**ABSTRACT**

Around 1 billion people in the world are suffering from neurological disorders, such as Alzheimer’s, Parkinson’s, epilepsy, strokes and so other related diseases. Parkinson’s disease (PD) is the second most common chronic neurodegenerative disease that affects motor skills and cognitive performance. There have been various conventional/alternative approaches for the management of PD that are justable to alleviate symptoms. In terms of thus exploring for achieving novel substances with therapeutic benefits in PD patients is the focus of a wide range of current investigations. The aim is thus to comprehensively review phytochemicals with protective or therapeutic activities in PD and hence then focus on their neuropsychopharmacology mechanisms. Various subgroups of polyphenols (flavonoids, phenolic acids, stilbenes, and lignans) and terpenes that are the most abundant groups of phytochemicals with well-established antiparkinsonian effects. Also the Other phytochemical categories, such as carbohydrates, amino acids, alkaloids, cinnamates, and fatty acid amides, also have some representatives with positive effects in PD. Phytochemicals perform their antiparkinsonian effect through several mechanisms of action, including one is suppressing apoptosis (via the reduction of Bax/Bcl-2, caspase-3, -8, and -9, and α-synuclein accumulation), other reducing the expression of proinflammatory cytokines (such as prostaglandin E2, interleukin-6, interleukin-1β, and nuclear factor-xB), decreasing dopaminergic neuronal loss and dopamine depletion and modulation nuclear and cellular inflammatory signaling, elevation of neurotrophic factors, and improvement of antioxidant status. The various Plant-derived natural products can be considered as future pharmaceutical drugs or adjuvant treatment with conventional therapeutic approaches to improve their efficacy and attenuate or alleviate their psychological adverse effects in the management of PD. Well-designed recent clinical trials that are mandatory to evaluate the protective and healing benefits of phytochemicals are promising as future drugs in the management of neurodegenerative diseases.

**Keywords:** Medicinal plant; natural product; neurodegenerative disease; Parkinson’s disease; phytochemical.

**Introduction**

Neurodegenerative diseases are the most emerging diseases nowadays. Around 1 billion people in the world are suffering from neurological disorders, such as Parkinson’s, Alzheimer’s, epilepsy, strokes and so other related diseases.

Parkinson’s disease (PD) is an age-related neurodegenerative disorder of ageing population, originally described by James Parkinson in 1817 (Mirza et al., 2014; Kailash Kumar et al., 2018; Nag and Jelinek et al., 2019). It is a synucleinopathy, one of the mechanism of PD, that damages neurons in defined parts of the brain, causing basic motor signs (Armstrong and Okun, 2020) of muscle stiffness, tremor, the paucity of voluntary movements and postural instability (Shahpiri et al., 2016; Mirza et al., 2014; Warren et al., 2017).

The main cause of it remains as mystery till now (Naoi et al., 2019). The symptoms such as cognitive deficits and autonomic failure often occur as the duration of disease increases (Armstrong and Okun et al., 2020). It is diagnosed that disease pathogenesis is usually due to progressive loss of specific dopaminergic neuronal populations (Satish et al., 2016) or due to aggregation of the synapatic protein α-synuclein (Shahpiri et al., 2016) in the form of Lewy bodies (LB) or Lewyneurites (LN) (Dinda et al., 2019; Zhu et al., 2019).

The symptoms of PD also persist in many disorders such as dementia with LB, autosomal recessive juvenile parkinsonism (AR-JP), front temporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), pure akinesia, hereditary progressive dystonia, multiple system atrophy, progressive supranuclear palsy, structural lesions, brain injury, treatment with antipsychotic drugs, poisoning by carbon monoxide or manganese. Several gene mutations such as α-synuclein, parkin, tau, ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and GTP cyclohydrolase I (GCH-I) genes were also discovered accounts for 5-10% reported cases of PD (Teismann and Schulz, 2004). Various environmental factors like polymer, accumulation of manganese, mercury, selenium and iron, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure, rotenone, paraquat (N,N-dimethyl-4,4′-bipyridine dichloride), circadian rhythm, maneb, also contribute towards PD pathophysiology. Use of pesticides or insecticides increase...
the risk of PD while caffeine intake can reduce the risk of having PD. Worldwide, only fewer patients are suffering from familial PD or parkinsonism, otherwise, it is always sporadic and about 1% of people above age 65 are reported to have PD (Shahpiri et al., 2016; Kailash Kumar et al., 2018). It is reported to occur mainly in males as compared to females (Warren et al., 2017).

The drugs used in the treatment of PD either act on dopaminergic system or cholinergic system. The drugs acting on dopaminergic system acts either via increasing the dopamine concentration in the brain (basal ganglia), and in improving many of the clinical features of the disorder or by acting as dopamine agonist/precursors like pramipexole, ropinirole, levodopa, and carbidopa (Dinda et al., 2019; Warren et al., 2017). Rasagiline, selegiline, safinamid, entacapone, and tolcapone are the drugs that reduce the metabolism or degradation of levodopa and dopamine by selectively inhibiting the enzymes catechol-O-methyl transferase or monoamine oxidase B. Levodopa is a major dopamine precursor that restores the dopaminergic activity effectively (Warren et al., 2017), but it produces wearing off effect or on/off effect on prolong use. Safinamide is a drug (monoamine oxidase inhibitor), which is useful to decrease the off effect of levodopa and keep it in “ON” effect. The antimuscarinic drugs, are an alternative approach to restore the normal balance of dopaminergic and cholinergic system in the brain like trihexyphenidyl, and benztropine.

