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# Analysis of Parkinson's disease and its potential therapy with medicinal plants and phytochemicals – a review

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## ABSTRACT

Parkinson's disease is a chronic, progressive neurodegenerative disease in which, both, motor and non-motor symptoms show up. Loss of striatal dopaminergic neurons leads to the development of motor symptoms, which involves, resting tremor, bradykinesia, and, muscle rigidity. This disease is associated with multiple risk factors and mutations. Oxidative stress, formation of free radicles and multiple environmental toxins are some of the risk factors of this disease. 'SNCA' was identified as the first gene, responsible for Parkinson's disease. Almost 5-10% PD patients suffers from a Parkinson's disease, where autosomal dominant mutations occur in SNCA, LRRK2 and VPS35 genes and autosomal recessive mutations in PINK1, DJ-1 and Parkin genes, which cause this disease with high penetrance. However, most PD occurs by the combined action of common genetic variants with environmental factors. Abnormal aggregation of α-Synuclein and spread of pathology in different regions of Brain probably underlie the development and progression of Parkinson's disease. This aggregated 'α-Synuclein' binds the proteasome and inhibits its activity. Ubiquitin accumulates in Lewy Bodies, and, Parkin and UCH-L1 also interact with the Ubiquitin proteasomal system, the resulting proteasomal dysfuction is thought to contribute in Parkinson's disease. Many plants, such as – Mucuna puriens, Vicia faba L, Crocus sativus L, Curcuma longa, Ginkgo biloba, Gastrodia elata, Scutellaria baicalensis, Withania Somnifera, have been found to be potentially therapeutic against Parkinson's disease. Many phytochemicals such as – Chrysin, Vanillin, Asiatic acid, Ferulic acid and Curcumin also have shown the potential to serve as therapeutic molecules against Parkinson's disease.

**Keywords:** SNCA**,** Alpha-Synuclein, Lewy bodies, Phytochemicals.

## 1. INTRODUCTION

Parkinson's disease was described at first by Dr. James Parkinson in 1817 as a "shaking palsy". It is a chronic, progressive neurodegenerative disease in which, both, motor and non-motor symptoms show up. It progressively effects mobility and muscle control. Loss of striatal dopaminergic neurons leads to the development of motor symptoms, which manifests in this disease. The motor symptoms of this disease involves, resting tremor, bradykinesia, and, muscle rigidity. This disease is the most common cause of parkinsonism. **[1-4].**

Research also suggests that the pathophysiological changes associated with Parkinson's disease may start before the manifestation of motor symptoms. These maybe a number of non-motor symptoms, such

as sleep disorders, depression and cognitive changes. Thus, we need such researches that focus on prevention and protection therapy. **[1,5].**

Although this disease mainly show up in elderly people, but some individuals developed this disease in their 30s and 40s also. **[1,6].** This disease show gender differences in 3:2 ratio of males to females. It shows up late in females because of the neuroprotective effect of Estrogen on the nigrostriatal dopaminergic system. **[1, 7, 8].**

This disease is associated with multiple risk factors and mutations. Oxidative stress, formation of free radicles and multiple environmental toxins are some of risk factors of this disease. **[1, 9, 10].** However, data which supports genetic associations with Parkinson's disease are limited. Few genetic mutations have been identified. **[1, 11-13].** Interestingly, there's inverse relationship between cigarette smoking, caffeine intake and the risk of developing Parkinson's disease. It maybe because tobacco smoking inhibits Monoamine oxidase enzyme, and, caffeine exhibit adenosine antagonist activity. **[1, 14].** Environmental factors and genetic factors, along with ethnic differences may all play role in the pathogenesis of this disease. **[1, 15, 16].** Biomedical researches are going on to help identify additional risk factors to help in the discovery of its prevention and treatment. **[1, 18-21].**

