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Review

Nutraceuticals In Treatment Of Parkinson's Disease

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Abstract

Parkinson's disease is one of the most important age related disorder in the world. They progressively lost their dopaminergic neurons in the substantia nigra. Low level of dopamine cause dyskinesia, cognitive deflicits and depression. Several factors involve in the Parkinson's disease conditions such as distrupt in anti-oxidant pathway and mitochondrial dysfunction. It is followed by formation of lewy bodies cause CNS damage. In this article we tries to improve the utilization of plant resources in the parkinson's diease. Nutraceutical plays an significant role in the Neuro-degenerative diseases. They are low toxic and better therapeutic action and also improve the patients's quality of life. Some of the nutraceutical provide significant results in experimental models and pre-clinical studies. We explain the present and future prospects of nutraceuticals in Parkinson's disease. We importantly focused in mucuna pruriens, nigella sativa, vicia faba, curcumin and gallic acid in parkinson's disease.

Keywords: L-dopa; Parkinson's disease; tissue;

INTRODUCTION

Parkinson's is the second most common age-releated disease after Alzheimer disease.[24] Parkinson's disease is a Neurodegenerative disorder. It is known from the ancient time. In Sanskrit it is named as " Kampa " .It is mentioned in Indian Ayurvedic system resting and intentional tremor differentiated by Galen in A.D169.[8] In 1584 yikuisun described about the tremors of hands, feet and head. [8] Doctor James Parkinson's published about the disorder in 1817. The name of the disease is named after him. It is titled as, "An essay on the shaking palsy".[13] In 1895, Richer and meiga reported the clinical and morphological defects in the Parkinson's disease.[3] In 1880s William Gowers examined about 80 patients and identified that the disease affects men more than women.[13] In 1872, James martin Charcot and his students identified that the tremors are not essential condition for the disease. They created a vibrating chair (fauteuil Trepidant) which created a trembling experience as in the Train. It creates an oscillation by electricity and creates a train carriage experience. They created Clinical trials in Parkinson's patients, daily for 30 minutes for one week and the symptoms are seen to be reduced. The patients experienced a light feeling and comfort sleep.[12] The complete detail of drug induced Parkinson's disease are documented in

1954 by steck.[3] In 1960s the chemical research developed and identified that the patients are affected by low level of dopamine in "substantia Nigra", it is a brain cell that causes degeneration..[13] It affects the movement of the body, balance and stiffness. Parkinson's disease mostly occurs in elder peoples. People above the age of 70 are mostly affected by this disease. Diagnosis of Parkinson's disease is not specified in laboratory studies. The patients suffered about the difficulties in walking pattern. The patients additionally suffered from the deposition of abnormal protein majorly alpha-synuclein which leads to dementia and hallucinations. Bradykinesia and rigidity are the symptom occurs after the tremor.[11] Parkinson's disease is a hypokinetic disorder. There are three main types of Parkinson's disease, they are idiopathic Parkinson's, early onset and familial. [14]

1. Idiopathic Parkinson's occurs in 55-65 years old peoples. It is caused due to the dying of basal ganglia and produce less amount of dopamine. It reduces the communication between the brain and the motor cells.
2. Early onset Parkinson's disease exact cause is not identified. It more likely occurs due to genetics. It may occur due to stress, depression and parenting.
3. Familial Parkinson's disease occurs by the passing of genes from parent to children.

There are some other types of Parkinson's occurs such as,
Vascular Parkinsonsism: It is atypical Parkinsonsism. This occurs due to multiple times of minor strokes. These types of Parkinson's produce poor response against levodopa medication.[14]
Drug induced Parkinsonsism: It is the most common secondary Parkinsonsism disorder. It occurs because of taking dopamine affecting drugs. It may sometimes cause due to sudden stopping of medicament.[14]

The Parkinson's disease contains six stages. They are:[15]
Stage 1: The lower medulla of the patients affected due to dysfunction. It may change the facial expression of the patients.
Stage 2: The second stage affects the walking and posture of the patients. It is due to the damage in the raphe's lower nuclei.
Stage 3: In this stage the motor functioning of the patient starts dysfunction. The substantia nigra is disturbed and cause abnormal nerve fibre damage and difficulty in balancing.
Stage 4: In this stage the temporal mesocortex and neocortical temporal fields are affected.
Stage 5: In this stage the patients cannot do their day to day activities. They need an assistance to take care of them.
Stage 6: In this stage the patients are completely paralyzed and get hallucinations.[15]