Current pharmacotherapies that are available for the disease do not provide the much desired permanent curative benefits to patients. But Nutritive Scientists have identified natural products has the potential of adjuvant treatments to conventional drug therapy to attenuate the PD symptoms and reducing anti-Parkinson drugs and adverse events incidence. With long term treatment with Levodopa high rate of dyskinesia and relapse of Parkinsonian symptoms is there (Alskhog JE et al., 2000). But Combination therapy with natural herbal products for PD has demonstrated substantial benefits in lowering levodopa- related complications (Rao SS et al., 2006). However, it is investigated that there are no long-term effect of combination therapy and potential interactions with drugs that are currently used in the PD treatment thus remain unclear. It is also found that Adjunct therapy with natural products may prove subsequent useful for reducing the dose of levodopa for managing PD symptoms.

While many natural products are promising for the treatment of PD and management of Parkinsonism symptoms, currently available pharmacological interventions thus provide only limited efficacy in reversing the underlying neuropath logical changes in PD and will provide only symptomatic relief for patients with PD. Therefore, the need to clinically identify therapeutic agents that can attenuate or ameliorate, or slow down the deleterious deliberate processes associated with PD. One such motive is to explore the possible contribution of natural products that might interfere with PD pathology. As it have been found that Natural products have been increasingly found to have specific molecular or pharmacological effects that are likely to contribute to the development of neuroprotective agents against PD and in neuropathological changes also (Armstrong and Okun, 2020).

The various bioactive derivatives of plants such as polyphenols, flavonoids, stilbenoids and alkaloids possess potent anti-oxidative and anti-inflammatory properties that are having an ameliorative interest for the treatment of PD. These naturally occurring phytochemicals can also promote the mitochondrial function and they can also serve as important cognitive enhancers in PD. Moreover, these natural compounds or herbs act as inhibitors for α- synuclein aggregation, c-Ju N-terminal kinase (JNK) activation, and monoamine oxidase production, and are agonists for dopaminergic neurons in Parkinson. Considering the socioeconomic burden and undesirable side effects of synthetic drugs, natural remedies are promising avenues in the treatment of PD (Armstrong and Okun, 2020).

**Literature Review**

**Definition**

Parkinson’s disease (PD) is the second most common progressive chronic neurodegenerative disease of the central nervous system that affects an estimated 6 million people worldwide often including tremors (Gopalakrishna and Alexander, 2015). The dopamine level in the brain is dropped due to the nerve cell damage in brain that further leads to sparing of the dopaminergic neurons causing PD.

**Symptoms**

The various significant debilitating most common symptoms of Parkinson that are commonly associated with PD disorder include TRAP that is tremor, rigidity, akinesia, and postural instability, also it includes autonomic dysfunction, drooling, depression, anxiety, cognitive dysfunction, and sleep disturbance (Bassani et al., 2015; Gopalakrishna and Alexander, 2015). These symptoms are caused by the progressive loss or damage of dopaminergic neurons in the substantia nigra (SN) to the striatum (ST), which is associated with the motor deficits of the disease (Qualls et al., 2014; Bassani et al., 2015; Gopalakrishna and Alexander, 2015; Moon and Paek, 2015).
Risk Factors

The various Risk factors for the Parkinson’s disease include:

**Age:** Many young adults very rarely experience PD. The mean age of patients experiencing the PD is at the beginning of 55 years of age. The usual prevalence of PD is estimated to be seen approximately up to 1% to 4% in people over 60 years of the age that is in old age (Blesa *et al*., 2015; Moon and Paek, 2015; Ortiz-Ortiz *et al*., 2010).

**Heredity:** Hereditary may also affect the occurrence of the PD that is when one may having a close relative with PD then there are increase number of the chances that you’ll develop the disease.

**Sex:** It is Exposure to toxins: The long-term ongoing exposure to the various agricultural herbicides and pesticides may slightly increase your risk of PD to the one. Since agricultural fields account for 37.7% of land area worldwide therefore the use of pesticides is a very important risk factor in neurodegeneration and parkinsonian effect, there is a crucial need to focus on the association and management between pesticides and PD (Mansa *et al*., 2019).

reported to occur mainly in males as compared to females (Warren *et al*., 2017) that is Men are more likely to develop PD than that when compared to that of women.

### Stages of Parkinson’s disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Worsen</td>
</tr>
<tr>
<td>3</td>
<td>Mid</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>Debilitating</td>
</tr>
</tbody>
</table>

**Fig. 2 : Different Stages of Parkinson’s Disease**

**Stage One**
This is the initial stage, in which the person has mild symptoms that mostly do not interfere with daily activities. The symptoms that occur are Tremor and other movement symptoms on one side of the body only. Rest noticeable changes are changes in posture, walking and facial expressions (Satish *et al*., 2016).

**Stage Two**
In this, the symptoms start getting worse. The symptoms this time occur on both sides irrespective of stage 1 PD like Tremor, rigidity another movement symptoms affecting both sides of the body. Also the Walking problems and poor posture may become apparent. In this stage, the person is still able to live alone, but day to day task completion becomes more difficult and may take longer (Satish *et al*., 2016).

