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A Review Article on the Therapeutic Potential of Leaves Extract of *Adhatoda vasica* on Antiparkinsonism Activity

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ABSTRACT:

Medicinal plants have been used in treatment since ancient times. Medicinal plants play a central role in disease prevention, and their promotion and use are compatible with all existing prevention strategies. The research and use of medicinal substances of plant origin in the treatment of diseases is increasing every day. Natural and unique medicinal plants are used to treat various diseases and earn income. Ayurveda and other Indian literature have mentioned the use of plants in the treatment of various human health ailments. Medicinal plants are an important resource in the fight against serious diseases worldwide. This study focuses on the knowledge and research related to the medicinal use of plants to confirm their medicinal values and the role, contribution and benefit of medicinal plants in neurodegenerative diseases such as Parkinsonism[1].

Phytochemical analysis of ELEAV revealed the presence of alkaloids, flavonoids, terpenoids, saponins, phenols and steroids. ELEAV also showed antioxidant capacity with 69.23% inhibition of 1,1-diphenyl-2-picrylhydrazil (DPPH) radical. ELEAV had strong inhibitory effects on the scavenging of nitrogen oxide, superoxide, and hydroxyl radicals, 65.24%, 61.54%, and 61.24%, respectively. In addition, ELEAV showed a concentration-dependent reducing power and a strong inhibitory effect on iron-induced lipid peroxidation. 68.26%) in bovine brain extract. These findings confirm the biological effectiveness of A. vasica as a potential source of natural antioxidants[1].

1. Introduction

Parkinson's disease is a brain disorder that causes involuntary or uncontrolled movements such as tremors, stiffness, and difficulty with balance and coordination.

Symptoms usually start gradually and get worse over time. As the disease progresses, people may have difficulty walking and talking. They may also experience mental and behavioral changes, sleep disturbances, depression, memory problems and fatigue.

The most visible signs and symptoms of Parkinson's disease occur when neurons in the basal ganglia, the area of the brain that controls movement, weaken and/or die. Normally, these nerve cells, or neurons, produce an important brain chemical called dopamine. As neurons die or weaken, they produce less dopamine, which causes the movement problems associated with the disease. Scientists still don't know what causes neurons to die. People with Parkinson's disease also lose the nerve endings that produce norepinephrine, the main chemical messenger in the sympathetic nervous system that controls many bodily functions, such as heart rate and blood pressure. The loss of norepinephrine may help explain some of the non-motor symptoms of Parkinson's disease, such as fatigue, irregular blood pressure, decreased food passing through the digestive tract, and a sudden drop in blood pressure when a person sits or stands.

Many brain cells in people with Parkinson's disease contain Lewy bodies, which are abnormal clumps of the protein alpha-synuclein. Researchers are working to better understand the normal and abnormal functions of

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alpha-synuclein and its relationship to genetic variants that contribute to Parkinson's and Lewy body dementia. Some cases of Parkinson's appear to be hereditary, and some cases may be linked to specific genetic variants. Although genetics is thought to play a role in Parkinson's disease, the disease does not seem to run in families in most cases. Many researchers now believe that Parkinson's disease is caused by a combination of genetic and environmental factors, such as exposure to toxins. Symptoms of Parkinson's disease There are four main symptoms of Parkinson's disease: • Tremors in the hands, arms, legs, jaw or head • Muscle stiffness, where the muscle remains contracted for a long time • slowness of movements • Deterioration of balance and coordination, sometimes leading to falls

Other symptoms may include: • Depression and other mood changes • Difficulty swallowing, chewing and speaking • Problems urinating or constipation • Skin problems

People with Parkinson's often develop a parkinsonian gait, which involves a tendency to lean forward; take small, quick steps; and reduces arm swing. They may also have difficulty starting or continuing to move. Symptoms often start on one side of the body or even on the other side of the body. As the disease progresses, it eventually affects both sides. However, symptoms may be more severe on one side than the other. Many people with Parkinson's disease report that before their stiffness and tremors, they had trouble sleeping, constipation, loss of smell, and restless legs. Although some of these symptoms may occur with normal aging, consult your doctor if these symptoms worsen or begin to interfere with daily life.

