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PHYTOCHEMICALS AS FUTURE DRUGS FOR PARKINSON'S DISEASE: A REVIEW

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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 mostcommon chronic neurodegenerative disease that affectsmotor skills and cognitive performance. There have been various conventionaltherapeutic approaches for the management of PD that are justable to alleviate symptoms. In terms of thus Exploring for achieving novelsubstances with therapeutic benefits in PD patients is the focus of a wide range of current investigations. The aim is thus to comprehensively review phytochemicalswith 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. Phytochemicalsperform 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-κB), decreasing dopaminergic neuronal loss and dopamine depletion and modulating 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 as promising as future drugs in the management of neurodegenerative diseases.

Keywords: Medicinal plant; natural product; neurodegenerativedisease; 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 relateddiseases.

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 synucleiopathy, 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 synaptic 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, safinamide, 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 PDsymptoms.

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 deliberateprocesses 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 estimated6 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).

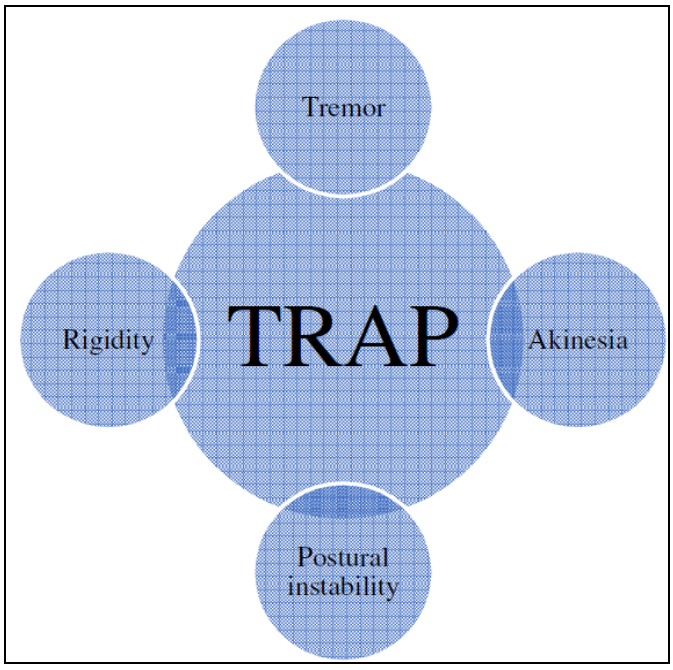

Fig 1. : A TRAP in Park! Motor symptoms of Parkinson's disease

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 to1% 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