**Stage Three**
In this Stage it is considered as mid-stage of PD in the progression of the disease. There is Loss of balance and slowness of movements is the basic hallmarks of this stage or phase. The person Falls are more common. Even though the person is still fully independent, symptoms significantly impair the basic day to day activities of daily living activities such as dressing and eating (Satish *et al*., 2016).

**Stage Four**
In this stage of Parkinson’s, symptoms appear to be severe and very limiting. It’s seemed possible for a person to stand without assistance, but movement thus may require a walker. The person needs proper help with day to day activities of daily living and is unable to live alone anymore (Satish *et al*., 2016).

**Stage Five**
In this stage it is the most advanced and debilitating stage of PD. There is Stiffness in the legs which may make it impossible for a person to stand or walk. Therefore, the person requires a wheelchair or is bedridden completely. Around-the-clock nursing care is completely or must require for all activities. The person may also experience symptoms like hallucinations and delusions. While stage five focuses on the motor symptoms, the Parkinson’s community has acknowledged that there are many more important non-motor symptoms as well (Satish *et al*., 2016).

**Phytoconstituents**
The Phytochemical agents as future medicinal resources for mental diseases:-

The Herbal therapy possesses a life long history of safe and efficacious use and administration as a therapeutic agent, alternative or complementary medicine, or dietary supplement forth treatment of a wide range of different pathologies in different nations all over the world.

Naturally occurring plants or Herbal medicines, with their thus wide variety of phytochemical molecules, therefore have revealed their protective and therapeutic benefits in
many indications, such as neuropsychological diseases like Parkinson’s and Alzheimer’s disease. Nowadays, the tendency towards the various plant-derived natural products as future medicines is rising remarkably (Farahani et al., 2015; Nirumand et al., 2015).

The consumption of natural medicinal plants has been strangely but subsequently elevated with the rate of nearly 380% (Ang-Lee et al., 2001). As it is estimated that around 14% of the people of the world are using the naturally occurring medicinal plants and that this level of using the natural herbs or naturally occurring medicinal plants have been growing exponentially (Anderson et al., 2012). There are different several systematic reviews on the therapeutic effects of natural products in the management of different psychological disorders, including Parkinson’s, Alzheimer’s disease, generalized anxiety disorder, insomnia, depression, and schizophrenia (Lakhan and Vieira, 2010; Xie et al., 2013; Yu et al., 2014; Bahrami-Soltani et al., 2015; Farahani et al., 2015; Farzaei et al., 2016). Thus whether single or combined with current pharmaceutical drugs that are provided the, plant derived natural molecules or phytochemical agents provide a widespread research area in the management of PD. Thus, the current study query revolves around the available phytochemical compounds with well-established protective or therapeutic activities in PD and discusses their prediction neuropsychopharmacology mechanisms in the PD.

Chemical categories of natural compounds with therapeutic and protective effects in PD

Polyphenolic compounds

Polyphenols consists of a large and numerous diverse families of compounds that have the common chemical structure having a phenol ring (Farzaei et al., 2015; Shay et al., 2015). Polyphenolic compounds are mainly divided into several further categories including flavonoids, phenol acids, stilbenoids, tannins, phenolic alcohols, and lignans (Basheer and Kerem, 2015). Polyphenols have very powerful antioxidant properties that are mainly due to their free radical scavenging or rummage capacity and because of their iron-chelating activity. The therapeutic effects comprising to polyphenols are anti-inflammatory, antiviral, antibacterial, neuroprotective, and anticarcinogenic activities (Basheer and Kerem, 2015).

Flavonoids

Flavonoids are the most in numerously abundant group of polyphenols that are divided into six subclasses: flavonols, anthocyanins, flavones, flavonones, and isoflavones and flavanones, (Pandey and Rizvi et al., 2009). The various Anti-inflammatory, antithrombotic, anticancer, and antimicrobial, immunomodulatory, and antiviral activities are the numerous biological properties of flavonoids (Sodagari et al., 2015).

Naturally present compound Acacetin is aflavone that is naturally present in plants, such as Calaminth spp, Linaria spp, Chrysanthemum morifolium, Carthamus tinctorius, Robinia pseudo acacia (also called black locust), and Turnera diffusa (known as damiana). It shows its antiparkinsonian effect by inhibiting the various inflammatory factor that is production of inflammatory factors, including prostaglandin E2 (PGE2), nitric oxide (NO), and tumor necrosis factor-α (TNF-α) as well as reducing dopaminergic neuronal loss, and cyclooxygenase-2(COX-2)glial activation, inducible NO synthase (iNOS), and increasing DA level (Kim et al., 2012).