Medicines for Parkinson's disease

Medicines can help treat the symptoms of Parkinson's by:

- Increasing the level of dopamine in the brain
- Having an effect on other brain chemicals, such as neurotransmitters, which transfer information between brain cells
- Helping control non-movement symptoms

The main therapy for Parkinson's is levodopa. Nerve cells use levodopa to make dopamine to replenish the brain's dwindling supply. Usually, people take levodopa along with another medication called carbidopa. Carbidopa prevents or reduces some of the side effects of levodopa therapy — such as nausea, vomiting, low blood pressure, and restlessness — and reduces the amount of levodopa needed to improve symptoms[2]

2. DISCUSSION

2.1. Pathophysiology of Parkinson's Disease

Although we are learning more about the pathophysiology of Parkinson's disease every day, it is still largely considered idiopathic (of unknown cause). This is probably related to host sensitivity and a combination of environmental factors. A small number of cases are genetically linked, and genetic factors are intensively studied. Physiologically, the symptoms associated with Parkinson's disease are caused by the loss of several neurotransmitters, especially dopamine. Symptoms worsen over time as more and more cells affected by the disease are lost. The course of the disease is highly variable, with some patients having very few symptoms as they age, while others have rapidly progressive symptoms. Parkinson's disease is increasingly recognized as a complex progressive neurodegenerative disease. There is strong evidence that it first affects the dorsal motor nucleus and olfactory bulb and nucleus, then the locus coeruleus, and finally the substantia nigra. Cortical regions are affected at a later stage. Damage to these different nervous systems results in multifaceted pathophysiological changes that result in impairments not only in the motor system but also in the cognitive and neuropsychological systems**.** [3]

2.2 The Role of Dopamine

Dopamine, like other neurotransmitters, transmits chemical messages from one **neuron** to another across the synapse, **which is the** space between the presynaptic cell and the postsynaptic receptor. Dopamine is **released** from membrane storage vesicles in the presynaptic **membrane of the synapse.** It crosses the synapse and binds to the postsynaptic membrane, where it activates dopamine receptors. Unused dopamine **left** in the synapse is absorbed back into the presynaptic cell; **after returning to** the presynaptic cell, excess dopamine is repackaged into storage vesicles and released **back** into the synapse. **When** dopamine **is transported** from one cell to another, two enzymes, MAO (monoamine oxidase) and COMT **(catechol-O-methyltransferase)**

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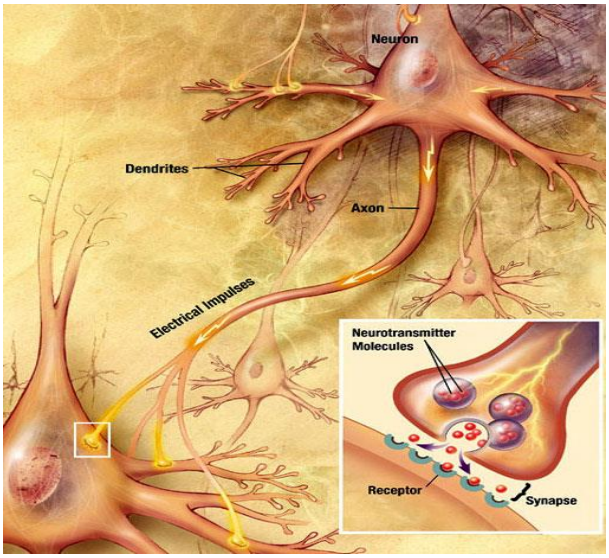
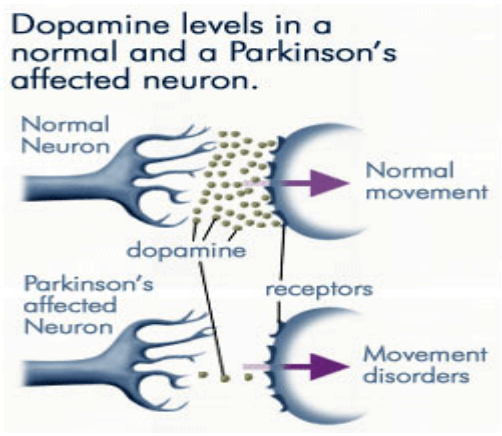
can break it down and render it inactive at the synapse. One **treatment** strategy introduces **an** MAO inhibitor into the synapse, which interrupts the **activity** of the MAO enzyme and prevents the breakdown of dopamine. This allows more dopamine to remain in the synapse and increases the likelihood that it will bind to the postsynaptic membrane.

