parkinson's disease. Further research and investigation must be undertaken to understand the etiology of PD to be able to develop drugs that are able to combat its progression.

Current treatment strategies

Current treatment of Parkinson's involves three different strategies employed to lower the symptom's effects and provides relief to the patients. The three strategies are: to increase the signaling of dopamine, inhibition of COMT (catecholamine-o-methyltransferase) and maintenance of acetylcholine neurotransmitters. Dopamine treatments are the most preferred one[57]. Injecting dopamine into the body itself does not yield any effect, as dopamine cannot cross the blood brain barrier.

However, levodopa, a precursor of dopamine can do this. By administering levodopa, it is then metabolized into dopamine via enzyme dopa-decarboxylase found within the nigrostriatal neurons. Since these enzymes may also be found within the other parts of the body, levodopa is often administered with carbidopa which helps in inhibiting enzyme action until levodopa passes the blood brain barrier.

Administering levodopa is the main strategy to increase dopamine signaling, there are also other ways of treatment. However, studies in animals have shown that increasing levodopa levels can cause a buildup of toxic metabolites and oxidative stress[58].

Inhibition of COMT is another strategy used for the alleviation of PD symptoms. Together with MAO-B (monoamine oxidase B), they degrade levodopa and dopamine[8]. Inducing the inhibition of these two enzymes can lower the degradation of dopamine. MAO-B metabolizes dopamine to create metabolites like homovanillic acid, 3,4-dihydroxyphenylacetaldehyde, hydroxyl radicals and hydrogen peroxide.

The reactive oxygen metabolites are known to worsen the degeneration of dopamine[42]. COMT also functions in a similar manner. This makes it an important strategy in ameliorating PD symptoms. To tackle the non-motor symptoms of PD, targeting the production of acetylcholine has been proven effective. The enzyme acetylcholinesterase is an important target that is linked to mood disorders and cognitive impairments[244].

Phytocompounds against Parkinson's disease

Since time immemorial, plants with medicinal properties (Ayurveda) have been administered as an alternative medication for various diseases related to the central nervous system including Parkinson's disease, Alzheimer's disease, schizophrenia and more[67]. Herbal plants contain a large variety of phytochemicals which have been found to have therapeutic and protective benefits. There has also been a meteoric rise of people who have turned to plant derived products as future medicine.

A seven-year study has shown that consumption of medicinal plants has risen exponentially by over 380% and there are no signs that this may slow down any time soon[5]. In the Indian subcontinent, Ayurveda has been used to fight against Parkinson's disease[23]. Seeds from the plant *Mucuna pruriens* have high concentration of levodopa. Studies from clinical trials have shown that patients taking powdered forms of the seed have displayed no boost in dyskinesia[25,39].

Synthetic counterparts of drugs for ameliorating Parkinson's disease symptoms have shown varying degrees of success as well, but it was found to have notable negative side effects such as drowsiness, fatigue, dry mouth, trouble with balance, apprehension etc.[45] There are some plant-based phytochemicals that have shown promise in cognitive effects but neither their mechanism of action nor their observed effects have been properly studied.

Alkaloids: Alkaloids are secondary metabolites with amine groups as their functional groups. Specific plants and trees are cultivated for large-scale production of alkaloids. Alkaloids are mostly known to occur as neurotoxins in nature. However, there are some alkaloids that are therapeutic in nature and medicinally useful. They have been used in the production of narcotic drugs, antidepressants and potent analgesic drugs. They stimulate nicotinic receptors

and cause inhibition of enzymes that control cholinesterase activity. They also cause interference with major neuronal pathways with a unique mechanism of action[30].

Berberine and its related derivatives are isoquinoline alkaloids extracted from *Berberis* sp. and *Coptis* sp. Their interactions against macromolecular targets commonly found during onset Parkinson's disease have been studied both *in silico* and *in vitro*. Berberine 2 has displayed promising pharmacokinetic properties showing to strongly bind to α-synuclein, PDE4 and MAO-B in *in silico* studies. This class of alkaloids can be investigated in much further depth for development of multi target agents against PD[53].

Caffiene, one of the most prevalent psychoactive drugs used around the world, is an alkaloid that has also shown promise in mitigating select symptoms of PD. A study examined the potency of caffeine extracted from *Coffea arabica*, with its primary concept based on the fact that caffeine is a well-known antagonist to adenosine receptors. Resulting tests concluded that due to its interaction with the central nervous system, caffeine led to the regulation of gene expression of phosphoprotein DARPP-32 and dopamine. Due to the widespread availability of caffeine across the globe, it is heavily recommended to investigate further for its potential as a more readily available medication for PD symptoms[17].