Baicalein is again one of the major flavonoids that are found in the root of the naturally occurring Chinese medicinal herb Scutellariabaiacalensis. Baicalein is antiparkinsonian that it protects against PD by inhibiting apoptosis and thus also increases in the cell viability in SH-SY5Y cells (increase of the thrice cloned subline of the neuroblastoma cell line). It is thus has been reported from cellular studies that of PD that baicalein significantly improves the various morphological properties and cell viability ofPC12 cells, which is a cell line from the pheochromocytoma of the rat in the adrenal medulla and is used commonly as well known animal model of PD. The enhancement of the enzyme tyrosine hydroxylase (TH)-results in the positive neuronal loss and diminishing the immune reactivity of protein of the glial fibrillary acidic protein (GFAP) present in neurons are thus among various other antiparkinsonian mechanisms of baicalein (Mu et al., 2009). Also The protective effect offlavonoid Bu-7, a biologically active flavonoid which is isolated from the leaf extracts of Clausenaalansium against the development or betterment of PD, is associated with increasing the neural cell viability and hence reducing the cell apoptosis by suppressing the phosphorylation status and also the expression of enzyme which is mitogen-activated protein kinase (MAPK) protein family, having JNK and p38, which have a major role in apoptosis in neural cells. Also it has been confirmed that the pathway MAP signaling pathway possesses a major key contribution to the intrinsic cell apoptosis mitochondrial process, which thus in turn has a pivotal o major role in the understanding of the pathogenesis of the neurodegenerative disease. This flavonoid is also useful in reducing the expression of gene53, which is a tumor-suppressing gene, which suppresses it significantly. This flavonoid also suppresses the expression of the specific proteins that are used to regulate neural cell death, and the ratio of proteins that are Bcl-2-associated X protein/B-cell lymphoma (Bax/Bcl-2), and in also the expression levels of cleaved cells (presumably active) caspase-3 in neuron cells (Li et al., 2011).

Epigallocatechin-3-gallate (EGCG), is an pivotal polyphenol obtained from green tea, and thus can be effective in the various neurodegenerative diseases treatment such as PD through the improvement of progress is seen in neural cell viability (Tai and Truong, 2010; Ye et al., 2012). The antiparkinsonian effect of EGCG is mediated or shown by the increase in reactivator that is peroxisome proliferator-activated receptorcoactivator- 1α (PGC-1α) and also in the silent mating-type protein information regulation 2 homolog (SIRT1) protein expression. SIRT1 and PGC-1α are thus among the major important metabolic regulatory transcriptional agents that are meant to have a contribution showing the modulation of the cellular performance of the cells in the stress condition of the neurodegenerative disorders such as PD. This phenolic compound EGCG also enhances the level of the mRNA and enzymatic expression of enzymes, superoxide dismutase (SOD) 1, enzymes catalyses (CAT), striate antioxidative and glutathione peroxidase 1 (GPx1) as well as also in the reduction of ROS (Ye et al., 2012). EGCG promotes the TH protein expression and also the TH activity, showing a significant role in catecholamine and synthesis of dopamine and also prevents dopaminergic neuronal loss in
the ST (Levites et al., 2001). It also increases the proteomic expression of protein kinase Ca (PKCa), which is having a vital role in the function of neural cell membrane and also in the tight junctions. Thus, by Enhancing the proteomic expression of the antiapoptotic protein Bcl-2 as wells areduced inthecell up regulation of the apoptotic agent that is Bax are therefore among the other mechanisms of EGCG in the crucial management of PD (Levites et al., 2001; Mandel et al., 2004).

Likewise, Theaflavin, also a major constituent of black tea that reduces the loss of nigra TH-positive neurons and also that exerts a cell antiapoptotic activity via the suppression of the caspase-3, -8, and -9 in SN (Anandhan et al., 2012).

Fustin is a methanolic extracted flavanonol isolated from the methanolic extract of Rhus verniciflua (heartwood). Flavanolof Fustin demonstrated the mechanism of the neuroprotection via the suppression of cell apoptosis, which is then mediated by the reduction in caspase-3 activation, Bax/Bcl-2 ratio, p38 phosphorylation activation, and ROS generation.

Hesperidin, is a flavanone that is mainly found in the citrus plants, that can protect neurons in the area SN pars compacta by the protection of membrane of mitochondrial membrane potential (MMP), and the enhancement of cell proliferation and also the increase or attenuation of apoptotic cell markers. It thus also enhances the antioxidant performance that is including the decrease in the lipid peroxidation and also in the intracellular ROS formation, as well as the elevation of reduced glutathione (GSH) (Tamilselvam et al., 2013).

Silymarin flavonoids, that are isolated from the seeds of plant Silybum marianum, having the restored DA content and also preserved TH-positive neurons in the SN (Kumar et al., 2013; Pérez et al., 2014). The Silymarin flavonoids also increase the protein expression vesicular monoamine transporter-2 (VMAT-2) and the mRNA and protein expressions and decrease cytochrome P 450 2E1 (CYP2E1) activity of protein. Silymarin also helps in elevating the antioxidant agents, that are glutathione- S-transferase A4-4 (GSTA4-4), and GST mRNA expression and activity and it also suppresses the lipid per oxidation and the nitrite production. The antiapoptotic effect of silymarin is because of the suppression of protein P-p53, Bax, and caspase-9 expression (Kumar et al., 2013).

Moreover, another the flavonoid Silibinin, which is the major active constituent of silymarin, have represented the very beneficial effects as anti Parkinsonian in PD by increasing the TH-positive fibers and also the cell reduction of dopaminergic neuronal loss in both the ST and the SN as well as in the prevention of MMP disruption (Lee et al., 2015).

Quercetin also possesses the inhibitory activity on the enzymes like catechol-O-methyltransferase (COMT) and the enzyme monoamine oxidase (MAO) enzymes and therefore can thus increase the bioavailability of L-dopa that is levodopa in the brain (Singh et al., 2003).