Chemical Synaptic Transmission



An electrochemical wave called an action potential travels along the axon of a neuron. When the action potential reaches the presynaptic terminal, it provokes the release of a small quantity of neurotransmitter molecules, which bind to chemical receptor molecules located in the membrane of the postsynaptic neuron, on the opposite side of the synaptic cleft. [4]

2.3 Progressive Loss of Dopamine



As neurons in Parkinson's disease produce less and less dopamine, there is much less dopamine that binds to dopamine receptors on the postsynaptic membrane. **[5]** Although the loss of dopamine cells cannot be directly measured, measurements in neurologically normal humans and primates show a slowly progressive loss of dopamine with age. In Parkinson's disease, the loss occurs much more rapidly, and both biochemical measurements and imaging studies show that dopamine levels are significantly reduced by the time motor symptoms appear. According to this view, Parkinson's disease is an accelerated version of the cell death seen in normal aging. [6] This can be seen in the graph below, which shows the decline of dopaminergic neurons in normal aging, idiopathic PD, and environmentally induced PD. or genetic factors and early onset of PD. Degeneration of dopamine neurons is particularly evident in a part of the substantia nigra called the pars compacta. In particular, loss of dopamine in the pars compacta increases overall excitability in the basal ganglia , which disrupts voluntary motor control and leads to typical symptoms of PD. Normalization of motor function is initially observed with levodopa treatment **[7]** *The main components of the basal ganglia are the striatum (caudate nucleus and putamen), Globus pallidus, substantia nigra, nucleus accumbens and subthalamic nucleus. As PD severity increases, dopamine depletion leads to further changes in basal ganglia pathways, including dysfunction of other basal ganglia neurotransmitters such as glutamate, GABA, and serotonin **[7].** Although there is a relative vulnerability of dopamine-producing neurons in the substantia nigra, not all dopamine cells are affected in Parkinson's disease; in some parts of the brain, dopamine-producing neurons are relatively spared **[6]**

2.4 Lewy Bodies and Alpha-Synuclein

Lewy bodies are abnormal protein aggregates and inclusions that form in the neurons of people with Parkinson's disease. Aggregates usually consist of insoluble fibrillar aggregates containing misfolded proteins. A large number of molecules have been identified in Lewy bodies, but the main component is a protein called alpha-synuclein**.**

Lewy Bodies (Alpha-Synuclein Inclusions)

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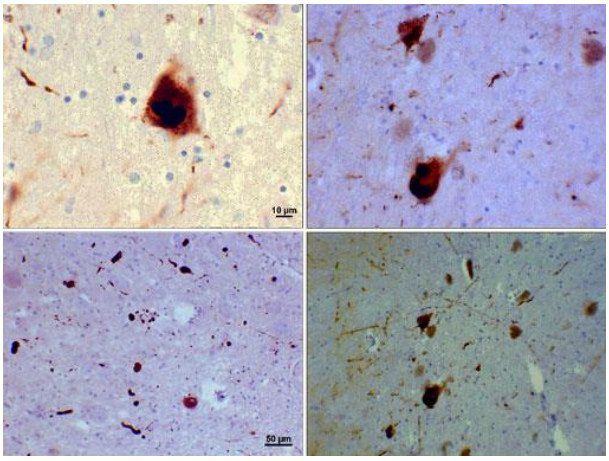

Photomicrograph of regions of the substantia nigra of a Parkinson's disease patient showing Lewy bodies and Lewy neurites at different magnifications. Upper panels show 60x magnification of intraneuronal inclusions of alpha-synuclein aggregated to form Lewy bodies. Lower panels are 20x magnification images showing filamentous Lewy neurites and round Lewy bodies of various sizes. Photos by Suraj Rajan. Lewy pathology involves many areas of the brain, and some reports have indicated that the substantia nigra is not the first place where Lewy bodies form in Parkinson's disease. The inclusions and aggregates probably symbolize the final stage of a complex sequence of events. The earlier stage may be more directly related to the pathogenesis of the disease than the inclusions themselves, which may represent diagnostic features. Lewy bodies are also seen in "dementia with Lewy bodies", suggesting that these diseases share a common pathology and possibly a common etiology. Cell loss or Lewy body formation are not strictly specific for PD, but both are required for the diagnosis of PD according to current definitions.[6] Neurodegenerative diseases such as Alzheimer's disease, frontotemporal degeneration, prion disease, Huntington's chorea and motor neuron diseases are increasingly found to share common cellular and molecular mechanisms, including protein aggregation and the formation of inclusion bodies in certain regions of the nervous system.. [10]