Flavonoids: Flavonoids are polyphenolic compounds present in multiple plant species that play important roles on human health with their unique biological activity. With more than 6000 flavonoids characterized, there are many divisions of compounds within the flavonoids such as flavonols, flavones, isoflavones, chalcones, proanthocyanidines and anthocyanins. In the CNS, flavonoids help in maintaining the homeostasis by modulating the neuronal oxidative metabolism and neurotransmitters and having anticonvulsant and antianxiety effects. They act upon the signaling cascades that contribute to oxidative damage like P13/Akt and MAPK, preventing neuronal death. Because of the specifically unique functional groups, flavonoids are capable of acting as potent inhibitors of neurodegenerative enzymes leading to the major contribution for scavenging of ROS[19].

Acacetin is a flavone isolated from many natural sources such as *Linaria* spp., *Turnera diffusa*, *Calamintha* spp., *Chrysanthemum morifolium*, *Robinia pseudoacacia* and *Carthamus tinctorius*. It is known to inhibit the production of well-known inflammatory factors such as TNF-B, NO and prostaglandin E2 (PGE2). Other effects of it include activation of glial cells, lowered loss of dopaminergic neurons, overall reduced levels of cyclooxygenase-2 (COX-2) and NO synthase and increased levels of dopamine[27].

Baicalein, a flavonoid extracted from root of *Scutellaria baicalensis*, possesses neuroprotective properties that are effective against several neuronal disorders and diseases. An experiment was conducted on baicalein and 6-OHDA treated neuronal cells to determine its mechanisms. Baicalein restricts the collapse of inner mitochondrial membrane potential, reducing the dysfunction that follows in cells treated with 6-OHDA. It also inhibited caspase-9 and caspase-3 activation which usually occurs due to malfunctions of the mitochondria. Furthermore, it was noted that baicalein also significantly reduced the phosphor-JNK levels, a well-known apoptotic mediator of cell death[335].

Bu-7, derived from the leaves of *Clausena lansium*, is a biologically active flavonoid linked to increasing neural cell viability. It also has means of suppressing various apoptotic processes involved in the development of PD. One such method is the suppression of expression of MAPK protein family (mitogen activated protein kinase) like p38 and JNK. Another means is by suppressing the phosphorylation status of these proteins. MAPK signaling pathway plays a key role in the intrinsic mitochondrial apoptotic process, then contributes to the pathogenesis of PD. This flavonoid suppresses the ratio of Bax/Bcl-2 levels, expression of p53 and caspase 3[38].

Fustin is another flavanonol extracted from heartwood (*Rhus verniciflua)*. By reducing the overall activation of p38 phosphorylation and caspase 3, it suppressed apoptosis. Other mechanisms include reduction of Bax/Bcl-2 ration and inhibition of ROS generation[65].

Hesperidin, flavanone, has the ability to protect neurons found in the substantia nigra pars compacta. Its main function is the protection of the mitochondrial membrane potential, but it can also attenuate effect of apoptotic markers and enhance cell proliferation. Hesperidin's other documented effects include decreasing overall lipid peroxidation, enhancing antioxidant performance, elevating reduced glutathione and suppressing intracellular ROS formation as well[65].

Lycopene is a well-known carotenoid found in *Lycopersicon esculentum*. It was found that ingesting tomato powder rich in lycopene prevented dopamine levels from decreasing in mice models pretreated with MPTP after a four-week experimental period[64].

Flavonoid (n-hexadecanoic acid) and aldehyde (z-9,17-octadecadienal) compounds extracted from the plant *Clitoria ternatea* have also shown positive *in silico* results for inhibition of MAO-B and MAO-A. When tested against reference compounds such as kaempferol-3-monoglucoside, this shows the potential of phytocompounds extracted from *Clitoria ternatea* plant against treated Parkinsonian symptoms[41].

Wogonin is a flavonoid extracted from herb *Scutellaria baicalensis*. Its anti-inflammatory properties have been tested against many types of cells. Studies show that microglial cells, once activated, can produce toxic mediators that contribute to the pathology of many neurodegenerative

diseases including Parkinson's disease. Therefore, wogonin's anti-inflammatory effects against activated microglial cells are worth investigating. Production of nitric oxide, tumor necrosis factor-α and interleukin-1β was initially induced in BV-2 mouse and rat models. Then microglial cells were treated with wogonin and yielded a marked inhibition of NO, TNF- α and IL-1 β. These results show that wogonin has the capability to impede inflammatory activation of microglial cells via molecular mechanisms that inhibit NO, TNF- α and IL-1β production[36].