Kaempferol is also a natural flavone that is widely existed in a number of plants species. Kaempferol thus therefore exhibited the neuroprotective effects by the prevention of TH-positive neuronal loss, increasing or attenuating the depletion of the levels of the striatal DA and its metabolite, that is 3,4-dihydroxyphenylacetic acid (DOPAC), as well as increase in the activity of the various antioxidant enzymes (SOD and GPx) (Li et al., 2011). It has been thus also reported that the natural flavanone kaempferol thus helps in decreasing the ROS formation, and also protects MMP, and hence improves the mitochondrial turnover by the autophagy (Filomeni et al., 2012).

Moracenin D, is a phytochemical or phytoconstituent that is isolated from the root bark of plant Morus alba, that have demonstrated protective effects on the neurons via decreasing the a-syn mRNA and also the protein levels and hence increasing the protein expression of nuclear receptor related 1 protein (nurrl) mRNA and protein, which has a vital role in the development and particular specification of the midbrain Dopaminergic neurons (Ham et al., 2012).

Phenolic acids and phenols

Phenolic acids are the secondary plant metabolites that are naturally occurring in the whole territory of the different species or the world plants. They contain the acidic compounds like hydroxybenzoic acids and hydroxycinnamic acids. Also the various important pharmacological and biological properties of these compounds include anticancer, antioxidant, anti-inflammatory, anticarcinogenic, and antimutagenic activities (Stalikas et al., 2007).

Salvianic acid, which is derived from the plant Salvia miltiorrhiza, is capable of ameliorating cell death rate and attenuate the performance of the antiapoptotic function by reducing the ROS formation, and also in relieving the changes in the nuclear morphology of cells, also in the protecting of MMP, and also modulating the cell apoptopic/antiapoptotic agents, and decreasing the ratio of Bax/Bcl-2 ratio, and thus reducing caspase-3 activity (Wang and Xu, 2005).

Syringic acid is naturally occurring one of the major fruit that is benzoic acid derivatives found in fruits and edible plants. The Syringic acid exerts an antiparkinsonian properties that is in treating the PD by lessening the lipid per oxidation, and also by improving the GSH level, and suppressing the proinflammatory cytokines expression, that are such as TNF-α, interleukin (IL)-β1, and COX-2 enzyme. In chronic motor dysfunction the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)/probenecid induced motor dysfunction, which is an experimental model of the neurodegenerative disease like PD, it prevented by the loss of striatal DA and its vital metabolites and thus ameliorated the expression level of TH and VMAT-2 in SN (Rekha et al., 2014).

Rosmarinic acid, is a cinnamonate derivative, which is a phenolic compound that is mainly found in various naturally occurring medicinal plants, such as Salvia officinalis, Ocinum basilicum, Rosmarinus officinalis, Melissa officinalis, and Origanum majorana (Du et al., 2010). This compound exhibited a tremendous remarkable neuroprotective activity or antiparkinsonian activity by ameliorating the cell viability, and protecting MMP, also by blocking intracellular ROS production (Renet et al., 2009; Du et al., 2010), and increasing the DA content, and thus by modulating Bcl-2/Bax ratio. It could also prevent cell nuclear condensation and the various cell morphological changes, which are then mediated by restoring complex I activity of
the mitochondrial respiratory chain and also the inactivation of caspase-3 (Du et al., 2010).

Phenols are themselves a class of polyphenolic compounds that are comprising of a hydroxyl group joined to an aromatic hydrocarbon group, which are then synthesized by plants in response to ecological stresses such as insect or pathogen that is attack and wounding (Klepaka et al., 2011; Bahramisoltani et al., 2015).

6-Shogaol, is an extractable pungent ingredient present in ginger, possesses a neuroprotective effects via decrease in suppression of the neuroinflammatory factors, such as NO and iNOS, TNF-α, andCOX-2, and microglial activation in the SN pars compact and ST (Park et al., 2013).

Likewise, sesamol is a natural occurring lignin obtained from the plant species Sesamum indicum with very well-established neuroprotective properties that is used as antiparkinsonian .Sesamol enhances the activities of the various antioxidant enzymatic enzymes that include [SOD, CAT, GPx, and glutathione reeducates(GSR)] and nonenzymatic antioxidant enzymes (GSH, vitamin C, and vitamin E)antioxidants and thus therefore also alleviates the levels of the lipid per oxidation and nitrite level to near normal value. (KhadiraSereen et al.,2014).

Stilbenes

Stilbenes are natural occurring polyphenolic compounds that are found in many plant species, including the wine grape belonging to plant species (Vitis vinifera), another is cocoa obtained from plant (Theobroma cacao),and tomato obtained from plant fruit (Lycopeisson esculentum), strawberry obtained from fruit of plant (Fragaria x anannasa), peanut obtained from the fruit of plant (Arachis hypogaea), and also many tree species like (Pinus spp. and Piceaspp.).

Stilbene compounds possess many numerous beneficial properties for the prevention of the factors like oxidative stress, age-related diseases(such as obesity and type 2 diabetes mellitus), and also the neurodegenerative diseases (such as age-related macular degeneration and Alzheimer’s disease; Parkinson’s disease) (Reinisalo et al.,2015). The Dysregulation of the autophagic pathway is then was observed in the brains of the patients with neurogenetative disorder like PD and in experimental models of the disease PD, indicating that the key role of autophagy and in the pathphysiology of neurodegenerative diseases like PD.