By the survey, genetically caused Parkinson's disease is only about 10% and these are especially seen in young aged people. Remain the 90% of the people are affected by idiopathic type. [11]

The symptoms of the Parkinson's disease are divided into types. They are motor type and non-motor type. Motor types are related to movement related symptoms. They are resting tremor, slowed movements, ridigity, stiffness in muscle, poor balance, difficult in walking, blinking less than usual. Non-motor types are other than movement related symptoms. They are loss of smelling, fatigue, early awakening, drooling, constipation, hallucination, difficult in speaking, difficult in swallowing food, weight loss, etc.

Wright Willis conducted a survey in united states in above 65 years old peoples from 1995-2005. According to the survey white American males (2168) are affected more than the others. Followed by white males, blacks (1036) and Asians (1138) are get affected. The black Africans are affected much lower than the other peoples. The Parkinson's disease mostly affects the people at the age of 60. It is the 1% of population in the world. The main problems involves in the diagnosis of the Parkinson's disease is every patients have a different kind of symptoms according to their severity & progression. Every individual have their own symptoms of Parkinson's disease. Cardinal motor symptoms in Parkinson's disease identification: The most commonly identified motor symptoms of Parkinson's disease is presence of bradykinesia, rigidity, loss of postural reflexes and during the disease progression other clinical features such as bulbar dysfunction, neuro-opthalmologic abnormalities and respiratory disturbances are identified.[20]

Bradykinesia: the most common primary motor symptoms of Parkinson's disease is bradykinesia, it is defined by slow movements and problematic fine motor control, which is due to the decreased neurnal density in the substantia nigera. Patients suffering from bradukinesia are unable to provide sufficient energy to have muscles and thus fail to implement fast movements. It involves the slowness of reactions and causing difficulties in performing simultaneous blinking can be included.[20]Tremor: it is a rhythmic muscle contraction and relaxation mainly on the extremities. Postural tremor is also described in patients having Parkinson's disease. It is an outstretched horizontal position against gravity.[20] Postural instability: the main symptom of postural instability is loss of postural reflexes. This is the main symptoms responsible for most falls of Parkinson's patients and subsequent fracture.[20]

Causes and risk factors

Parkinson's disease is a chronic and progressive neurological disorder. It causes trembling, rigidity, and postural problems.

Causes

1. Genetic factor: Genetic mutation plays an important role in the development of Parkinson's disease in about 5-10% cases. They are linked formation of the synuclein alpha (SNCA) and leucine rich repeat kinase 2(LRRK) genes. These mutations allow synuclein alpha to build up and form lewy bodies, impacting the natural release of dopamine, which play an important role in controlling of voluntary and involuntary movements.
2. Mitochondrial dysfunctions: The dysfunction of mitochondria leads to cause of Parkinson's disease. It is involved in the respiration and energy production. The dysfunction in the brain cells of substantia nigra leads to their degradation.
3. Oxidative stress: Reactive oxygen species (ROS) are naturally found molecules in the cells. They play an important role in the cellular communication to help area of the body to communicate.
   ROS- in the result of mitochondrial dysfunction causes oxidative stress, which can damage or degenerate cells leading to Parkinson's disease.
4. Exposure of toxins: exposure to environmental toxins can cause Parkinson's disease, which increases the oxidative stress, exposure to certain pesticides such as paraquat and rotenone and oxidative stress causes Parkinson's disease.[19]

Risk factors

1. Head trauma: A history of head trauma is associated with Parkinson's disease. It may be due to falls or contact sport which shows mild to moderate effect and thereby increasing the chances of the disease.
2. Environmental exposure: a person being exposed to chemical and toxins may develop the chance of the disease.
3. Pesticides and Herbicides: In agricultural process, the person working with pesticides or herbicides have chances to increase in developing of Parkinson's disease.
4. Airborne disease: the regular exposure to environment which have high levels of pollutants like copper, manganese or lead may increase the chances of Parkinson's disease.
5. Solvents: working with or being exposed to certain industrial solvent regularly like paints, especially trichloroethylene has found to be cause of Parkinson's disease.
6. High diary consumption: Studies have found that the higher rate of Parkinson's disease occurs in people who consuming excess of dairy products like milk, cheese and others.
7. Insufficient vitamin D: another risk factor involved in Parkinson's disease is not getting sufficient vitamin D. the common source of vitamin D is getting enough exposure to direct sunlight but it is not linked with chances of increasing the developing Parkinson's disease.[19]

Pathophysiology of parkinson's disease

The pathology of Parkinson's disease is still not understood. It may be resulted due to various factors such as

1. Oxidation of substantia nigera due to oxidative stress.
2. Toxic conformations of protein and
3. Sarcosome dysfunction.