**Dopamine metabolism:**

Dopamine is the neurotransmitter for signal transduction in dopaminergic neurons. It is an intermediate formed during the formation of norepinephrine and epinephrine. **[22, 23].** There are two steps of synthesis of Dopamine in catecholamine neurons. In the first step, the amino acid 'Tyrosine' is converted to 'L-DOPA' by tyrosine hydroxylase. Then, in the next step, L-DOPA is decarboxylated to Dopamine by aromatic amino acid decarboxylase. **[22, 24].** When neurons are activated, 'Dopamine' is released into the synaptic cleft for the signal transduction. This released Dopamine can be used up and degraded by neighboring astrocytes and microglia or may also be absorbed back into the vesicles of the presynaptic neurons via DA transporters to be used again. Dopamine is unstable in the cytosol and will undergo oxidation. **[22, 25].**

Especially under basic condition, auto-oxidation of Dopamine can occur, to generate small-molecule reactive oxygen species and highly reactive 'dopamine quinones'. **[22, 26].** Oxidation of Dopamine can be facilitated by enzymatic catalysis (Tyrosinase) or may also be mediated by transition metal ions, such as, Iron, Copper and Mangnease ions. **[22, 27].** Other than 'Cytosol' catalysis of Dopamine is also done by 'Monoamine oxidases' to produce DOPAL, which is a reactive and toxic metabolite of Dopamine, and a reactive oxygen species. **[22, 28].**

**Pathogenesis of Parkinson's disease:**

It is a progressive neurodegenerative condition, which is associated with the deposition of aggregated α-Synuclein. Various researches and studies including, biochemical studies, investigation of transplanted neurons in Parkinson's diseased patients, and cell and animal model studies, suggest that abnormal aggregation of α-Synuclein and spread of pathology in different regions of Brain probably underlie the development and progression of Parkinson's disease. At the level of cell, mitochondria, lysosome and endosome have been found to function abnormally, in both, monogenic and sporadic Parkinson's

disease. Recent work has also shown that, maladaptive inflammatory and immune responses, possibly triggered in gut, enhances the progression of the pathogenesis of Parkinson's disease. **[29].**

**Genetics of Parkinson's disease:**

'SNCA' was identified as the first gene, responsible for Parkinson's disease. Almost 5-10% PD patients suffers from a monogenic form of Parkinson's disease, where autosomal dominant mutations occur in SNCA, LRRK2 and VPS35 genes and autosomal recessive mutations in PINK1, DJ-1 and Parkin genes, which cause this disease with high penetrance. Mutations in DNAJC6 is predominantly atypical, but also cases with typical Parkinson's disease. However, most of the PD is complex at the genetic level, i.e., it occurs by the combined action of common genetic variants with environmental factors. **[30]**

**Pathological proteins - Parkinson's disease:**

Alpha-Synuclein is the main focus of this disease because it aggregates to form Lewy bodies. This aggregated 'α-Synuclein' binds the proteasome and inhibits its activity. Ubiquitin accumulates in Lewy Bodies, and, Parkin and UCH-L1 also interact with the Ubiquitin proteasomal system, the resulting proteasomal dysfuction is thought to contribute in the pathophysiology of Parkinson's disease. A number of experiments suggest that neurotoxins may interact with α-Synuclein and other proteins of Parkinson's disease to to contribute to its pathophysiology. **[31].**