Amurensin G, is an oligostilbene compound which is isolated from the root of the plant Vitis amurensis(which is a type of wild grape), the modified autophagosome markers thus by increasing the level of the various autophagic markers, that are light chain (LC)-3II, and decreasing in the level of p62. Amurensin G also enhances the cell viability intheSH-SY5Y cells and therefore inhibit the cell cycle and then arrest by decreasingG2/M and protein suppressing α-syn and ubiquitinated proteins(Ryu et al., 2013).

Resveratrol, which is a natural stilbene compound in various plants that includes grape skin and seeds and obtained from the plant Polygonum cuspidatum, and thus could have applied protectiveeffects on the animal and cellular models of PD (Chao et al., 2008; Wang et al., 2011). The In vitro studies on antiparkinsonian effect have revealed the capability of resveratrol to reduce the enzyme level of lactate dehydrogenase (LDH) release and thecaspase-3 activity. Its hydroxylated derivative, which is oxyresveratrol, have showed the similar attenuated neuroprotective effects via the reduction of intracellular formation of ROS, attenuation of phospho-JNK-1and phospho-JNK-2, and also the increase in SIRT1 cytosolic levels(Chao et al., 2008). In an illustrated animal model of PD, the protective effects of natural stilbene resveratrol and its liposome’s on nigral dopaminergic neurons was reported clearly, which is attributed to the amplification or modification of the number of total nigral cells and dopaminergic neurons, and in the increase in total antioxidant capacity(T-AOC), and apoptosis of nigral cells. The liposomal forma demonstrated and stronger neuroprotective effect (Wang et al., 2011).

Curcumin

Curcumin or called diferuloylmethane is a polyphenolic compound obtained from the rhizome of the plant Curcuma longa (Ortiz-Ortiz et al., 2010; Du et al., 2012; Qualls et al., 2014). In a model of the antiparkinsonian rat model of the6-hydroxydopamine (6-OHDA)-lesion rat model of PD, curcumin treatment is reversed via the dopaminergic neuronal losses well as DA and DOPAC depletion. In addition, to this activity curcumin also possessed iron-chelating activity and reduced iron-positive cells in the SN (Du et al., 2012). In vitro results have showed that curcumin treatment have reduced caspase-3 levels and also increased the LRRK2 mRNA and protein expression, which is thus involved in the vital pathological inclusions (Ortiz-Ortiz et al., 2010; Qualls et al., 2014).

Terpenes

Terpenes are one of the most extensively naturally occurring compounds with the greatest molecular variation among the secondary metabolites occurring in nature or naturally (Gonzalez-Burgos and Gomez-Serranillos, 2012; Ikram et al., 2015). Terpenes are mostly highly used in the commerce as flavors, fragrances, nutraceuticals compounds, pharmaceuticals as therapeutic agents, and industrial chemicals (Ikram et al., 2015). Terpenes are mainly categorized as mono-, sesqui-, di-, ses-, tri-, and tetraterpenes which is classified as depending on the number of isoprenoid units present in it (Fabio et al., 2014). The biological and pharmacological properties of the terpenoids include the cancer and the chemo preventive effects, antihyperglycemic activity, antimicrobial, antifungal, antiviral, anti-inflammatory and antiparasitic activities (Paduch et al., 2007).

Carnosic acid is thus a phenolic diterpene which is isolated from the herb rosemary (R. officinalis; Park et al., 2008). In cellular models of cell apoptosis, the canonic acid increased neural cell viability (Park et al., 2008; Chen et al., 2012) by enhancing the antioxidant performance, and thus by including γ-glutamylcysteine ligase catalytic subunit (GCLC), GSR, and SOD, activation of nuclear factor-E2-related factor 2 (Nrf2) pathway, γ-glutamylcysteinylglutamic acid modifier subunit (GCLM), and brain-derived neurotrophic factor (BDNF) release (Park et al., 2008; Chen et al., 2012). Therefore, It suppresses the protein expression and activity of apoptotic agents, such as Bel-2/Bax ratio (Wu et al., 2015), cleaved caspase- 3, caspase-3 and -12 activation (Park et al., 2008), poly (ADP-ribose) polymerase (PARP); (Chen et al., 2012), ratio of cleaved caspase-3/ caspase-3, and cleaved PARP/PARP in animal models of PD (Wu et al., 2015).
Enhancement of JNK phosphorylation in the canonical acid (Park et al., 2008; Chen et al., 2012), and also the activation of p38, and reduction of intracellular ROS generation are among other alleviated neural mechanisms by which this natural molecule exhibits its neuroprotective effect (Chen et al., 2012).

Ginkgolide B, is the main one of diterpenes that exist in the plant extract of Ginkgobilboa extracts, that protects against neurotoxicity by suppressing the elevated concentration of intracellular calcium concentration and also the cell death and decreasing the activity of caspase-3. Calbindin D28K protein present in it is calcium-binding protein that induces neurite outgrowth in dopaminergic neuronal cells and thus is able to protect dopaminergic neurons against the pathological process of PD. In vitro evidence of the terpene have confirmed that ginkgolide B possesses a remarkable potential in restoring the protein calbindin D28K mRNA (Meng et al., 2007).

