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Review Article

PARKINSON'S DISEASE: A REVIEW ON ETIOPATHOGENESIS AND HERBAL THERAPY

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ABSTRACT
Parkinson's disease is common hypo kinetic disorder mainly occurs by the neurodegeneration in central nervous system affecting the 2-3% of population all over the world above age 60 years. Major symptoms are tremor, rigidity, bradykinesia and posture instability. There are predisposing factor like metal exposure, family history, extreme stress and head trauma that promote the progression of Parkinson's disease. Other risk factors includes the advanced age, environmental toxins, oxidative stress, inflammation, viral infections and intake of several dopamine antagonists play a contributory role in development of Parkinson's disease. The Parkinson's disease occurs due to a reduction in the striatal dopamine content in excess of 80%. The primary area of neurodegeneration in PD is the loss of dopaminergic neurons in the Substantia nigra par-compacta. Several proteins like α-synculine, ubiquitine-carboxy hydrolase terminal-1, PINK1 and DJ-1 are involved in the formation of lewis bodies which is hall mark of pathogenesis of Parkinson's disease. Currently dopamine agonist, Monoamine oxidase A, B inhibitors are widely used for the treatment of Parkinson's disease, although it bears the risk of adverse reaction. Now a day the medicinal plants which are less toxic and more preferred over the conventional therapeutics. In this review we have focus on pathophysiology, risk factors and possible traditional medicine useful for retarding the progression of Parkinson's disease.
Keywords: Parkinson's disease, Risk factor, Pathophysiology, Herbal plants

INTRODUCTION

Parkinson's disease (PD) is the most common hypo kinetic disorder and the second most common late-life neurodegenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia). As a consequence, PD patients have increasing difficulty with controlling their body movements. According to the National Institute of Neurological Disorders and Stroke (April 2005): "Parkinson's disease is a progressive neurological disorder that results from degeneration of neurons in a region of the brain that controls movement. This degeneration creates a shortage of the brain signalling chemical (neurotransmitter) known as dopamine, causing the movement impairments that characterise the disease." Epidemiological studies suggest that PD is the second most common neurodegenerative disorder after Alzheimer's disease (AD) affecting 2 – 3 % of the population over the age of 60 years. PD cases are far more unusual in people under the age of 40, and usually these called juvenile onset types associate with a clear genetic origin, while non- genetic disease types are principally considered a disease of the elderly. The average age of onset for the sporadic, non-genetic form of PD is approximately 55-60 years, with the rate of PD rising sharply after the fifth decade Among persons over age 65 the prevalence of PD has been estimated at 1800 per 100,000 (1.8%) individuals, increasing from 600 per 100,000 (0.6%) for persons between the ages of 65 and 69 to 2600 per 100,000 (2.6%) for those 85 to 89 years [1, 2].

Clinical Presentation [3]

Table 1: Clinical presentation of Parkinson's disease

Motor symptoms	Non- motor symptoms
Tremor, Rigidity, Bradykinesia / Hypokinesia / Akinesia, Postural instability	**Neuropsychiatric symptoms** Dementia, depression, psychosis, apathy, anxiety, slowness of thought **Autonomic dysfunction** Neurogenic bladder, erectile dysfunction, urinary dysfunction, constipation, sialorrhoea, seborrhoea, orthostatic hypotension **Sleep disturbances** Sleep fragmentation, rapid eyeball movement (REM) sleep disturbances, excessive daytime sleepiness, nocturnal akinesia/tremor **Sensory symptoms** Diminished sense of smell, pain, numbness, Paresthesiae