2.5 Inflammation and Immune Response

The trigger for dopaminergic degeneration appears to be multifactorial, with endogenous and environmental factors contributing. Inflammation and immune responses are increasingly recognized as important mediators of dopaminergic degeneration. Large population studies have shown that subjects using nonsteroidal anti-inflammatory drugs (NSAIDs) have a lower risk of developing idiopathic PD, suggesting that NSAIDs may be promising disease-modifying drugs for patients with Parkinson's disease. [8] New research included anti-inflammatory therapies, specifically the search for an objective biomarker for therapies aimed at reducing inflammatory changes in PD patients. Researchers are using neuroimaging machines to develop a relevant biomarker to test in large clinical imaging studies. The results of these studies will inform the testing and monitoring of the progress of anti-inflammatory therapies in PD and will help identify a timely therapeutic window to stop or at least slow down inflammation-induced dopaminergic degeneration. [8]

3.1. Genetic Factors in Parkinson’s Disease

For many **years** it was **believed** that most forms of **Parkinson's** disease **had no** genetic basis. **However, in** the late 1990s, studies of **several** patient **groups** documented that the risk of **Parkinson's** disease among first-degree relatives of an affected **person** is 2 to 14 times higher than in the general population. As **genomic** technologies have become more cost-effective and **accurate,** genetic linkage maps have improved dramatically, **enabling the study of** the genetic **causes** of disease. **Whole-genome-sequencing analyzes** are now **performed** on individual patients at a reasonable and **ever-decreasing cost. A** small number of genes **may** be involved in up to 6% of **all** PD cases, and there are probably other genes that increase the risk of **Parkinson's disease** without necessarily causing it. Up to 15% of **people with** PD have **an immediate** family member who **also** has PD.

3.2 Park Family of Genes

A gene family is a group of genes that share important characteristics. The PARK gene family has been of particular interest and has been extensively studied. Mutations in PARK genes affect the function and survival of neurons critical for normal movement, balance and coordination.[9] Mutations in three known genes (SNCA, UCHL 1 and LRRK 2) have been reported in families with dominant inheritance. Mutations in three other genes (PARK 2, PARK 7 and PINK 1) were found in affected individuals who had siblings with the disease but whose parents did not have Parkinson's disease

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(recessive inheritance). There is evidence to suggest that these genes are also associated with early-onset Parkinson's disease (diagnosed before age 30) or dominantly inherited Parkinson's disease. The following table lists the PARK family genes with the accepted symbol in the first column and the previous names in the middle column. Approved symbols are used in this part of the course.

Genes in the PARK Family[11,12]

Approved Symbol	Previous Name	Comments
SNCA	PARK 1, PARK 4	Provides instructions for making alpha-synuclein.
PARK 2 (parkin)	---	Provides instructions for making a protein called parkin.
PARK 3	---	---
UCHL 1	PARK 5	Provides instructions for making an enzyme called ubiquitin carboxyl-terminal esterase L1, which is probably involved in the cell machinery that breaks down unneeded proteins.
PINK 1	PARK 6	Provides instructions for making a protein called PTEN induced putative kinase 1. Appears to help protect mitochondria from malfunctioning during periods of cellular stress, such as unusually high energy demands.
PARK 7	---	Provides instructions for making the DJ-1 protein. One of the protein's functions may be to help protect cells, particularly brain cells, from oxidative stress.
LRRK 2	PARK 8	The LRRK 2 gene provides instructions for making a protein called dardarin.
ATP13A2	PARK 9	May play a role in intracellular cation homeostasis and the maintenance of neuronal integrity.
PARK 10	---	---
PARK 11	---	---
PARK 12	---	---
HTRA2	PRSS25	Also known as PARK 13
PLA2G6	---	Provides instructions for making a type of enzyme called an A2 phospholipase. This type of enzyme is involved in metabolizing fats called phospholipids.
FBXO7	---	Also known as PARK 15
PARK16	---	---
VPS35	---	Also known as PARK 17
EIF4G1	EIF4G, EIF4F	Also known as PARK 18

