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THERAPEUTIC POTENTIAL OF VARIOUS PHYTOCHEMICALS IN THE MANAGEMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is second largest neurodegenerative disorder which is seen mostly in elder people than the younger ones. PD is mainly caused by depletion of dopaminergic neurons in substantia nigra part of the brain and formation of Lewis bodies. The exact cause for PD is not known but genetic mutation, mitochondrial dysfunction, oxidative stress and protein misfolding are few causes for PD. PD is basically manifested by Rigidity, tremor, bredykinesia, Postural disability, Depression and anxiety, freezing and sleep disturbances. It is more common to occur in man than in woman but mortality rate is higher in woman than in men. There are almost 7 million cases of PD worldwide. Some available drug treatments for PD are dopaminergic (pramipexxol), non-dopaminergic (NMDA antagonist), Psychotropic Treatment (Trazodone, SSRI, SNRI), Tremor (Levodopa, dopamine agonists), Deep Brain stimulation surgery etc. Other than this, various phytochemicals have been explored to treat PD such as rosmerinic acid, curcumin, resveratrol, baicalein, quarcetin and naringenin. Till now no exact treatment has been discovered but symptomatic treatment is been carried out to treat PD symptomatically, numerous studies are in progress to discover appropriate treatment for PD. In this review we try to collect information regarding various phytochemicals which are explored in the management of Parkinson's disease by using animal models.

Keywords: Parkinson's disease; Phytochemicals; Neurodegenerative disorder; Dopaminergic neurons; Oxidative stress

1. INTRODUCTION

In the 1817, James Parkinson introduced a clinical condition Parkinson's disease in his "Essay on Shaking Palsy" which is also termed as Paralysis agitans **[1]**. PD is chronic progressive neurodegenerative disorder which is related to both motor and non-motor system disfunction including resting tremor, stiffness, difficulty in walking, balance and coordination. There are some other neurodegenerative disorder whose clinical symptoms are similar to that of PD and those are Dementia and Multiple system atrophy **[1]**.

Older ones are more prone to this disease than younger ones. Male are more prone to PD than Female but progression of disease and mortality rate is higher in females. In America the population which is suffering from PD is approximately 1 million and on an average 60,000 people diagnose with PD every year and approximately 7-10 million people are suffering from PD worldwide[1]. Loss of dopaminergic neurones in the substantia nigra part of the brain is the most common cause of PD and clinical symptoms starts to appear only when 70% to 80% dopaminergic neurones are destroyed, therefore it is very important to diagnose patient between the period of early dopaminergic cell degeneration and appearance of the clinical symptoms, so that effective treatment can be provided for PD **[1]**.

α-synuclein is a protien and a potential biomarker of PD, whose aggregation causes the loss of dopaminergic neurons in SN. When α-synuclein starts to make abnormal clusters then they cause harm to the SN. Once the formation of Alpha Synuclein cluster start it results in the transmission of toxic Alpha synuclein from infected cell to the normal cells which causes the formation of lewies bodies followed by apoptosis after that the continuous process of degeneration of dopaminergic neurones starts with the further spread of pathogenic Alpha synuclein to all other cells **[1]**.

Multiple system atrophy syndromes: striatonigral degeneration, nigrostriatal dopaminergic neurons, and the presence Shy-Drager syndrome, sporadic olivo-pontocerebellar of intraneuronal proteinacious cytoplasmic aggregates are pathological markers of PD. Degeneration (OPCA), parkinsonism (motor neuron disease) "Lewy Bodies" (LBs) are progressive pallidal atrophy. The organelles of the cells the SNpc contains progressive supranuclear palsy of nigrostriatal neurons, which project Familial Neurodegenerative

Diseases affecting the putamen in particular. Hallervorden-Spatz illness is characterised by a large quantity of neurotoxin. The hallmark gross manifestation of Huntington's illness is melanin. Neuropathological feature in Lubag is SNpc depigmentation (X-linked dystonia-parkinsonism) **[2]**.