Ginsenosides are the biologically active triterpenoids that are obtained from the plant ginseng. Out of more than 100 known species of the ginsenosides, most studies have assessed the ginsenosides Rb1, Rg1, Rg3, Rd, Re, Rh1, and Rh2 (Ardah et al., 2015). Therefore it has been found that ginsenoside Rb1 and Rg1 have possess remarkable beneficial effects in PD that is an antiparkinsonian effect, which is mediated by the inhibition of the α-syn fibrillation and the then seeding process of α-syn aggregation and also α-syn oligomerization. In an in vitro model of PD, Rb1 demonstrated that, while in the presence of this triterpenoidal ginsenoside, the inhibition of the α-syn fibrils were disaggregated (Ardah et al., 2015). Ginsenoside Re that could easily rescue the mitochondrial dysfunction in PD by increasing the proteins like chaperones, such as leucine-rich pentatricopeptide repeat-containing (LRPPRC), heat shock protein (Hsp) 90, and Hsp60. Chaperones are the specific kind of proteins that are involved in the folding of nascent proteins and that are able to protect the proteins against stress induced misfolding, which thus then indicates their important role in protection against the development of PD. Also the Restoration of NO level and signaling and the improvement of complex IV deficiency in the dopaminergic neuronal cells affected by enzyme PINK1, which is a kinase enzyme that is involved in PD, are among other various neuropharmacological mechanisms of this natural agent of terpene (Kim et al., 2012a). The molecular mechanisms involve in the neuroprotection of oleuropein, a main component of olive leaf extract, include the enhancement of this cell viability and diminution biochemical markers of cell death or apoptosis, including intracellular proteins formation like ROS, Bax/Bcl-2 protein ratio, caspase-3 activation, and DNA fragmentation (Pashan-Aliaabadi et al., 2013).

Paenoflorin is the majorly active ingredient isolated from the plant species Paeoniae alba radix (red peony root; Liu et al., 2006). Paenoflorin possesses the neuroprotective effects against neuronal injury or antiparkinsonian effect in both the mouse model of PD and PC12 cells. It was found that the naturally occurring paenoflorin attenuates the α-syn accumulation via the increase in protein expression of LC3-II, specific marker of phagophores and autophagosomes. In addition, to this paenoflorin modulates an acid-sensing ion channel (ASIC) currents and their cell’s protein expression in PC12 cells, resulting in increasing cell viability (Sun et al., 2011). In animal models of PD illustrated, paenoflorin improved dopaminergic neuronal loss, microglial and astrocytic activation, production of proinflammatory molecules, and activation of the adenosine A1 receptor (A1AR; Liu et al., 2006).

The two main phytocannabinoid that are: one is Δ9-tetrahydrocannabinol (Δ9-THC) and other is cannabidiol, are thus the two phytocannabinoids derived from Cannabis sativa, exerted neuroprotective actions by the very similar mechanisms through the reduction of DA and DOPAC depletion and increasing TH activity in SN (Lastres-Becker et al., 2005). Another phytocannabinoid, that is Δ9-tetrahydrocannabivarin (Δ9-THCV), also protects the nigral neurons from the cell death by affecting the receptors of the cannabinoid (CB) 1 and 2 receptors, and thus increase in the glutamate content of the ST, reduction of dopaminergic neuronal loss, and also in the attenuation of microglial activity (Garcia et al., 2011).

Celastrol is a triterpene compound that is obtained from the plant species of Tripterygium wilfordii (which is an ivy-like vine). Celastrol treatment as antiparkinsonin diminishes the dopaminergic neuronal loss and therefore also suppresses the DOPAC and DA level depletion as antiparkinsonian effect. This triterpene hence alleviates the production of different - different mediators of the inflammatory process, such as TNF-α and nuclear factor-κB (NF-κB). Celastrol thus also induces an increase in Hsp70 and also then attenuates the cytoplasmic Hsp70 nuclear translocation (Celeron et al., 2005).

Madecassoside is a bioactive compound from the Chinese medicinal herb obtained from the plant species Canella Asiatic, and thus lessens or alleviates the depletion of DA and its metabolites, homovanillic acid (HVA) and DOPAC, in ST and reduces malonyldialdehyde (MDA) level, which is a marker of lipid per oxidation. Madecassoside significantly enhances striatal BDNF level, which is mainly associated with the protection, growth, and differentiation of neurons and synapses. Also it also modulates and alleviates the ratio of antiapoptotic/apoptotic agents (Bcl-2/Bax) and enhances antioxidant molecules such as GSH concentration (Xu et al., 2013). The various Cellular and animal investigations showed that various terpenoid compounds, that are including), pedicularioside A (a phenylethanoid ingredient from Buddleia lindleyana), Δ3,2-hydroxybakuchiol (a meroterpenoid of Psoralea corylifolia and tenuigenin (an terpenoid component of Polygonum tenuifolia root), possess dopaminergic neuroprotective activity as antiparkinsonian effect, which are mediated by preventing the morphological abnormalities of ST cells, dopaminergic neuronal loss, and DA/nor epinephrine uptake in synaptosomes, thus by elevating the number of TH-positive dopaminergic neurons, suppressing the apoptotic enzymes such as cleaved PARP and caspase-3, and reinforcing as the antioxidant performance (Li et al., 2008; Zhao et al., 2009; Liang et al., 2011).