3.3 Dominant Genes in PD

Mutations in a group of genes that encode alpha-synuclein and LRRK 2 are transmitted in a **dominant** fashion and generally lead to Lewy body pathology, with alpha-synuclein being the major component of these pathologic protein aggregates. [13]Although genetic tests

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can test for the presence of the LRRK 2 mutation, they cannot be used to make a definitive diagnosis of PD.

SNCA

The discovery of mutations in the SNCA gene was the first evidence of a genetic cause for PD. This gene encodes the protein alpha-synuclein, the main component of Lewy bodies and the noted pathology marker in autopsy slides of PD brains. Mutations of the SNCA gene, including nucleotide changes, and duplications, triplications, and extra copies of the SNCA gene, account for about 2% of familial cases, though not all persons with these changes have developed PD. The mean age of onset in individuals with mutations in this gene is 46 years [13]

Recent studies have demonstrated that alpha-synuclein regulates the release of neurotransmitters at the presynaptic terminal. In addition, alpha-synuclein seems to modulate intracellular dopamine concentration through interactions with proteins that regulate dopamine synthesis and uptake .[13]

LRRK 2 (PARK8)

The LRRK 2 gene (formerly PARK8) is a signaling protein that becomes toxic when it mutates [13]. The LRRK 2 gene encodes for a protein called **dardarin**. One segment of the dardarin protein contains a large amount of an amino acid called leucine. Proteins with leucine-rich regions appear to play a role in activities that require interactions with other proteins, such as transmitting signals or helping to assemble the cell's structural cytoskeleton. Other parts of the dardarin protein are thought to be involved in protein-to-protein interactions [12]

Nearly a dozen different mutations have been reported in the LRRK 2 gene. Mutations in LRRK 2 are the most common known cause of familial and sporadic PD, accounting for approximately 5% of individuals with a family history of the disease and 3% of sporadic cases. Sergey Brin, one of the two noted co-founders of Google, has a known mutation in this autosomal dominant gene for PD, with the resulting 20% to 80% chance of developing PD. His mother, Genia Brin, carrying the same mutation, was diagnosed with PD in 1998 at the age of 50.

Recessive Genes in PD

Mutations in PARK2 (parkin), PINK1 (PARK 6), and DJ-1 (PARK7) cause recessive Parkinson's disease, in which pathology often lacks the typical Lewy bodies in surviving neurons. Interestingly, recent findings highlight the role of these genes in mitochondrial function, suggesting a common molecular pathway in recessive Parkinson's disease.[13]

PARK2 (Parkin)

The PARK2 gene, one of the largest human genes, provides instructions for making a protein called parkin, which **is involved** in **breaking down unnecessary** proteins. It does this by tagging damaged and excess proteins with molecules called ubiquitin. Ubiquitin **acts** as a signal to **transfer unnecessary** proteins **to special cellular** structures **called** proteasomes, where the proteins are **broken down.**.[11]

The ubiquitin-proteasome system acts as **a cellular** quality control by **removing** damaged, **misfolded** and excess proteins. This system also regulates the availability of **several** proteins involved in critical **cellular functions,** such as the timing of cell division and growth. Because **Parkin works** in the ubiquitin-proteasome system, **it** belongs to a group of proteins called E3 ubiquitin **ligases.** [11].

Parkin also appears to be involved in the maintenance of mitochondria, the energy-producing centers **of** cells. Genetic and cell **biology** work **over** the last decade **has revealed the central role** of **Parkin** and PINK1 in mitochondrial quality control. PINK1 **detects** damaged mitochondria and recruits and activates **Park** to degrade and recycle damaged mitochondria. **A large body of** evidence **indicates** that defects in this pathway **can lead to** PD. [14]