Regulation: The direct and indirect circuits are the two main distinct pathways regulate the movement. Those pathways extended from striations.[9]

Direct pathway

The direct pathway involves in the stimulation of thalamic activity. The inhibition of GPi neurons by activation of protein kinase A signal pathway. This promotes the cortical activity of movements. [9]

Indirect pathway

The Indirect pathway increases the inhibitory output in thalamus to inhibit the movement. The D2 receptor activation reduces the pka activity and decrease the cyclic adenosine monophosphate by inhibiting the adenylcyclase signaling pathway. The decreased activity decreases the Gpi activation to promote movement.[9]

There are four main causes for Parkinson's disease. They are,

1. Dopamine depletion
2. Oxidative stress
3. Inflammation
4. Mitochondrial dysfunction

Dopamine depletion

The excessive loss of dopamine in the patients affected by Parkinson's disease leads to increase the activity of Gpi/SNpc circuits and dysfunction of gamma aminobutyric acid. The prevention of activity of thalamus also causes increases in cholinergic activity. Loss of dopamine is highly caused by consumption of more amount of alcohol.[7]

Oxidative stress

The dopamine is majorly synthesized in substantia nigra (SN). It is a part of the brain that leads to oxidative stress. It is mostly iron content, mono amine oxidase beta enzyme, easily oxidase the dopamine to form hydroxy free radicals due to availability of ferrous iron. The exceeding hydroxy free radicals damage the Dopaminergic neurons of the substantia nigra. The poor antioxidant causes ultimately cell death due to interfere with the neurons. In Parkinson's disease inadequate function of VMAT2 mRNA has been reported,which is caused by various route of pathological. Such as enzymatic oxidation of dopamine, non-enzymatic auto-oxidation by dopamine by the presence of oxygen and enzymatic oxidation of dopamine by mono amine oxidase.[1]

Inflammation

The abnormal accumulation of lewy bodies leads to formation of clamps,that stimulates the inflammation activity in the central nervous system. Neuroinflammation is one of the most important resulting factor in Parkinson's disease that causes damage in the cells and tissues. The alpha-synuclein accumulation leads to initiate the microglia to release pro-inflammatory molecules which is harmful to the neurons. The Parkinson's disease patient have increased concentration of pro-inflammatory cytokines in the SNpc compared to healthy objects.[9]

Mitochondrial dysfunction:

Mitochondrial dysfunction is a causative factor of idiopathic and family Parkinson's disease. The deficiency in the mitochondrial complex-I leads to Parkinson's disease. It is reported in post-mortem studies in the SNpc of Parkinson's affected brain. Depletion of complex-I occurs in skeletal muscle and platelet of Parkinson's patient also reported.

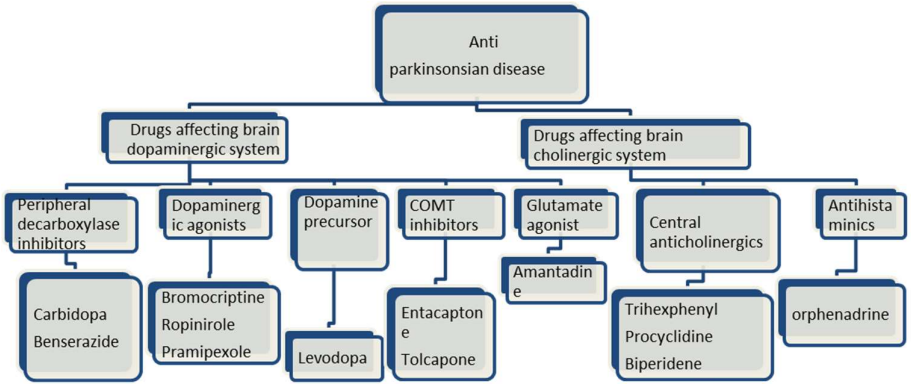
Complications of parkinson's disease

Parkinson's disease is a neurological condition in which it affects a wide range of functions. The common symptoms of Parkinson's disease are tremors, slow movements and rigidity. Also, the affected person may have difficulty in co-ordination, various non-motor symptoms and other complications