Polyphenolic Compounds: Polyphenolic compounds consist of a large and diverse family of chemical compounds, all with a common phenolic ring in their structures[16]. This family of compounds has many divisions such as flavonoids, lignans, stilbenoids, phenolic alcohols, phenolic acids and tannins. Polyphenols are known to possess extremely effective antioxidant properties with iron chelating activity and free radical scavenging capacity. Other medicinally beneficial effects of polyphenolic compounds are antibacterial, anti-inflammatory, antiviral, neuroprotective and anticarcinogenic activities[6].

Curcumin is one polyphenolic compound extracted from *Curcuma longa* has been studied for treatment in 6-hydroxydopamine-lesioned rat models and it showed a reversal in loss of dopaminergic neurons and lowered DOPAC and DA depletion. Curcumin has also shown to elevate protein and LRRK2 mRNA expression and reduce caspase 3 levels[48]. In addition to these properties, curcumin also reduces iron positive cells in the substantia nigra and iron chelating activity[14].

Rubrofusarin and other compounds extracted from *Cassia obtusifolia* have many documented mechanisms that can be used against PD pathology. Experiments showed that rubrofusarin has protect the mice models induced with MPTP influence Parkinson's disease from neurodegeneration in the striatum, substantia nigra and dopaminergic neurons. When tested in other cell models within the same study, supplementation of rubrofusarin has shown to weaken ROS generation, mitigate cell destruction and depolarize the mitochondrial membrane[56].

S-allylcysteine, one of garlic's major organic compounds, is an organosulfur compound with multiple beneficial properties, including neuroprotective properties with the help of its free radical scavenger mechanism. This could have potential in anti-parkinsonian drug discovery as prior studies suggest that oxidative stress and subsequent free radical production are major factors in 1-methyl-4-phenylpyridinium (MPP+) induced toxicity. Rat models observed an overall attenuation of MPP (+) neurotoxicity, which led to an overall lowered reduction of dopamine levels. Introduction of s-allylcysteine in their diets has been directly linked to the complete blockage of lipid peroxidation, reducing the superoxide production of free radicals. Overall behavorial analyses of these rats showed an improvement in MPP (+) neurotoxicity induced locomotion impediment by 35%. As a result, it can be concluded that s-allylcysteine weakens MPP(+) induced neurotoxicity due to its antioxidant properties[55].

Sesamin, a lignan that is also one of the core phytochemicals found in sesame, has shown to protect neuronal cells from MPP(+) induced cell death by stabilizing tyrosine hydroxylase levels.

It was also found that sesamin hosts a range of protective characteristics to neuronal cells including raising superoxide dismutase activity, lowered nitric oxide (NO) synthase protein expression and catalase activity and had an overall anti-inflammatory effect in the microglial cells treated with MPP(+) induced interleukin. These characteristics reveal the enormous potential, lignan sesamin has in the realm of neurodegenerative disease treatment[34].

Withanone, withanolide, withaferin and withasomidienone are all lactones found in the root extract of Indian Ginseng plant (*Withania somnifera*). The plant itself has seen extensive use for over 4000 years in India and has shown to have some effect on locomotive function and neuronal growth. When the effect of withanone and other compounds of *Withania somnifera* were tested upon catecholamines in PD mice models, it was found that they reduced the levels of Levodopa (DOPAC), dopamine (DA), glutathionine (GSH) and other catecholamines in the mice models.

This led to an overall improvement in motor function and lowered physiological abnormalities. The results of this study show that phytocompounds found within *Withania somnifera* show promising results and can be used in creating more effective medication for Parkinson's disease[50].

Stilbenes are polyphenolic compounds that possess multiple beneficial properties that can be used to counteract age related diseases, neurodegenerative diseases and prevention of overall oxidative stress[52]. Stilbenes have also been observed to have a key role in dysregulating autophagy in studies with Parkinson's disease models. Resveratrol is one such natural stillbenoid that has long been studied for its anticancer properties. However, studies suggest that it can also play an important role in mitigating many neurodegenerative disorders, including Parkinson's disease[3]. Resveratrol's mode of action is directly linked to the activation of the SIRT1 genes.

When activated, they produce sirtuins, a family of enzymes that have preferential deacetylase activity. SIRT1 genes has shown significance as a requirement to mediate resveratrol's neuroprotective ability in an experiment conducted on the neuroblastoma cell line SK-N-BE exposed to a cell-permeable, toxic form of protein alpha-synuclein. However, when the expression of SIRT1 gene was downregulated, resveratrol's neuroprotective ability was inhibited as well[2].