**Potential therapy:**

**Medicinal plants:**

1. **Mucuna pruriens:** This plant belongs to **Fabaceae** family, and, can be used for the treatment of Parkinson's disease. **[32, 33].** One of the main components of this plant is 'L-dopa'. **[32, 34].** When the food endocarp of the seeds of this plant in the dose of 5 g/kg was combined with Carbidopa – 50 mg/kg, that showed better effect than L-dopa, in the mice. **[32,35].** When the seed extract of this plant, was given to the rats in the dose of 400 mg/kg, then too this extract showed anti-Parkinson effect in those rats. **[32, 36].** When powder of Mucuna pruriens was given in the dose of 2.5 or 5 g/kg/d, that enhanced the level of L-dopa, dopamine, norepinephrine and serotonin in the substantia nigra of rat model having Parkinson's disease, induced by 6-OHDA. **[32, 37].** In Ayurveda, 'HP-200' is a commercial medicinal preparation derived from M. pruriens which is proponed to exhibit anti-Parkinson effects. The effect of the endocarp of M. puriens, in the form of 'HP-200' was studied, on the monoaminergic neurotransmitters in the different areas of the rat's brain. Those areas of brain were – substantia nigra, striatum, cortex and hippocampus. Results showed that M.puriens enhanced the concentration of dopamine in the brain cortex of the rats. However, data also showed, that, 'HP-200' does not affect the amount of L-dopa, dopamine, serotonin and norepinephrine in the nigrostriatal pathway of rats. **[32, 38].** When the powdered seeds of this plant was orally administered in the patients of Parkinson's disease in a clinical trial, in the dose ranging between 15 to 40 g, that showed symptomatic control with the 4.5 to 5.5% of L-dopa. **[32, 39].** When Carbidopa was added to M.puriens, that significantly led to the improvement of motor activities in a 48 years old women, who was the patient of Parkinson's disease. This finding confirmed that the usage of a dopa-carboxylase inhibitor to M.puriens can be helpful for management of PD patients. **[32, 40].**

2. **Vicia faba L.:** Vicia faba is known as broad beans, horse beans, or field beans is used as food, for many years, in Mediterranean area, India, Pakistan and China. Its seeds naturally contain L-dopa, proteins, carbohydrates, fiber, and vitamins. **[32, 41].** In a report, when the patients of Parkinson's disease, were treated with V. faba, motor activity ameliorated. **[32,42].** Various scientific documents tell, that if V.faba is taken, plasma concentration of L-dopa can get enhanced and the motor proficiency of the patients of Parkinson's disease can get improved. **[32, 43, 44].**

3. **Crocus sativus L.:** Crocus sativus or 'Saffron' belongs to 'Iridaceae' family. It is grown in many different countries, including Iran, Turkey, Afghanistan and Spain. **[32, 45].** This plant and its components can be used for the treatment of various cognitive disorders and some neural disorders as well. In Iranian traditional medicine, this herb is also used as smooth muscle relaxant agent. **[32,46-48].** In animal studies, saffron and its components have been found to be useful and effective in the neurodegenerative disorders. **[32, 49].** In a mouse model, acute Parkinson's disease was induced, using 'MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)'. In that model, when C. sativus was administered 0.01% w/v, in drinking water, it saved the dopaminergic cells of the substantia nigra pars compacta. **[32, 50].** When toxic amyloid structures form and collects, then as a result, neurodegenerative disorders, like Parkinson's disease and Alzheimer's disease can get induced. Two main components of C. sativus, 'Crocin' and 'Safranal', have been reported to inhibit the fibrillation of apo-α-lactalbumin, which causes damage to the neurons under amyloidogenic conditions. **[32, 51].** C. sativus in the dose of 50 mg/kg, has also shown, to exhibit the preventive effect against the development of Parkinson's disease when this disease was made to develop by, lead(Pb)-induced damage in the nervous system. This preventive effect was associated with the rise of the TH level in different areas of Brain, which included – substantia nigra pars compacta, locus coeruleus, dorsal striatum and medial forebrain bundle of mice. **[32, 52].** When MPTP-induced cell death in the substantia nigra of the mice, was treated using 'Crocin', then too improvement was observed in the mice. **[32, 53].** The results of various research studies that, 'Crocin' derived from C. sativus , protects PC12 cells against MPP+-caused injury and can also improve the cytotoxicity related to endoplasmic reticulum. **[32, 54].**

4. **Curcuma longa:** Curcuma longa, also known as 'turmeric' is widely grown in the south-east Asian countries. This medicinal plant contains, such natural polyphenol and non-flavonoid, which modulates the oxidative damage of the nervous system and other body parts also. **[32, 55-57].** This plant exhibits various medicinal properties, such as, anti-inflammatory and anti-cancer properties. **[32, 58].** In a study, in the brain of a mice, C. longa in the dose of 560 mg/kg, was also found to inhibit 'Monoamine oxidase A', which metabolizes dopamine. **[32, 59].** Water-soluble extract of 'Curcumin' in the dose of 50-200 mg/kg, was found to increase the serotonin and dopamine level in the brain tissues. At the dose of 50 mg/kg, it enhanced the anti-depressant like effect. **[32, 60].** When 'curcumin' was administered, at the doses of 50, 100 and 200 mg/kg, that improved the cognitive problems and mitochondrial dysfunction in the mice. **[32, 60].** Protective effects of C. longa and Curcumin has been observed on Parkinson's disease. **[32].**