Etiology

Although a number of different mechanisms have been proposed in the aetiology of PD i.e., the sequence of events which lead to degeneration of the nigrostriatal tract, none have been considered to have absolute predominance. Epidemiologic studies indicate that a number of factors either may increase or decrease the risk of developing Parkinson's disease.
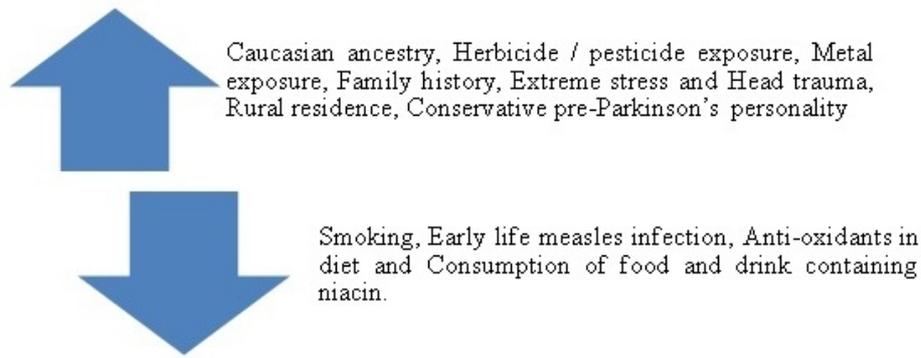
Caucasian ancestry, Herbicide / pesticide exposure, Metal exposure, Family history, Extreme stress and Head trauma, Rural residence, Conservative pre-Parkinson's personality

Smoking, Early life measles infection, Anti-oxidants in diet and Consumption of food and drink containing niacin.

Figure 1: List of factors that increased or decreased the risk of developing the Parkinson's disease.

Other risk factor in Parkinson disease

Age

The possible role of aging in the etiology of Parkinson's disease is suggested by its usual occurrence in late middle age and by marked increases in its prevalence at older ages. However, whereas the gradual loss of striatal dopaminergic markers and substantia nigra pars compacta neurons with age has recently been confirmed, the pattern and timing of these losses differ from what occurs in Parkinson's disease, indicating that aging itself is not likely to play a direct role in the degenerative process. So, it remains unclear what precise role aging plays in the etiology of Parkinson's disease [5].

Environmental Factor

A number of exogenous toxins have been associated with the development of Parkinsonism including trace metals, cyanide, lacquer thinner, organic solvents, carbon monoxide, and carbon disulfide. There has also been interest in the possible role of endogenous toxins such as tetrahydro-isoquinolines and β-carbolines. The most compelling evidence for an environmental factor in Parkinsonism relates to the toxin 1, 2, 3, 6-methyl-phenyl-tetrahydropyridine (MPTP). MPTP induces toxicity through its conversion in astrocytes to the pyridinium ion (MPPC) in a reaction catalyzed by monoamine oxidase - B (MAO-B). MPPC is then taken up by dopamine neurons and causes a mitochondrial complex I defect similar to that found in Parkinson disease [6].

Oxidative Stress

Oxidative stress causes or contributes to the etiology of a variety of disorders of the central nervous system particularly Parkinson's disease. Oxidative stress has received the most attention in Parkinson's disease because of the potential of the oxidative metabolism of dopamine to yield hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS). Furthermore, the presence of oxidative stress in Parkinson's disease has been associated with increased oxidation of lipids, DNA and proteins [7].

Mitochondrial Dysfunction

A selective 30–40% decrease in complex I activity of the mitochondrial respiratory chain has been found in the substantia nigra pars compacta of Parkinson's disease patients. A mitochondrial complex I defect could contribute to cell degeneration in Parkinson's disease through decreased ATP synthesis and a bio-energetic defect. A mitochondrial complex I defect could also lead to cell damage through free radicals generated directly at this site or by way of a compensatory increase in respiration at complex II. A complex I defect might also contribute to the development of apoptosis. However, the exact cause of the decreased complex I activity in Parkinson's disease remains a mystery [8].

Excitotoxicity

Excitotoxicity is an established cause of neurodegeneration that has been implicated in Parkinson's disease. Intracellular calcium is important for a number of physiological processes, but excessive amounts may contribute to the over stimulation of normal activity thus damaging dopaminergic neurons. This form of injury appears to be predominantly mediated by excessive influx of calcium into neurons through ionic channels triggered by the activation of glutamate ionotropic receptors. A glutamate-mediated rise in cytosolic calcium results in activation of inducible form of nitric oxide synthatase with increased nitric oxide (NO) production. NO reacts with superoxide radical to form peroxynitrite and hydroxyl radical, both are powerful oxidizing agents for dopaminergic neurones and ultimately leads to degeneration of these neurons and produces Parkinson's disease [9].