1. Speaking: Parkinson's disease affects the muscles of the patients. Due to this the voice of the affected person is becomes softer and it is very difficult to understand for others. The social interaction of the person may affected by this.
2. Chewing and swallowing: At the later stage of the condition, chewing and swallowing is very difficult for the patients. This may due to changes in autonomic nervous system or the muscles in the throat are get stiffed. This may cause a high possibility of the food getting stuck in the throat and cause choking. Pneumonia can occur if a person breathes the food into the lungs accidentally.
3. Depression and anxiety: Depression causes worst feeling in the Parkinson's disease people. In around 40-50% people with Parkinson's disease may experience depression stage. There some other neuropsychiatric symptoms include. [18]
    - Mood disturbances
    - Anxiety
    - Sleeping problems
    - Psychosis
    - Changes in behaviour and thinking.
4. Sexual dysfunction: various factors in Parkinson's disease can affect libido. Due to this condition, the person may find difficult to have an orgasm or an erection. The fall in dopamine level leads to drop interest in sex and physical function.
5. Sleep: sleeping problems are most common problems in people having Parkinson's disease. It affects the regulation of the sleeping and leads to early awakening.
6. Urinary problems: about 30-40% of people experience urinary problems, due to change in the autonomic nervous system the patients find difficult to pass urine or may leak urine.
7. Constipation: some statics says that two third of people having Parkinson's disease may experience constipation problems the reason may be,[18]
    - Muscle weakness
    - Reduction in fluid intake
    - Impact of Parkinson's disease on the digestive system.

8. Dementia: changes of patients in the brain such as, Lewy bodies can cause dementia in Parkinson's disease. There are about 50-80% of develop dementia eventually with Parkinson's disease. The symptom involve are,
   - Difficulty in remembering thing
   - Hallucination
9. Pain: the physical gain associated with Parkinson's disease is musculoskeletal and most of the people describe the sensation of burning, cramping and aching.
10. Blood pressure: the blood flow and blood pressure is controlled by the autonomic nervous system. Parkinson's disease affects the system leads to change in blood pressure. Hypotension can occurs due to drop in blood pressure causing the person dizzy or faint while standing. Hypertension may occur at night fluctuations leads to heart problems.
11. Sense of smell: people affected with Parkinson's disease experience loss in their sense of smell due to the impact condition of their nervous system.[18]

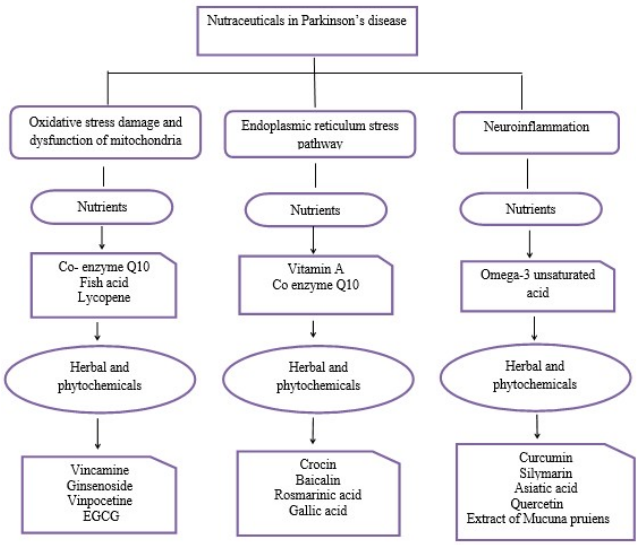
Allopathic remides



Nutraceuticals management

Nutraceuticals consists of combination of two words they are 'nutrition' and 'pharmaceuticals'. Nutraceutical is a process in which the diseases are cured by dietary supplements. The formulation of nutrients helps to prevent the disease causing substances.