Neurologic imaging serves a little role in the diagnosis of Parkinson's disease and is not commonly employed. Studies such as magnetic resonance imaging (MRI), ultrasonography, and positron emission tomography (PET) scans are not effective in diagnosing PD. PD worsens with time in both motor and nonmotor components, despite the finest medical and surgical treatments available today, still there is high mortality rate in PD patients. Regardless of the age of onset or the quality of illness care, the mean age of death is nearly the same (mid-70s) **[3]**. Today the need for daily consumption of fruits and vegetables is much needed because they contains numerous phytochemicals. Phytochemicals can be easily found in nature and are shown to have therapeutic effects against oxidative stress and neuroinflammation the pathology involved in PD. Common phytochemicals which people use in their daily life are curcumin, quercetin, caffeine, Resveratrol, Rosmerinic acid, baicalein etc. **[4]**.

It has been seen that plant based medicines are far better than synthetic drug used in treatment of PD.in india and most of the asian countries more than 20% medicines are plant based which are used as neuroprotective, There are various herbal plants suc as Acorus calamus, Allium sativum, Centella asiatica, Ginkgo biloba, Glycyrrhiza glabra, Terminalia Chebula etc. **[5]**.

2. REVIEW OF LITERATURE

2.1. Symptoms

The symptoms of PD are classified into motor symptoms and non motor symptoms, and symptoms related to motor system are Bredykinesia, Tremor, Rigidity and postural instability **[6]**.

2.1.1 Bredykinesia

One of the Peculiar symptom of Parkinson disease is bredykinesia which is indicated by the slowness of motor activity. Bradykinesia is one of the basal ganglia disorders which results in difficulty in posture balance and movement. Initially it causes difficulty in carrying out daily activities and delay in response time. Other clinical features like deprivation of spontaneous movement, dribbling due to diminished swallowing and reduction in back and forth arm movement

while walking are the indication of bredykinesia. Bredykinesia is a symptom which can be easily identified in Parkinson disease. PD also linked with the emotional state of the patient, for example if the patient is not mobile but when they get excited then they are able to make Rapid movement such as catching a baseball. This phenomena is called kinesia paradoxica Which indicates that a person with PD has a proper motor programs but they cannot execute those motor movement without any external stimulus, for example A loud noise **[6]**.

2.1.2 Tremor

In PD tremors are classified into two categories:- static tremor (rest tremor) and kinetic tremor (action tremor). The major clinical symptom of Parkinson disease is postural tremor which is seen in approximately 68%-100% of the patients but isolated postural tremor is the initial indication of Parkinson disease in some patients. However the mechanism of postural tremor is not known but it is seems that it is caused when there is decrease in uptake of striatal F-Dopa which is measured by PET. So it is assume that rest tremor is associated with nigrostriatal dopamine deficiency. The second most common type of tremor is kinetic tremor or action tremor which leads to more difficulty for the patients in comparison to the resting tremor because one cannot perform the social task properly. Action tremor is linked with the motor disability and results in weakness and bradykinesia **[7]** .

2.1.3. Rigidity

Rigidity in PD is expressed as the feeling of stiffness which results in increased resistance while voluntarily stretching muscles **[8]**. It is basically characterized by "cogwheel" phenomena, especially when combined with an underlying tremor, all along the passive movement of limbs (flexion extension and rotation), proximally around neck and Shoulder and distally around wrists and ankles **[6]**. The physiology of rigidity is not known but an increased monosynaptic stretch reflex has been seen in some cases **[8]**.

2.1.4. Postural disabilities

In all the multiple radial abnormalities the most common one is stopped posture in which neck and trunk are bent anteriorly, elbow shows flexion and arms are adducted. Lenticular lesions are responsible for this posture which indicates that basal ganglion plays an important role in maintenance of radial position. James Parkinson in 1817 described dorsal psychosis in which the trunk is bend forward and the chin is bent down and immobile. In the last stages of

disease lateral flexion of trunk is most common to occur. Camptocormia, Pisa syndrome and Neck flexion are the other examples of Postural deformities **[9]**.

2.1.5. Depression and anxiety

Depression and anxiety comes under the non-motor symptoms of Parkinson disease in which 30 to 40% of patient affected with depression and approximately 40% of patient shows symptoms of anxiety. basically these non-motor symptoms start to appear before the occurrence of motor symptoms Which signals the occurrence of Parkinson disease. The pathophysiological mechanism involved dopaminergic, serotonergic and noradrenergic mechanism **[10]**.