Phenols and Phenolic Acids: Phenolic acids are naturally found in all plants. Phenolic acids contain two types of acids: hydroxycinnamic acids and hydroxybenzoic acids. They are used in medication for their antioxidant, anticarcinogenic, antimutagenic and anti-inflammatory properties[63]. Phenols are a subcategory of phenolic acids that contain a hydroxyl group combined with their aromatic hydrocarbon group. Plants synthesizes phenols when exposed by environmental stresses like wounding, insect attacks or pathogenic attack[28].

6-Shogaol is one of the phenolic compounds extracted from *Zingiber officinale* that has shown promise in its neuroprotective capabilities. Although this compound is more well known for its anti-cancer properties, in a report investigating its potential in spinal cord injuries of rat models, it was shown that 6-shogaol prevented apoptotic cell death of neurons and impeded on the loss of dopamine in the model's striatum. These findings can be utilized in studies of parkinsonian drug designing as these effects can be implemented to slow down the symptoms of onset PD[31].

Quercetin and Rutin are two phenolic compounds found predominantly in the mulberry fruit (*Morus alba*). Both possesses multiple bioactive characteristics that make them ideal for study having anti-inflammatory, anti-oxidant and neuroprotective functions. Mulberry extract, with quercetin and rutin in them, was found to inhibit nitric oxide and ROS generation, modulates the Bcl-2/Bax protein ratio and inhibits caspase 3 activity[32].

Rosmarinic acid is a phenolic compound and cinnamate derivative isolated from multiple plants such as *Melissa officinalis, Ocimum basilisum, Rosmarinus officinalis, Origanum majorana* and *Salvia officinalis*. This compound was found to ameliorate cell viability drastically via the blockage of intracellular ROS production, protection of mitochondrial membrane potential, modulation of Bcl2/Bax ratio and overall increase in dopamine production. Rosmarinic acid could also prevent cell morphological changes by preventing nuclear condensation and restoring mitochondrial respiratory chain's complex I activity. It is also known to inactivate caspase 3, preventing apoptotic processes as a result[13].

Terpenes: Terpenes and terpenoids are the main compounds found in essential oils extracted from a plant source with medicinal significance. Due to their having GABA (B) receptor binding properties that fortify nervous system, these compounds have been analyzed for their pharmacological properties and thus have been used for medicinal purposes. There are multiple subtypes of terpenes in existence and all of them display varying degrees of antioxidant, anti-inflammatory and anti-apoptotic activity.

However, similar to other phytocompound categories, they are capable of interfering biological pathways and promoting neuronal survival from degenerative mechanisms[30].

Bacosides, phytocompounds extracted from *Bacopa monnieri* plant, have also been studied immensely and well documented for its nervous system enhancing properties. Bacosides, well known terpenoids, have shown t multiple mechanisms that can be used in potential medication for PD. In one study, extracted bacosides were tested with cell lines pretreated with paraquat (PQ), an herbicide known to be a potential risk factor of causing onset PD.

Results show that they have protected cell lines of PD models against PQ induced toxicities and 1-methyl-4-phenyl-pyridinium iodide (MPP_1) induced toxicities. Bacosides also prevented depletion of glutathionine (GSH) and preserved mitochondrial membrane potential by regulating mitochondrial complex I activity.

Pretreating the cell lines with bacosides also led to inhibition of intracellular reactive oxygen species and lowered mitochondrial superoxide levels. Other documented effects of this family of phytocompounds include preservation of overall mitochondrial activity, cellular redox homeostasis and promotion of cell survival pathways[60].

Betulin, extracted from bark of *Betulin* sp, is a pentacyclic, lupine-type triterpene known to possess anti-inflammatory, anticancer and antimicrobial properties. Betulin lowers a-synuclein accumulation and overall ameliorate symptoms of Parkinson's disease in *C. elegans* models.

A study also revealed that betulin reverses the decrease in lifespan to afflicted *C. elegans* model, reduced abnormalities in the food sensing behavior and reduced neuron degeneration of 6-hydroxydopamine-induced dopaminergic neuron. The molecular mechanism of betulin that takes place against PD is that it downregulates the apoptosis pathway gene EGL-1 and promotes the expression of RPN1 gene[66].

Ginkgolides is found in the extract of *Gingko biloba* known to have antioxidant and anti-inflammatory effects in the body. A study was conducted to test the efficacy of the ginkgolides' capacity to inhibit MAO-A and MAO-B levels in rat models. MAO-B levels specifically were found to be lowered by at least 50% in the blood platelet levels. Subsequent dosage was done in human models as well and yielded much more positive results than rat models. The results make it clear that the compounds extracted from *Ginkgo biloba* can be studied further to develop more efficient drugs that lower MAO-B levels, thereby alleviating related PD symptoms as well[68].