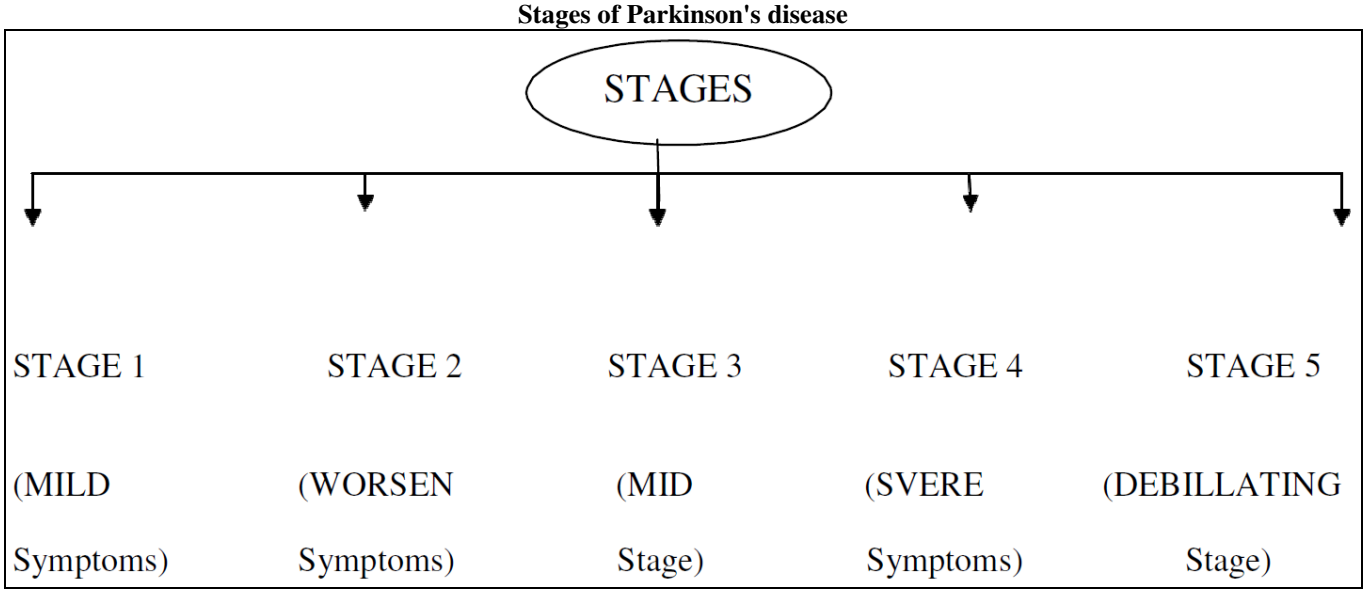

Fig. 2 : Different Stages of Parkinson's Disease

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 onside 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 symptomsaffecting 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 theworld.

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; Bahramsoltani *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 thePD.

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 lingams (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, flavones, 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*, *Robiniapseudo 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, andcyclooxygenase-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 *Scutellariabaicalensis*. 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 *Clausenalansium*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 genep53, 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 transcriptive 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 Cα (PKCα), which is having a vital role in the function of neural cell membrane and also in the tight junctions. Thus, by Enhancing the proteoinic expression of the antiapoptotic protein Bcl-2aswellasreduced 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 thecaspase-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). FlavanololFustin demonstrated the mechanism of the neuroprotection via the suppression of cell apoptosis, which is then mediated by the reduction incaspase-3 activation, Bax/Bcl-2 ratio, p38 phosphorylation activation, and ROSgeneration.

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 per oxidation 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 antioxidative 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 antiparkinsonian in PD by increasing the TH- positive fibers and also the cell reduction of dopaminergic neuronal loss in both the ST and the SN also 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 *Morusalba*, that have demonstrated protective effects on the neurons via decreasing the α-syn mRNA and also the protein levels and hence increasing the protein expression of nuclear receptor related 1 protein (nurr1) 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 *Salviamiltiorrhiza*, 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 apoptotic/antiapoptotic agents, and decreasing the ratio of Bax/Bcl-2 ratio, and thus reducing caspase-3activity (Wang and Xu,2005).

Syringic acid is naturally occurring one of the major fruit that is benzoic acidderivativesfound 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 cinnamate derivative, which is a phenolic compound that is mainly found in various naturally occurring medicinal plants, such as *Salviaofficinalis*, *Ocimumbasilicum*, *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 (Ren*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 group that is 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 (Klepacka *et al*., 2011; Bahramsoltani *et al*., 2015).

6-Shogaol, is an extractable pungent ingredient present in ginger, possesses a neuroprotective effects via decrease in the neurons via the dopaminergic neuronal loss, and then 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 (Lycopersicon esculentum), strawberry obtained from fruit of plant (Fragaria x ananassa), 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 neurogenertaive disorder like PD and in experimental models of the disease PD, indicating that the key role of autophagy and in the pathophysiology 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 in theSH-SY5Y cells and therefore inhibitsthe 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 *Polygonumcuspidatum*, 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-glutamylcysteineligase 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 Bcl-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 canonic 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 *Ginkgobiloba*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 haveconfirmed 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, Rb1demonstrated 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 asleucine- 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 (Pasban-Aliabadi *et al*., 2013).

Paeoniflorin is the majorly active ingredient isolated from the plant species *Paeoniae alba* radix (red peony root; Liu *et al*., 2006). Paeoniflorinpossesses 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 paeoniflorin attenuates the α-synaccumulation via the increase in protein expression of LC3-II, specific marker of phagophores and autophagosomes. In addition, to this paeoniflorin 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, paeoniflorin 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).

Celastrolis 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 *Polygala 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 numerousrange 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 antipakinsonian 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, diferoxymethane and tannins (Naoi *et al*., 2019).

Conclusion

PD is the second mostcommon chronic neurodegenerative disease that affectsmotor skills and cognitive performance. To date, in the various therapeutic approachesadministrated in order to manage psychological adverse effects and efficacy of PD are just able to alleviatesymptoms. Therefore, exploring for achieving the novel substances which can alleviate the psychological adverse effects also can improve efficacy withtherapeutic 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.

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Conflict of interest statement

The authors declare thatthey have no conflict of interest.

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