Other sensory abnormalities in PD are related to visual changes(contrast sensitivity and colour discrimination), decrease in olfaction and restless leg syndrome(RLS) **[11]**.

2.1.6. Freezing

Freezing, also known as motor blocks, is a type of akinesia (lack of movement) that is one of the most debilitating symptoms of Parkinson's disease. Although freezing is a common symptom of Parkinson's disease, it does not occur in all cases. According to responses from 6622 patients to a questionnaire distributed to 12 000 members of the German Parkinson Association, 47 percent of patients reported freezing; it happens more frequently in males than women and less frequently in patients with tremor as their primary symptom. The legs are the most usually affected by freezing when walking, but the arms and eyelids can also be affected. A sudden and fleeting incapacity to move is the most common symptom. This can involve a sudden inability to move the feet during a walk (start hesitation) or a hesitation when starting to walk **[6]**.

2.1.7. Sleep

Sleep disturbances are frequent in people with Parkinson's disease, affecting 60–98% of individuals. Excessive daytime sleepiness, sleep attacks, advanced sleep phase syndrome, early morning awakenings, and rapid eye movement sleep behavior disorder are the indications of sleep dysfunction. Circadian rhythm disturbance is linked to the progression of disease. Few of these sleep complaints can be treated with dopaminergic therapy; in fact, many of them are unavoidable adverse effects. With the probable exception of selegiline, nearly all anti-Parkinson drugs cause sleepiness as a side effect. The cause of circadian rhythm disruption in Parkinson's disease is unknown, and it's exacerbated by the usage

of PD drugs alongside other sleep-disrupting treatments like antidepressants and stimulants. Excessive daytime sleepiness (EDS) is linked to a Dopaminergic therapy **[11]**.

2.2. EPIDEMIOLOGY

As per the previously conducted health care service there are 5 out of 1,00,000 to 35 out of 1,00,000 new cases reported every year and this incident increases with age. In North America population people from age group of 45 - 54 the occurrence of p d increases as less than 1% whereas it is 4% in the people of age group 85 or older **[12]**. In European countries the occurrence of pd has been reported as 65.6/1,00,000 to 12500/1,00,000 where as in Asian countries it is lower and ranges from 15/1,00,000 to 328/1,00,000. this difference in the incidence can be because of different environmental risk factors and difference in gene susceptibility **[13]**.

Neuropsychiatric problems are common in PD. In a population- based study of 139 patients with PD, 61 % suffered from at least one neuropsychiatric symptom after 12 years of disease duration. The most common symptoms found were depression (38 %) and hallucinations (27 %) **[14]**.

2.3. ETIOPATHOGENESIS

After Alzheimer disease, PD is the second most common neurodegenerative disorder which occur in elderly people because people after the age 50 are mostly affected with PD **[15]**. There are various possible mechanism for PD eg- exogenous toxins and genetic mutations. In oxidative hypothesis low antioxidants system is seen in the patients with PD. dopamine is oxidatively metabolized by monoamine oxidase which results in the formation of peroxide and that peroxide is cleared out by the the glutathione but glutathione level are decreased in Parkinson disease as an results in the formation of more toxic free oxygen which causes the oxidative stress and further results in the damage of dopaminergic neurons. Decrease in the activity of proteasome can also results in neurodegeneration in PD as per few case studies it has been seen that a capacity of ubiquitin proteasome system(UPS), which degrades the proteins to clear out the misfolded protein from the brain, Can be a common characteristic for PD, These are some mechanism i.e. Impaired UPS function, imbalance in oxidative stress etc. **[15]**.

2.3.1. Mitochondrial Dysfunction

Tetrahydropyridine (MPTP) is a prodrug which act upon the mitochondria by

converting into a neurotoxin 1-Methyl-1,4-phenylpyridium (MPP+) and damage the mitochondrial cells and result in the developing symptoms of PD in the animal models. In another study in which rotenone was used as neurotoxin to inhibit normal mitochondrial function by inhibiting mitochondrial complex I, these two models clarified the role of mitochondria in the pathogenesis of PD **[2]**.

2.3.2. Oxidative stress

Evidence suggests that oxidative stress processes play a role in dopaminergic degradation in the substantia nigra in Parkinson's disease, indicating that this region is prone to oxidative stress and lacks protective systems.