Thymoquinone, a monoterpene compound, is a major bioactive constituent of black cumin seeds (*Nigella sativa*) with anti-inflammatory and antioxidant properties. In a study investigating its bioactive effects on rotenone and MPP(+) related toxicities, dopaminergic neurons from mice models were protected from these toxicities once treated with varying concentrations of thymoquinone.

Table 1
Phytocompounds and their pharmacological actions against Parkinson's disease

Plants	Phytoconstituents	Mode of actions
Bacopa monniera	Bacoside, Bacoside A, D-Mannitol, Betulinic acid	SOD and GSH restoration, reduced peroxidation of lipids, restored catalase levels, enhanced behavorial activity[62]
Cassia obtusifolia	Isorubrofusarin, rubrofusarin	Mitigated cell damage, attenuated ROS generation and mitochondrial membrane depolarization. SB and Striatal dopaminergic neurons protected from degeneration[56]
Camelia sinesis	Epicatechin-3-gallate	Attenuates DA depletion, iron dyshomeostasis and dopaminergic neuronal survival in the SN. Inhibition of DA uptake by blocking uptake of neurotoxin MPP+ injury. Regulation of extracellular signaling kinases[37]
Chaenomeles speciose	Catechin, epicatechin, rutin	Attenuates dopaminergic uptake by DA transport. Potent DA transport inhibitor, maintains cell viability, tyrosine hydroxylase activity[4]
Citrus sinensis	Naringenin, polymethoxyflavones	Mitigated dopaminergic neurons and tyrosine hydroxylase loss in SN of 6-OHD rat model[11]
Curcuma longa	Curcumin, bisdemethoxy curcumin, dimethoxy curcumin (DMC)	Protection of DA neurons against effects of a-synuclein and LPS, mitigation of dopamine loss leading to mitigation of oxidative stress. Restricted mitochondrial dysfunction[51]
Ginkgo biloba	Ginkgolides, bilobalides	Recovered and maintained tyrosine hydroxylase and DA levels in striatum and SN, inhibition of MAO activity, noted action against MPTP induced oxidative stress[68]
Mucuna pruriens	Levodopa (L-DOPA)	Cleavage of Caspase 3, Bax-Bcl-2 protein ration and antioxidant enzymes modulated[25]
Panax ginseng	Ginsenosides	Restoring homeostasis, reduced calcium influx, free radical generation, acting as a psychic energizer, protect neurons from mitochondrial dysfunction, glutamate elevation[33]
Polygala tenuifolia	Saponins, xanthones, oligosaccharide esters	Norepinephrine inhibited, causing anti-stress effects due to presence of TMCA (4,5-trimethoxycinnamic acid). Affected NO, ROS and caspase-3 activity and production[26]
Polugonum cuspidatum	Emodin, Reservatol	Lowered dopaminergic neuronal loss and neurobehavioral defects[29]
Pueraria thomsonii	Puerarin, daidzein, daidzin, genistein	Inhibited caspase 8 and caspase 3 activity[40]
Prunus dulcis	Morin (3,5,7,20,40-pentahydroxyflavone)	Weakened behavioral deficits and DA deprivation[69]
Uncaria rhynchophylla	Rhynchophylline, corynanthine, corynoxeine, hirsutine, catechin, epicatechin	Reduced caspase 3 activity and ROS generation. Maintained cell viability, GSH levels[21]
Vitis vinifera	Reservatrol, catechin, epicatechins.	Restricted apoptosis in MPTP induced neurons by regulating Bcl-2 expression and Bax gene[10]

The compound showed excellent results in both short terms and long-term models, rescuing as much as 83% of neurons in the long-term study of rotenone treated cultures[49]. Further list of other phytocompounds which have potential activity against PD has been mentioned in table 1.

Conclusion

This comprehensive review provides information about phytocompounds that are potential for prevention of PD. It also discusses about the etiology and potential treatment methods. The literature survey suggests that many phytochemicals are promising in targeting PD in *in vitro* studies though, *in vitro* studies need to be reconfirmed by *in vivo* studies. Screening of phytochemicals in cell lines often lacks clinical applicability due to biochemical, physiological and pharmacological relevancy.

The available literature from *in vitro* studies demonstrates that phytochemicals, such as baicalein, resveratrol, curcumin and epigallocatechin gallate showed promising therapeutic potential in inhibition of PD.

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