Neurotrophic Factors

The both nerve cells and astrocytes can synthesize mRNAs and protein for a variety of neurotrophic molecules, including ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF), that have the capacity to support the survival of neighbouring nerve cells. There is also strong evidence that a number of trophic molecules have the capacity to protect dopamine neurons from toxic insult. In the normal adult central nervous system, these trophic factors are constitutively expressed at low levels, but they can be up-regulated following injury and produces Parkinson's like features [10].

Apoptosis

There has been increasing interest in the concept that cell death in Parkinson's disease occurs by way of apoptosis rather than necrosis. It is now appreciated that neuronal apoptosis can result from a variety of insults, many of which may be relevant to the pathogenesis of Parkinson's disease. These include levodopa, dopamine, iron, glutathione depletion, excitatory amino acids, MPTP, 6-hydroxydopamine, rotenone, and pro-oxidants [11].

Inflammation

The role of inflammation in the pathogenesis of Parkinson's disease is unknown. Up-regulation of cytokines was found in

the brains and cerebrospinal fluid of patients with Parkinson's disease, and activated glial cells have been observed in post-mortem study. A wide range of pro-inflammatory as well as inflammatory factors has been implicated in the pathogenesis of Parkinson disease. These agents include immunological insults, such as lipopolysaccharide, environmental toxins (MPTP, Rotenone, 6-Hydroxy Dopamine), endogenous disease proteins (α-Synuclein) and neuronal injury. It has been shown that these agents are actively involved and may ultimately induce neurotoxicity by activating various inflammatory pathways [12].

Infection
A viral hypothesis suggesting that during the acute phase of infection, the influenza or similar virus may be carried in the circulation and can gain access to the nervous system. Antigens of *influenza A* virus have been detected in the brains of persons with post encephalitic Parkinsonism. The other causative viruses include *Japanese encephalitis B 121, coxackie B2, Western equine encephalitis* and *herpes simplex*[13].

Dietary Factor
Dietary influences on Parkinson's disease risk may be mediated by oxidative stress, which can lead to dopaminergic cell loss. Cholesterol and iron may have different mechanisms in relation to Parkinson's disease pathogenesis,

and thus their effects would be expected to be independent. Dietary intake of iron, a catalyst in the Fenton reaction, has been shown to increase Parkinson's disease risk either in association with animal fat, or alone. Elevated serum levels of cholesterol have recently been related to a decreased Parkinson disease risk. An increased risk of Parkinson disease from a dietary intake of low cholesterol in the presence of high iron may be part of the chain of events leading to death of dopaminergic neurons. It is possible that increased cholesterol intake may increase either the level of cholesterol in the brain, or the level of the antioxidant Co Q_{10}[14].

Drug induced parkinson's disease
About 7% of people with PD have developed their symptoms following treatment with particular medications. This form of PD is called Drug-induced Parkinsonism. People with idiopathic PD and other causes of PD may also develop worsening symptoms if treated with such medication inadvertently. The incidence of drug-induced PD increases with age. Drug-induced PD is more prevalent in older people and is twice as common in women as men. Akinesia is the most common presenting symptom while resting tremor, usually less prominent The use of the following drugs either in prolonged time or in higher doses are associated with drug induced PD. Various drugs that cause PD are as follows [15].

Table 2: List of drugs with potential to induce the progression of Parkinson's disease

High risk drugs	Intermediate risk drugs	Low risk drugs
Dopamine D_2-receptor blockers Butyrophenones derivatives (Haloperidol and others) Phenothiazines derivatives (Prochlorperazine and others) Thioxanthenes derivatives (Thiothixene) Dibenzoxazepine derivatives (Loxapine) Dopamine depleters: Reserpine, Tetrabenazine	**Mood stabilizer:** Lithium **Atypical neuroleptics:** Risperidone, Clozapine, and others (especially in higher dose) **Anticonvulsants:** Sodium valproate	**Antihypertensives:** Diltiazem, Captopril **Antiarrhythmics:** Amiodarone, Procaine **Immunosuppressants:** Cyclosporine, Tacrolimus **Antidepressants:** Fluoxetine, Tricyclic antidepressants **Antifungals:** Co-trimoxazole, Amphotericin-B **Chemotherapeutics:** Thalidomide, Cytarabine, Ifosfamide, Vincristine