• Enhanced dopamine oxidation and nevromelanin generation.

• Increased iron concentration and low ferritin concentration.

• Reduced glutathione production decreased and oxidized glutathione production increased.

The abnormalities described in the substantia nigra are unique to Parkinson's disease and not seen in other neurodegenerative disorders linked to dopaminergic cell degeneration. Changes in the quantity of dopamine and its metabolites malondialdehyde and 4-hydroxy-nonenalmodified proteins were used as indicators of oxidative damage in the substantia nigra **[16]**.

2.3.3. Protein misfolding (α-synuclein protein)

Protein misfolding (protein -synuclein) One of the most widely recognized ideas for the cause of nigrostriatal death is abnormal α-synuclein protein. α-Synuclein is a common protein found in CNS. The α-synuclein gene has mutations, which may alter the structure of the unfolded α-synuclein protein's structure and results in aggregation, which obstruct normal metabolic function the cell's pathophysiology.

Protein misfolding and the production of insoluble clumps can happen as a result of either genetic mutations or age. LB are intracellular inclusion structures that are thought to cause dementia. The pathologic hallmarks of Parkinson's disease (PD) are essentially a collection of Proteins containing α-synuclein **[2]**.

2.3.4. Genetic mutation

Initial autosomal recessive PD is associated with mutations in the PARKIN and PINK1 genomes. Both PARKIN and PINK1 have been coupled to a cellular pathway that usually includes macro-autophagy and the selective degradation of distorted mitochondria in lysosomes, a technique

known as "mitophagy." Mitophagy is hampered by the loss of function of these genes, leading in a buildup of defective mitochondria **[10]**. PARKIN also influences the levels of PGC-1alpha, an essential transcriptional regulator that coordinates the production of mitochondrial biogenesis genes as well as various antioxidant defences. PGC-1alpha levels too are low in sporadic PD, demonstrating that these findings apply to more than only rare genetic types of PD. These genetic linkages to mitochondrial degeneration and mitochondrial biogenesis suggest that mitochondrial turnover is defective in PD **[12]**.

2.4. Available drug treatment

Some studies indicate the use of dopamine agonist for example pramipexole treats the depression in PD but it has been seen that Mania precipitation occurs with the administration of pramipexole and ropinirole. Selegiline which is a monoamine oxidase inhibitor act as antidepressant but there is not enough evidence showing exact effect every time . some sort of treatment efficiency of dopamine agonist has been seen treating restless leg syndrome. there are other symptoms such as constipation dysautonomia and olfactory abnormalities which are not rated by the dopaminergic medications **[13]**.

2.4.1. Non- Dopaminergic treatment

NMDA antagonist (Bind to NMDA receptors which are present in neuron of substantia nigra) such as amantadine shows decrease in dyskinesia severity and decrease in motor fluctuations .Reversed action in haloperidol induced catalepsy and muscular rigidity has been reported in case of NMDA antagonist **[13]**.

2.4.2. Psychotropic treatment

Tricyclic antidepressants, tricyclic-related medications (trazodone), selective serotonin reuptake inhibitors (SSRI), venlafaxine, the serotonin and noradrenaline reuptake inhibitor (SNRI) reboxetine, and the pre-synaptic alpha-2 adrenoreceptor antagonist mirtazapine are all therapeutic agents. Antidepressant medications would be less effective in PD patients than in distressed non-PD people, however older patients and those with severe depression may react positively. In one meta-analysis (1 trial, 2 placebo controlled), both active treatment and placebo groups had a large composite reduction in depression rating scales, however there was no significantly difference between the two groups. A mitriptyline's worked as effective antidepressant in PD patients in an analysis

an also SSRI has not shown any effectivness as compared to plasibo **[10]**.