Much of the research has focused on the Parkin gene. In early 2013, in a major breakthrough, the crystal structure of Parkin was identified, providing new information about the function of this important gene. Jennifer Johnson, one of the scientists involved in the discovery of Parkin's crystal structure, says: "The crystal structure serves as a basis for how Parkin works. Scientists can see exactly how it works and then begin to develop compounds that target the areas of dysfunction and then better see if the compounds applied to the problem areas work[15]

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3. Herbal Plants Having Anti Parkinsonism Activity

1	Bacopa monnieri	Brahmi or waterhyssop	Bacopaside and bacoside	Redox stabilization, improves mitochondrial function, attenuate a-synuclein aggregation, attenuate apoptosis improves cognition [16,17,18,19]
2	Camellia sinensis	Green tea	Polyphenols, catechins [epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)]	Redox stabilization, inhibit ROS-NO pathway, metal chelation, Protects DA neurons in a nigral region[20,21,22,23,24]
3	Cassia obtusifolia	Java bean or Sicklepod	CSE supplementation, MPP+, MPTP's neurotoxic metabolite	reduce cell damage and attenuate ROS generation and mitochondrial membrane depolarization in 6-OHDA mediated pc12 cells., causes dopaminergic neuronal loss by inhibiting respiratory complex 1 activity in dopaminergic neuronal mitochondria[25]
4	Coffea Arabica and Coffea canephora	Arabica and Robusta coffee	Caffeine	exerts neuroprotective effects against dopaminergic neuronal failure induces motor deficiency reversal in models of PD mice[26,27,28,29]
5	Curcuma longa	Turmeric	Curcumin	Improves striatal dopamine level, mitochondrial Complex I activity, Reduces oxidative stress, up-regulate SOD and GPx activity, acetylcholine level, replenish mitochondria membrane potential and ATP production, inhibit a-synuclein fibrillization[30,31,32,33]
6	Delphinium denudatum	Jadwar	A diterpenoid alkaloid, vilmorrianone, denudatine, panicutine, condelphine, and isotalatizidine.	reduced 3,4-Methylenedioxyamphetamine (MDA) levels, increased glutathione (GSH) content, Superoxide dismutase (SOD), catalase (CAT) activities and increased dopamine levels[34]
7	Gingko Biloba	Maidenhair tree	EGb 761, Ginkgolide B	Improve DA level, behavior function, and muscle coordination, redox stabilization, uplift mitochondria Function and ATP production[35]
8	Fructus Alpinia oxyphylla	Black cardamom	Essential oils, Terpenes, Diary 1heptanoids, Flavones, Nucleobases and nucleosides, Steroids.	Restores dopaminergic (DA) neuron degeneration[36,37]
9	Juglandis semen	Walnut	Caffeic acid, a phenethyl ester derivative	Inhibits the MAO-B activity, protects against 6-hydroxydopamine-induced neuronal degeneration[38,39]

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10	Mucuna pruriens	Velvet bean	Glycoside, gallic acid, glutathione, Levodopa	Improves locomotor & behavior function, alleviate oxidative stress, metal chelation, mitochondrial and Synaptic function, TH expression[40,41,42,43]
11	Polygola	Milkworts or snakeroots	xanthones, saponins, and esters of oligosaccharides	Neuroprotective effect on dopaminergic neurons.[44]
12	Polygonum cuspidatum	Japanese knotweed	Resveratrol (RES)	Neuroprotective, antioxidant reduction and antiapoptotic capabilities are exerted[45]
13	Panax ginseng	Asian ginseng	ginsenosides	Rescuing dopaminergic neurons from degeneration increase antioxidant defenses and shields against neurotoxicity.[46]
14	Uncaria rhynchophylla	Hooked Uncaria	Rhynchophylline, corynoxeine, corynantheine, and hirsutine	Cytoprotective effect[47]
15	Withani asomnifera	Ashwagandha Or Indian ginseng	Withaferin, Withanolide	Alleviate oxidative stress, improve dopamine level, motor function, glutathione level, TH expression, inhibition of Inos[48]

4. Conclusion

Parkinson's infection (PD) may be a clinically heterogeneous clutter with a multi-factorial pathology. Different atomic components are included within the pathogenesis of PD, meeting to oxidative stretch and proteinopathy.

The above mentioned plants having antioxidant and flavonoid contents showing antioxidant activity .So our aim is to investigate the therapeutic potential of Antiparkinsonism activity in *Adhatoda vasica*.

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