5. **Ginkgo biloba:** Ginkgo biloba dropping pill (GBDP) is a leaf extract preparation of Chinease Ginkgo biloba. This leaf extract preparation has been found to exhibit anti-oxidant and neuroprotective effects and can be a potential therapy of Parkinson's disease. Moreover, GBDP was also found, to prevent the loss of dopaminergic neurons in a zebrafish. It was also found, to improve the cognitive impairment and neuronal damage in a mice, which was made to develop Parkinson's disease using MPTP. **[61].**

6. **Gastrodia elata:** This plant belongs to the family of 'Orchidaceae'. This is a herb which has been used as a common therapy in eastern nations since many years, because of its medicinal properties. **[62, 63].** Its major components include - Gastrodin, 4-hydroxybenzaldehyde, vanillyl alcohol, and vanillin. These compounds can cross the blood-brain barrier and exhibit many medicinal activities, such as, antioxidant, anti-asthmatic, antibacterial and antimutagenic activities. **[62, 64].** Several studies say that Gastrodia elata can be a promising therapeutic plant of Parkinson's disease. 10-200 mg/mL of Gastrodia elata improved cell viability and reduced apoptosis. Gastrodin reduced bradykinesia and motor deficits in the mice treated with MPTP. **[62, 63, 65].** These findings show that chemicals of this plant maybe used for the development of drug candidates to reduce the symptoms of Parkinson's disease. **[62].**

7. **Scutellaria baicalensis:** This plant belongs to the Lamiaceae family. This is a common and traditional medicinal herb in Chinease medicine. Its main bioactive components include, flavonoids, such as, baicalein, baicalin, scutellarin, and wogonin. These have been found to exhibit anti-inflammatory, antioxidant and neuroprotective properties. **[62, 66-68].** Many studies have proved that the extracts of this plant or its separated components show neuroprotective effects in different models of neurodegenerative diseases. **[62, 69-71].**

8. **Withania Somnifera:** This is one of the Nigerian medicinal herbs, used to treat several illnesses, such as Parkinson's disease, Stress, Arthritis, and other problems of our Central Nervous System. **[62, 72, 73].** The main mechanisms of action by which it shows neuroprotective effects are – improvement of mitochondrial and endothelial activity, reduction of apoptosis, anti-inflammatory properties, and, control of oxidative stress. **[62, 72, 74].**

**Phytochemicals against 'Parkinson's disease':**

Some phytochemicals, which have shown the potential to serve as therapeutic drug against Parkinson's disease are –

1. **Chrysin:** It is a natural polyphenol, which is a flavonoid. In vegetables, fruits, mushrooms, blue passion flowers, etc. flavonoids are ubiquitous. **[75, 77]. '**Chrysin' has been found to exhibit the neuroprotective effects. Some of its medicinal properties are – antioxidant, anti-inflammatory, and other pharmacological properties. **[75, 78].** It has also been found that Chrysin can easily cross the biological membranes. However, in the intestinal cells, its absorption can be limited, because of extensive sulfation and glucuronidation.**[75, 79].** Although, 'Chrysin' is considered to be safe for human consumption, without any toxic effects, if it is consumed daily, at the dose of 500mg to 3g. But, if it is consumed, at higher dosage than this range, it may cause some side

effects. **[75, 80].** It has been found that, 'Chrysin' increases the level of 'Dopamine' by inhibiting 'monoamine oxidase B'. As a result of this inhibition, Dopamine level increases and metabolism of Dopamine gets suppressed. **[75, 80].** Administration of Chrysin, also reduces the cognitive dysfunction and motor impairment in the animal models. **[75, 81].** Thus, Chrysin shows up as a potential therapeutic compound, against Parkinson's disease. **[75].**