2.4.3. Tremor

Tremor is a hallmark symptom of Parkinson's disease that most commonly shows as resting or reemerging tremor during holding tasks and may often be efficiently treated with traditional anti-parkinsonian drugs. Levodopa or dopamine agonists (DAs) are effective first-line medicines. A subset of PD patients, on the other hand, is afflicted by akinesia and rigidity to a lesser level and frequently has a slower disease course. As a result, traditional antiparkinsonian medications may be ineffective. Additionally, some patients have contraindications as a result of psychiatric comorbidities or an unique manifestation such as a postural tremor caused by medication intolerance. As a result, other medications for the treatment of tremor are sometimes required. Tremor is a hallmark symptom of Parkinson's disease that most commonly shows as resting or reemerging tremor during holding tasks and may often be efficiently treated with traditional antiparkinsonian drugs. Levodopa or DAs are first-line medicines **[17]**.

2.4.4. Deep Brain stimulation surgery

Antiparkinsonian drug reduction is frequently sought to treat NMS such psychosis, orthostatic hypotension, daytime somnolence, or ICDs. However, exacerbation of parkinsonian symptoms on reduced treatment obviously limits this. Bilateral subthalamic nucleus (STN) DBS surgery has the potential to significantly relieve "off-medication" motor symptoms while also allowing for large drug dose reductions. This method is becoming more commonly available, and it may be a viable therapy choice for people who are experiencing difficult medication-related side effects. In the case of DDS and ICDs, encouraging reports have been documented, with pathologic behaviors resolved or dramatically improved after DBS. The time history of decreases in dopaminergic medicines closely followed the behavioral benefits. also previously reported significant improvements in a variety of non-motor (sensory, neuropsychological, dysautonomic, and, to a minor extent, psychological) conditions **[18]**.

2.5. Phytochemicals

There are various phytochemicals **(Table 1)** which are explored in the management of PD which are showing anti-inflammatory, anti-oxidant and anti-cancer properties, e.g.Resveratrol, Rosmerinic acid, Quercetin, Biacalein, Curcumin, caffeine, neringenin etc. **[19]**.

2.5.1. Resveratrol

Resveratrol is a polyphenolic phytochemical present in a variety of plants, including grapes and berries. Resveratrol appears to have cardioprotective properties via decreasing free radicals and hydroperoxidase enzymes. In the PC12 cell line, resveratrol protects SH-SY5Y cells from rotenone-induced apoptosis and lowers -synuclein levels. A related study found that pretreatment of PC12 cells with resveratrol before MPP+ overdose results in reduced apoptosis **[20]**. Apoptosis was assumed to be inhibited by cytochrome C inhibition and nuclear translocation of the apoptosis-inducing factor (AIF). Resveratrol has been found to help with motor deficits, oxidative stress, and the degeneration of TH neurons in mouse models of Parkinson's disease. In rats with 6-OHDA-induced nigrostriatal neuron degeneration as a PD model, resveratrol inhibits mitochondrial hypertrophy and chromatin condensation while also lowering COX-2 and TNF- gene expression **[21]**.

2.5.2. Rosmerinic acid

RA is polyphenolic phytochemical which is found naturally and shows antioxidant and anti-inflammatory properties. In a recent study it has been observed that RA can protect dopaminergic neurons from 6-hydroxxydopamine (6-OHDA) induced neurotoxicity in rat model of PD. This experiment was done to check if RA can actually reverse the alterations made by 6-OHDA induced in rat model of PD. So intrastriatal 6-OHDA lesioned rat was administered with rosmerinic acid (20mg/kg, orally), after analyzing the results it has been seen that 6-OHDA caused deacrease in number of tyrosine hydroxylase immunoreactive neurons and decrease in dopaminergic neurons in striatum, thus administration of RA resulted in alteration of these changes in a positive way. One more study said that 6-OHDA cause increase in number of iron staining positive cells and Bax/Bcl-2 ratio which were reduced by rosmerinic acid. Thus it was proved that RA shows the neuroprotective action against 6–OHDA induced neurotoxicity **[22]**.

2.5.3.Quarcetin

Quercetin (QC) is a polyphenolic phytochemical that can be found in various foods like onions, broccoli, and shows various properties such as antioxidant, anti-inflammatory, and anticancer. A recent study has found that quercetin can cross the blood-brain barrier in in-situ rat models. In a stroke model generated by transitory global ischemia, quercetin also has a protective

effect. quercetin basically protect neuronal cells from oxidative stress-induced apoptosis. After injecting 6-OHDA, rats were given Quercetin (100-300mg/kg) which resulted in decrease in lipid peroxidation and increase in catalase and superoxide dismutase activity and minimized glutathione depletion. Therefore, it has been confirmed that Quercetin shows the neuroprotective action in 6-OHDA induced rat model of PD **[23]**.