Alkaloids

Alkaloids are the nitrogen-containing secondary metabolites that are first considered as the largest group of bioactive natural compounds that are obtained from plants (Barbosa-Filho et al., 2006). They have an extensive numeros range of biological activities, such as antimicrobial, antiviral, antihypertensive, anti-inflammatory, antidepressant, emetic, diuretic, antitumor, anticholinergic, and
sympathomimetic, hypnoanalgesic, and miorelaxant (De Sousa Falcon et al., 2008). Numerous alkaloid components that are suggested to have the most therapeutic potential in different neurodegenerative diseases such as PD and Alzheimer’s disease.

**Zingerone**, is an alkaloid component of ginger rhizome that is demonstrated as a remarkable antiparkinsonian potential in experimental researches. Zingerone reduces the depletion of DA and its metabolites that are (DOPAC and HVA) and enhances the antioxidative defense including the compounds like hydroxyl and superoxide scavenging activity (SOSA) along with suppressing oxidation (Kabuto et al., 2005).

**Acetylcorynoline** is an alkaloid isolated from the plant species *Corydalis bungeana*, encompasses the numerous neuroprotective effects by preventing the dopaminergic neuron loss, DA level depletion, and the aggregation of α-syn protein. It suppresses the cell apoptosis by reducing the expression level of the egg laying abnormal-1 (egl-1), which is an apoptosis modulator as an antiparkinsonian effect. The activities like Protein misfolding and aggregation, which can cause the production of inclusion bodies, have a key contribution in PD pathogenesis. It has been easily confirmed that acetylcorynoline can inhibit PD pathogenesis by enhancing proteolysis by a somatic proteasomic activity as an antiparkinsonian effect, which is mediated by raising the expression level of rpn-5, a proteasome regulatory subunit (Fu et al., 2014).

**Other compounds**

**Trehalose**, a carbohydrate which is derived from plants, such as *Botrychium lunaria Selaginella lepidophylla* and *Myrothamnus flabellifolius*, demonstrated the enormous protective effects against MPTP/probenecid-induced PD. The antiparkinsonian effect of this natural product in the treatment of PD is mediated by suppressing glial cell activation and astrocytic hypertrophy, reducing the depletion of DA and its metabolites, improving the DA transporter (DAT), and thus preventing the numerous morphological abnormalities of ST endothelial cells (Chakroborty et al., 2011).

**L-theanine**, which is an amino acid found in green tea obtained from the plant species (*Camellia sinensis*), demonstrated a remarkable effect in the neurodegeneration of neuroblastoma cells as antiparkinsonian effect by preventing the nuclear damage, modulating extracellular signal-regulated kinase 1/2 (ERK1/2)enzyme and caspase-3 activation, and improving the neurotrophic agents, glial cell line-derived neurotrophic factor (GDNF), and BDNF (Chao et al., 2008).

**Eicosanoyl-5-hydroxytryptamide**, which is a fatty acid amide (indole) derived from the coffee, is reported to have antiparkinsonian activity by inhibiting the mechanism of the demethylation of phosphoprotein phosphatase 2A (PP2A) and also the enhancing the viability of neuroblastoma cells (Lee et al., 2015).

**Sulforaphane**, which is an isothiocyanate mainly found in zoological Cruciferae family, showed cytoprotective effects as antiparkinsonian effect in cellular models of dopaminergic neuronal degeneration via the protection of main cell membrane integrity, also the reduction of proinflammatory cytokines and intracellular inflammatory pathways, and the improvement of antioxidant status, and also decrease in endoplasmic reticulum stress (Han et al., 2007; Brandenburg et al., 2010; Vauzour et al., 2010; Deng et al., 2012a,b). The compound also showed a vital *in vivo* antiparkinsonian effect via the decrease in dopaminergic neuronal loss, DNA fragmentation, and also the caspase-3 activation as well as the elevation of endogenous antioxidants as an antiparkinsonian effect (Morroni et al., 2013).

Polyphenols consisting of multiple hydroxyl groups on aromatic rings are categorized into flavonoids, phenolic acids (gallic and ferulic acid), stilbenes (resveratrol), curcumin, astaxanthin, diferroxymethane and tannins (Naoi et al., 2019).

**Conclusion**

PD is the second most common chronic neurodegenerative disease that affects motor skills and cognitive performance. To date, in the various therapeutic approaches administrated in order to manage psychological adverse effects and efficacy of PD are just able to alleviate symptoms. Therefore, exploring for achieving the novel substances which can alleviate the psychological adverse effects also can improve efficacy with therapeutic benefits in PD patients is the focus of a widerange of current investigations.

This review calls the attention to various phytoconstituents that deems crucial role in the management of neurodegenerative disorder including PD.

In this study, the current evidence on the effectiveness of phytoconstituents in various models of PD either cellular or animal models have been discussed.

The present review further revealed that plant derived natural products can be therefore considered as an adjuvant treatment with the other various conventional therapeutic approaches to alleviate the psychological adverse effects and improve efficacy in management of neurodegenerative disorder including PD.

**Acknowledgements**

This study has been partially supported by Lovely Professional University (LPU), Phagwara. I want to thank faculty and staff of Lovely school of pharmaceutical sciencesfor providing me required facilities to carry out this study.

**Conflict of interest statement**

The authors declare that they have no conflict of interest.

**References**


Phytochemicals as future drugs for Parkinson’s disease: A Review