2. **Vanillin:** It is a phenolic aldehyde, and is used as a flavouring agent throughout the world. It is present in large amount, in the plant species. It is used in food production, bevarage, pharmaceutical, perfume and cosmetic industries. **[75, 82].** Its pharmacological properties have also been studied. Its pharmacological properties are attributable to its structure and main bioactive metabolites, including vinyl alcohol and vanillic acid. Medicinal properties exhibited by 'Vanillin' are – antioxidant, anti-inflammatory and neuroprotective abilities. **[75, 83].** It can cross the blood-brain barrier and exhibit neuroprotective ability by increasing the biological activity of antioxidant enzymes and reducing the levels of lipid peroxidation and NO production. **[75, 84, 85].** Another study, done on an animal model of Parkinson's disease, showed that, Vanillin exhibits the neuroprotective ability. In that animal model, Parkinson's disease was induced by Rotenone. When Vanillin was administered in SH-SY5Y cells, it inhibited the generation of reactive oxygen species, induced by 'Rotenone'. It also inhibited the mitochondrial dysfunction and caspase activation and decreased the expression of signalling molecules. **[75, 86].** A study also showed that vanillin increases the striatal dopamine and its metabolites, which improved the behaviour. **[75, 87].** Vanillin was found to improve the depressive-like motor symptoms, by enhancing the level of Dopamine and Serotonin in the brain tissue. **[75, 88].** Such studies showed that 'Vanillin' actually exhibit the neuroprotective and anti-inflammatory properties in protecting the dopaminergic neurons. It also improves the behavioural functions, by inhibiting oxidative stress, inflammation and apoptosis. Thus, this phytochemical maybe a potential therapeutic drug against Parkinson's disease. **[75].**

3. **Asiatic acid:** It is a 'pentacyclic titerpenoid', which is a promising neuroprotective therapeutic molecule. It exhibit so many medicinal properties and has the potential to treat multiple different diseases. **[75, 89, 90].** In the experimental researches, this molecule has showed a wide variety of therapeutic abilities, such as – antioxidant, hepatoprotective, antidiabetic, anticancer, anti-inflammatory and neuroprotective properties. **[75, 90-92].** This molecule maintains the stability of the blood-brain barrier and protects the functions of mitochondria. An in-vitro research, showed that the administration of 'asiatic acid' reduced the production of reactive oxygen species by mitochondria. It also altered MMPs to regulate the mitochondrial function. **[75, 93].** Other in-vitro and in-vivo experiments also observed that, when Asiatic acid was administered, apoptotic cell death was reduced, mitochondrial production of reactive oxygen species was also reduced, MMPs were also stabilized. **[75, 94].** Findings of various scientific studies, shows that, this molecule maybe used as a potential therapeutic agent against Parkinson's disease, for both, prevention and therapy. **[75].**

4. **Ferulic acid:** It is a phenolic phytochemical. It is commonly found in apples, oranges, peanuts, wheat, rice, barley, coffee and various other dietary sources. **[75, 95].** Some reports revealed that,

taking vegetables, fruits and cereals through our diet, helps in the prevention of various diseases, such as – Cancer, Obesity, Caediovascular disease, Alzheimer's disease and Parkinson's disease. **[75, 96-98].** 'Salicylic acid' is structurally similar to 'Ferulic acid', and, salicylic acid can enter into our brain. Thus, it is speculated that, Ferulic acid can also cross the blood-brain barrier and enter into our brain. Ferulic acid has also been found a successful neuroprotective agent. **[75, 99].** Some in-vitro and in-vivo studies have shown that FA exhibited the increased levels of protective HO-1 activity in SH-SY5Y cells, upregulated the levels of CAT, SOD, GPx, and, GSH and also brought about a decrement in the lipid-peroxidation level in the mouse models, in which Parkinson's disease was made to develop by injecting MPTP. This confirmed that, FA is a potential antioxidant, which can prevent Parkinson's disease. **[75, 100].** Several researches have also shown that FA can inhibit the neuroinflammation and neural degeneration in the neurodegenerative diseases. Histological researches also revealed that administration of FA suppressed the activation of microglial cells and Bax/Bcl-2 ratio, which showed the reduction of inflammation and apoptosis respectively. It was also found to be effective on resulting behavioural functions and motor coordination. **[75, 101].** Thus, we can conclude that, 'Ferulic acid' is a potential anti-oxidant and anti-inflammatory therapeutic molecule and can be a therapeutic medicine against Parkinson's disease. **[75].**