2.5.4. Baicalein

Baicalein is a major phytochemical which is isolated from *Scutellaria baicalensis Georgi,* shows therapeutic effects in various experiments related to PD. In which baicalein (100-400mg/kg, orally) was given to the Sprague-dawley rats which were initially induced with rotenone. After the analysis it has been seen that behavioral impairment and depletion of dopaminergic neurons were improved with the administration of baicalein. Also it was observed that in rotenone-induced rat model, the administration of baicalein results in restoring mitochondrial function and improved mitobiogenesis which was examined by measuring mitochondrial density and key regulators which are involved in mitobiogenesis. And it was made confirmed that baicailein results in increased mitobiogenesis through cAMP-responsive element binding protein (CREB) and glycogen synthase kinase-3β pathways in rotenone-induced SH-SY5Y cells. Thus baicalein can improve the mitobiogenesis to restore mitochondrial function **[24]**.

2.5.5. Curcumin

Curcumin is a phenolic yellow phytochemical which is found in the rhizomes of plant curcuma longa (turmeric). Curcumin has shown protective action against rotenone-induced neuronal changes in PD. In order to ensure the effectiveness of curcumin in treatment of PD ratenone (2.5 mg/ml intraperitoneally) was injected into male albino rats for 21 days. Then after administration of curcumin (200 mg/kg) behavioral and electrophysiological changes were examined. Cylinder test was used to assess the motor activity. Electrical activity of neurons was analysed in hippocampus. Rotenone caused the reduction in electrical activity but curcumin results in the improvement of motor activity and electrophysiological changes made by rotenone. Thus after studying the rotenone-induced rat model shows that curcumin can be used in the treatment of PD **[25]**.

2.5.6. Caffine

Cafinine (1,3,7-trimethylxanthine) is one of the highly consumed psychotropic substance

and its therapeutic action was found for the treatment of PD by using Retenon-induced rat model. Rats were provided with caffeine (30 mg/kg, i.p.) for 45 days. After the administration of caffeine some data showed that there was decrease in oxidative stress, decrease in lipid peroxidation, increase in reduction of glutathione level, This research showed that caffeine can be used efficiently in PD treatment **[26]**.

2.5.7. Naringenin

In the peels of citrus fruits like grapes and tomatoes, a flavonoid is present termed as Naringenin which has shown protective effect against parkinson's disease. In the previous studies naringenin has shown protective action by lowering the oxidative stress via anti-oxidant pathways. Recently in a MPTP-induced animal model of PD, NGN's neuroprotective action was examined. A dose of (25, 50, 100mg/b.wt, i.p) was given to healthy C57BL/6J mice (18-20g b.wt) for successive 5 days. Then (80 mg/kg b.wt, i.p) of 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine (MPTP) was administered in two divided doses (2 x 40 mg/kg at 16h intervals). After 48 hours of MPTP administration, motor activity of animals was examined. After reporting the motor activity animals were euthanized for dissection of brain so that biochemical, molecular and histopathological factors can be studied. Pretreatment with NGN result in reduction of LPO level and increase in glutathione reductase and catalase enzyme activity, improvement of motor acitivity and reversed the toxic effects of MPTP. Some ongoing studies have sshown that NGN can be proved as primary phytochemical for treating PD **[27]**.

2.5.8. Ellagic acid

Ellagic acid is polyphenolic phytochemicals which is present in in variety of fruits such as pomegranates and raspberries. Ellagic acid is having neuroprotective, anticancer and anti-inflammatory properties. Neuroprotective properties has been analysed by using MPTP rat model of PD, for this experiment ellagic acid was given intraperitonially in the dose of 10mg/kg in the C57BL/6 C mice, during result analysis ellagic acid has shown various neuroprotective effects such as decrease in dopaminergic neuronal loss, restoration of antioxidant enzymes, decrease in glutathione depletion, reduction in level of COX-2 which was altered by MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration in rats **[28]**.