The term nutraceuticals is proposed by Dr Stephen de felice in 1989. He orginated the term nutraceuticals, food supplements, dietary supplements. The supplements are either directly used or extracted to form tablets, capsules, powders, liquids. Usually, the clinical trails are compulsory for pharmaceutical industry but in nutrient industry, there is no need for the trails. But in the recent years, the scientist become more aware and suggested to trails the supplement on the rats.



Mucuna pruriens

Synonyms: Carpopogon capitatus roxb,
Dolichos pruriens
Velvet bean.
Biological source: It is derived from the seed of mucuna pruiens.
Sub family: Faboideae
Family: Fabaceae
Mucuna genus family contains natural sources of L-dopa which is essential for treating Parkinson's's disease.

Mechanism of action

It contains NADH and co-enzyme Q10 in nature. Mucuna pruriens contains L-dopa is a primary constituent. It is widely used in the treatment of Parkinson's disease. NADH increases the dopamine level through upward regulation thyroid regulation. It also prevents the activity of mitochondrial complex. The divalent copper and L-dopa interact to form free radicals. The formed free radicals damage the DNA and neurons. Mucuna pruriens provides protection to neurons and DNA from free radicals. The combination of mucuna pruriens seed with carbidopa produce more effect compared to L-dopa. Alcoholic extract of mucuna pruriens are used to treat oxidative stress induced Parkinson's disease, because it has more potency to treat against oxidative activity. Various reports denote it have many benefits compared with synthesis L-dopa.[17] It also provide treatment in MPTP induced Neuro inflammation by preventing the nuclear translation of NF-KB and also inhibits the pro-inflammatory cytokines.[6]

Clinical trials

The patient administered with mucuna seed experience better therapeutic action compared to L-dopa. Dhanasekaran *et al* (2008) demonstrate the anti-oxidant and metal chelating activity of mucuna pruriens. It inhibits free radical formation and prevents the divalent copper ion damage of DNA by chelation.[6] Rai et al recently proposed the action of mucuna pruriens in MPTP most model of Parkinson's disease.[6] In 2004, katzenschlager et al conducted a double blind clinical and pharmacological study on Parkinson's disease by mucuna pruriens .Better effect can be observed when provide long term management of Parkinson's disease compared to conventional L-Dopa treatment because conventional L-Dopa treatment induce severe dyskinesia in long term treatment.[6] Mucuna pruriens seed extract provide neuro protective effect action against paraquat induced neurotoxicity in a mouse model of Parkinson's disease demonstrated by yadaw et al (2013).[6]

Nigella sativa

Synonyms: black cumin, nigella cretia mill
Biological source: It is derived from the seeds of nigerlla sativa.
Family: Ranunculaceae

Mechanism of action

Nigella sativa majorly contains thymoquinone. It is a bioactive compound of the black seed volatile oil. It produces potential anti-oxidant activity.[5] The oxidative stress leads to mitochondrial dysfunction and neuronal loss. The thymoquinone stimulate the Nrf2 signaling leads to the inhibition of NF-KB mediated neuro

inflammation.[2] Nrf2 is a transcription factor which regulates the cellular defence against oxidative and toxic effect induced by oxidative stress. The thymoquinone activates the Nrf2 signal while experience of ROS or other toxicants. The activated Nrf2 related factor translated from ECH associated proteins to nucleus. In nucleus, the anti-oxidant elements (AREs) activated by interaction of Nrf2 related factor .Many references are reported Nrf2-ARE provide defence from oxidative stress and promotes neuro protectants effect and also MPP+ (1-methyl 4-phenyl pyridinium) induced Parkinson's disease can be inhibited.[2]

Clinical trails

Sedaghat et al, in 2014 reported the thymoquinone provide anti-oxidant effect and prevent the degeneration of dopaminergic neurons by reducing the level of malondialdehyde.[2]

Gureer and Popov in 2019 reported the Nif2-ARE signalling plays major role in anti-oxidant activity and provide neuro protective effect.[2]

Animal studies

1. Parkinson's mouse model: 10mg/kg of thymoquinone given for one week before administration of MPTP. It inhibits the alpha-synuclein aggregation and cellular death.[3]
2. Male Wistar rat (8-10 months) received rotenone. Rotenone injection administered after the pre-treatment with TQ. (15 mg/kg/day). It shows potential action against 6-OHDA neurotoxicity. [3]
3. Adult Wistar rat of either sex is selected. CPZ dose administered for 21 days to induce Parkinson's disease. Then 200mg/kg of nigella sativa given orally. It acts on whole brain and increase the action against Parkinson's activity.[3]