5. **Curcumin: '**Curcumin' is an active ingredient in the turmeric. Curcumin is lipophilic in nature, therefore, it can cross the blood-brain barrier. **[76, 102].** It can exhibit, different protective activities in our brain, such as, protection against toxic metals and reactive oxygen species. Curcumin is a flavonoid, whose anti-oxidant properties are stronger than other antioxidants like Vitamin C and E. **[76, 103].** It donates H ion to protect mitochondria and neurons from getting damaged by the reactive oxygen species. In Parkinson's disease, oligomers of alpha-synuclein aggregates to form Lewy bodies. Curcumin has shown to prevent this aggregation of alpha-synuclein oligomer. **[76, 104-106].**

## DISCUSSION

Parkinson's disease was described at first by Dr. James Parkinson in 1817 as a "shaking palsy". It is a chronic, progressive neurodegenerative disease in which, both, motor and non-motor symptoms manifests. progressively effects mobility and muscle control. Loss of striatal dopaminergic neurons leads to the development of motor symptoms, which manifests in this disease. The motor symptoms of this disease involves, resting tremor, bradykinesia, and, muscle rigidity. Research also suggests that the pathophysiological changes associated with Parkinson's disease may start before the manifestation of motor symptoms. There maybe a number of non-motor symptoms, such as sleep disorders, depression and cognitive changes. Thus, we need such researches that focus well on prevention and therapy. This disease is associated with multiple risk factors and mutations. Oxidative stress, formation of free radicles and multiple environmental toxins are some of risk factors of this disease. 'SNCA' was identified as the first gene, responsible for Parkinson's disease. Almost 5-10% PD patients suffers from a monogenic form of Parkinson's disease, where autosomal dominant mutations occur in SNCA, LRRK2 and VPS35 genes and autosomal recessive mutations in PINK1, DJ-1 and Parkin genes, which cause this disease with high penetrance. Alpha-Synuclein is the main focus of this disease because it aggregates to form Lewy bodies. This aggregated 'α-Synuclein' binds the proteasome and inhibits its activity. Ubiquitin

accumulates in Lewy Bodies, and, Parkin and UCH-L1 also interact with the Ubiquitin proteasomal system, the resulting proteasomal dysfuction is thought to contribute in the pathophysiology of Parkinson's disease. A number of experiments suggest that neurotoxins may interact with α-Synuclein and other proteins of Parkinson's disease to to contribute to its pathophysiology. Many plants, such as – Mucuna puriens, Vicia faba L, Crocus sativus L, Curcuma longa, Ginkgo biloba, Gastrodia elata, Scutellaria baicalensis, Withania Somnifera, have been found to be potentially therapeutic against Parkinson's disease. Many phytochemicals such as – Chrysin, Vanillin, Asiatic acid, Ferulic acid and Curcumin also have shown the potential to serve as therapeutic molecules against Parkinson's disease. It is quite clear from this review that, those plants and phytochemicals, which contain, either precursors of Dopamine or exhibit anti-inflammatory or antioxidant properties or prevents aggregation of 'Alpha-Synuclein' or prevents cytotoxicity, all have the capability to treat Parkinson's disease.

## CONCLUSION

We need such researches which focus well on prevention and therapy of Parkinson's disease. Those plants and phytochemicals, which contain, either precursors of Dopamine or exhibit anti-inflammatory or antioxidant properties or prevents aggregation of 'Alpha-Synuclein' or prevents cytotoxicity, all have the capability to treat Parkinson's disease.

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