2.5.9. Magnolol

Magnolol is a phytochemical which is present in bark of *Magnolia obovata* which

exerts anxiolytic and antidepressant properties. Magnolol is also having neuroprotective effect on the central nervous system observed in MPTP rat model of PD. For this experiment Magnolol in the dose of 30mg/kg was given orally to MPTP treated C57BL/6 N mice. After the result analysis it has been observed that magnolol prevented the loss of dopaminergic neurons and reduction in oxidative stress **[29]**.

2.5.10. Amentoflavone

Amentoflavone is a polyphenolic phytochemicals which is obtained from *selaginella tamariscina* which exerts anti-inflammatory, anticancer, antimicrobial and neuroprotective properties. For experimenting neuroprotective properties AF was administered orally in the dose of 50mg/kg to MPTP treated C57BL/6 mice. After the result analysis it has been observed that AF has shown reduction in bradykinesia, reduction in the loss of dopaminergic neuronal loss, increase in Bcl/Bax ratio, and reduction in cell apoptosis **[30]**.

2.5.11. Carnosic acid

Carnosic acid is a polyphenolic phytochemical which is obtained from *Rosmarinus officinalis.* it is having antioxidant and neuroprotective properties. For experimenting CA's neuroprotective properties male wistar rat which was treated initially with MPTP, were given 20mg/kg dose of CA by oral route and after the result analysis it has been seen that there was improvement in the behavioral performance and apoptosis and Bcl/Bax ratio was also reduced upto certain level. Thus this experiment has proved the neuroprotective effect of carnosic acid in MPTP rat model of PD **[31]**.

2.5.12. Apigenin

Apigenin is a naturally occurring phytochemiccal which is present in various fruits and vegetables such as parsley, chamomile and celery. It is having anti-cancer, antibacterial and antispasmodic properties **[32]**. Apigenin also shows some neuroprotective properties in PD which was analysed by using MPTP rat model in which adult male swiss-albino rats were given apigenin in the dose of 10-20mg/kg orally and the result analysis showed that GFAP (Glial fibrillary acidic protein) level was reduced, BDNF (Brain derived neurotrophic factor) was increased and TNF-α was reduced. Thus this study has proved the neuroprotective property of apigenin and it can be used for the treatment of PD **[33]**.

2.5.13. Luteolin

Luteolin is a naturally occurring flavonoid which is found mostly in broccoli, carrots,

apple skin and celery. It is having anti-inflammatory, antioxidant and anticancer properties **[34]**. Some studies has shown the neuroprotective effects of luteolin in PD. For cheking these properties an MPTP rat model experiment was done in which adult male swiss-albino rats were treated with luteolin at a dose of 10-20mg/kg orally and the result analysis hsowen that there was improvement in the SOD (superoxide dismutase), CAT (catalase) and GSH (Glutathione) level, reduction in the lipid peroxidation and increase in tyrosine hydroxylase enzyme activity. Thus, this experiment shows that Luteolin can be used to treat PD patients **[33]**.

2.5.14. Tocotrienol

Tocotrienol is a naturally occurring compound present in palm oil, annatto seed and rice bran oil. It is having anti-inflammatory, anticancer, antioxidant properties. Tocotrienol which is derived from palm oil shows the neuroprotective effect against the neurotoxicity caused by oxidative stress. For this an experiment was done in which 6-OHDA treated Sprague-Dawley rat was gievn tocotrienol (10mg/kg) orally and after the result analysis it ahs been seen that forelimb retraction time was decreased, NF-L densisty was reduced, striatal astroliosis was reduced and dopaminergic neuronal loss was prevented **[35]**.

2.5.15. Hesperidine

Hesperidine is a bioflavonoid which is present mostly in oranges and lemos. It is having various anti-depressant, anticancer and neuroprotective properties. In a 6-OHDA rat model of PD hesperidine (50mg/kg i.p.) was given to C57BL/6 mice and after the result analysis it has been that there was improvement in behavioral performance, GSH level was reduced upto certain level and protection was seen against reactive species (RS). Thus, Hesperidine can be used in PD patients **[36]**.