Advantages

- Low toxicity level
- Not showing any renal and hepatic enzyme activity for five days of 50mg/kg of oil administration.
- Administration of 10 mg/kg in rats not shows any toxicity during observation of 48 hours.[4]

Disadvantages

- Below 100/m of TQ receiving cell leads to death within a few hours.
- 50/m and 25/m induce high necrosis.[4]

Vicia faba

Synonyms: broad bean, Faba bean, fava bean.[22]
Family: fabaceae[25]
Biological source: It is derived from the dried seeds of vicia bean.
Geographical source: India, Pakistan, china, and Mediterranean areas.[16]
Chemical Constituents: 40% protein, 4% lipids, 56% carbohydrates.
The seeds contain full of nutrients, carbohydrates and natural L-dopa. L-dopa content in faba leaves are high in new leaves and less in young leaves and also low level in flowering and ripening stage.[25]

Mechanism of action

In Parkinson's disease there is a deficiency of glucose 6-dehydrogenase. It is Due to the degeneration of dopaminergic neuron in the brain.[22] The Parkinson's disease patients cannot synthesis the dopamine from their motor cells.[16] Vicia faba contains L-dopa it has ability to cross the blood brain barrier and convert the L-dopa into dopamine. It converts the phenolic compound into dopamine. It cannot cure the Parkinson's disease it only supress the symptoms.[25] Vicia faba is also used as vigra. The drugs should be avoided with the combination with dopamine precurors because it leads to increase in blood pressure.[16] Elder people suggest that children to not take the raw seeds of vicia because it causes jaundice.

Curcumin

Synonyms: turmeric yellow, kurkum.
Family: zingiberaceae
Biological source: it is derived from the rhizome of curcuma longa.[23]
Geographical source: India, china, South East Asia.
Curcumin is used as an ancient ayruvedic drug for the treatment of Parkinson's disease. It is mainly used as an anti-oxidant and also as an anti-inflammators.[23]

Mechanism of action

Curcumin is a polyphenolic compound.[22] It has an ability to cross the blood brain barrier due to its lipholophlic nature. The Parkinon's disease is occurred due to the reduction in 6-OHDA (6-hydroxy dopamine).[22] It damages the structure of DNA. The curcumin is reduces the oxidative stress with the help of glutathione and protects the protein oxidation[23]. It reduces the amount of reactive oxygen species and supress the inflammation. It also increases the level of dopamine in the body.

Gallic acid

Gallic acid is the member of hydroxyl benzoic acid group. It is found in methyl acetate fraction and hydroalcholic extract from schinus terebinthufolius (Brazilian pepper tree). Gallic acid is used to prevent the oxidative damage of scavenging the reactive oxygen species, which takes place in biomolecules.[21]

Mechanism of action

The disease is not definitive but drugs like levodopa and amantadine are used for the treatment of Parkinson's disease. Some studies indicated that long term treatment of levodopa decreases the activity of protase system and inhibits the mitochondrial complex activity. Therefore, levodopa has failed to satisfy the therapeutic expectations to Parkinson's disease. In recent research preclinical model were used to study the therapeutic effects of gallic acid on Parkinson's disease. [21]

Preclinical studies

The effect of gallic acid on Parkinson's disease are found to be, The rat is administrated with reserpine to induce Parkinson's disease. Effects like various chewing movements observed. When the gallic acid dose of 4.5, 23.5, 40.5 mg/kg/dose is administered. The rat induced with 6-OHDA (50, 100, 200 mg/kg) the results like avoidance of passive memory and chewing movements are observed.[21]

CONCLUSION

The overall review explains the mechanism of Parkinson's disease and currently available therapies. Parkinson's disease usually affects the aged persons only, the exact cause of Parkinson's disease is still unclear. This may be due to gene or exposed to certain toxins may increase in older peoples. The person with Parkinson's disease dies between the age of 78-81. Children or infants can be rarely affected by Parkinson's disease due to genetics or side effects of medications. In here, we discussed about the nutraceuticals in Parkinson's disease treatment.

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