2.5.16. Genistein

Genistein a isoflavone which is present mostly in soybeans. It is having great antioxidant property as it has shown protective action against neurodegeneration caused by MPTP in rats. For this experiment Genistein (10mg/kg i.p.) was given to C57BL/6 mice and it has been seen that genistein caused reduction in neurodegeneration caused by neurotoxin MPTP, prevention in dopaminergic neuronal loss and reduction in Bcl gene expression level. Thus, genistein can be used for the treatment of PD **[37]**.

3. CONCLUSION

Parkinson's disease is a neurodegenrative disorder which caused by loss of dopaminergic neurons in the substantia nigra part of the brain. It is manifested by Tremor, Bradykinasia, Poatural disability and freezing. There are various phytochemicals which are used for the treatment of PD such as apigenin, luteolin, Hesperidine, Genistein, Curcumin, Neringenin and carnosic acid. These phytochemical are occurring naturally and have shown neuroprotective effect in PD

Table 1: Phytochemicals explored in Parkinson's Disease using animal models

Phytochemicals	Dose	Route of administration	Animal used	Model used	Observation	References
Rosmerinic acid	20mg/kg	Oral	Wistar rats	6-OHDA	Decrease In dopamine content Decrease in TH immunoreactivity Decreased Ratio of Bax/Bcl-2 at genetic level Decreased Iron level in SN	[22]
Quarcetin	100-300mg/kg	Oral	Wistar rats	6-OHDA	Decrease in Escape latency Retention time incresed Improved learning and memory	[23]
Baicalein	100-400mg/kg	Oral	Sprague-dawley rats	MPTP	improved Motor activity increase in No. of TH^+ cell increase in ATP level Mitobiogenesis was increased	[24]
Curcumin	200mg/kg	Intraperitoneal	Albino rats	MPTP	No. of rearing increased Body weight was increased Improved motor impairment	[25]
Resveratrol	10-40mg/kg	Oral	Sprague-dawley rats	6-OHDA	Decrease in COX-2 & TNF-α Decrease in inflammatory reaction	[38]
Caffine	30mg/kg	Intraperitoneal	Wistar albino rats	MPTP	Improved AchE activity Increase in GSH level	[26]
Naringenin	25- 100mg/kg	Oral	C57BL/6J mice	MPTP	Decreased nuclear pigmentation Activity of Glutathion reductase was Improved behavioural performance was improved	[27]
Ellagic acid	100mg/kg	Intraperitonial	C57BL/6C mice	MPTP	Dopaminergic neurons loss decreased Antioxidant enzyme restored Glutathione depletion was decreased Level of cox-2 was reduced	[28]
Magnolol	30mg/kg	Oral	C57BL/6N mice	MPTP	Dopaminergic neuronal loss was prevented Oxidative stress was reduced	[29]
Amentoflavone	50mg/kg	Oral	C57BL/6 mice	MPTP	Bradykinesia was reduced Dopaminergic neuron loss was reduced Bcl/Bax ratio was increased Cell apoptosis was decreased	[30]
Carnosic acid	20mg/kg	Oral	Male wistar rat	6-OHDA	Behavioral performace was improved Apoptosis was reduced Bcl/Bax ratio was increased	[31]

Apigenin	**5,10& 20mg/kg**	**Oral**	**Adult male swiss-albino rats**	**MPTP**	**GFAP level was decreased Increase in BDNF TNF-α level was reduced**	**[33]**
Luteolin	**10-20mg/kg**	**Oral**	**Adult male swiss-albino rats**	**MPTP**	**SOD activity was improved CAT and GSH were improved Lipid peroxidation was reduced Increase in tyrosine hydroxylase enzyme**	**[33]**
Tocotrienol	**10mg/kg**	**Oral**	**Sprague-Dawley rat**	**6-ODHA**	**Decrease in forelimb retraction time NF-L density was reduced Striatal astroliosis was reduced Dopamine neuronal loss was reduced.**	**[35]**
Hesperidine	**50mg/kg**	**Oral**	**C57BL/6 mice**	**6-OHDA**	**Behavioral performance was improved Reduction in GSH level was prevented Protected against elevated ROS level**	**[36]**
Genistein	**10mg/kg**	**Intraperitonial**	**C57BL/6 mice**	**MPTP**	**Neurotoxicity was reduced Dopamine neuronal loss was prevented Reduction in Bcl-2 gene expression was inhibited.**	**[37]**

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