Pathophysiology
The primary deficit in Parkinson's disease is a loss of the neurons in the substantia nigra pars compacta that provide Dopaminergic innervations to the striatum (caudate and putamen). The current understanding of the Pathophysiology of Parkinson's disease can be traced to neurochemical investigations that demonstrated a reduction in the striatal dopamine content in excess of 80%. This paralleled the loss of neurons from the substantia nigra, suggesting that replacement of dopamine could restore the function. These fundamental observations led to an extensive investigative effort to understand the metabolism and actions of dopamine and to learn how a deficit in dopamine gives rise to the clinical features of PD [16]. A model of basal ganglia functions in normal and dopamine deficiency states. This model proposes that dopamine deficiency produces dysfunction in the striatum, leading to: (1) Decreased activity in the direct pathway, from GABAergic striatal neurons to the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNpr) and (2) Increased drive through the indirect pathway, involving particularly the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN). As a consequence, there is disruption of the activity in basal ganglia output structures (GPi and SNpr), which in turn

disrupts the activity in brain stem motor areas, including the pedunculo-pontine nucleus and the thalamo-cortical motor system. This disruption is thought to be responsible for the difficulty in initiation of movements and the poverty of motion that are characteristic of PD [17]. The primary area of neurodegeneration in PD is the loss of dopaminergic neurons in the SNpc. Neuronal loss occurs in PD may be due to increased oxidative stress with increasing age. However, dopaminergic neuronal loss in PD may extend beyond the midbrain to include basal ganglia and even cortical dopaminergic neuronal loss. The loss of SNpc dopaminergic neurons alone is sufficient to produce motor manifestations of Parkinson's disease [18].

Outside the SNpc, another predominant area of primary catecholaminergic neuronal loss in PD is the locus ceruleus which is the main source of norepinephrine to the forebrain. In PD, As with the SNpc, the locus ceruleus demonstrates neuronal loss, depigmentation and the presence of Lewy bodies. Whether norepinephrine loss results in clinical manifestations in PD is unclear, and requires further study [18]. Acetylcholine levels, as measured by activity of choline acetyltransferase, in PD may be reduced in substantia nigra (SN), basal ganglia and cortex. Whether these alone correlate to dementia requires further investigation. Confounding these

interpretations is that reduced levels of choline acetyltransferase in basal ganglia may result from the reduced presence of dopamine rather than neuronal loss *per se*. However, the overlap between Alzheimer's patients presenting with signs of PD and PD patients with cortical dementia remains intriguing [18]. Serotonin levels are reduced in the striatum and SN of some PD patients, though serotoninergic neuronal loss is not recognized as a neuropathologic component of the disease. It is plausible that serotonin regulation is dependent upon catecholaminergic activity which itself is reduced in PD. Whether serotonin levels result in clinical manifestations in PD requires further investigation [18].

There are numbers of single gene mutations which have been identified. Total 11 genes have been mapped by genetic linkage with six genes identified: α-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes. These single gene defects with the notable exception of LRRK 2 are responsible for only a small number of patients with PD, though more importantly their identification and the proteins that they encode for are providing significant insight into the disease mechanisms that may be responsible for PD and other neurodegenerative diseases. α-synuclein is an intrinsically unstructured or natively unfolded protein but has significant conformational plasticity. The physiological function of α-synuclein is unclear but α-synuclein is considered to play a central role in the pathophysiology of PD. Moreover, the identification of fibrillar forms of the α-synuclein protein as a major structural component of Lewy Body's (LBs) in PD [19]. A number of factors enhance α-synuclein aggregation or fibrillization in different systems. Mitochondrial complex-I inhibitors such as rotenone and paraquat clearly lead to aggregation and accumulation of α-synuclein, and other forms of oxidative and nitrosative stress also promote α-synuclein aggregation and produces lewy body formation which is the main hallmark of PD[19]. The mechanism by which parkin confers neuroprotection, or specifically, promotes the survival of dopaminergic neurons, is a central unanswered question. Consistent with a role in maintaining mitochondrial integrity, over expression of parkin in cultured cells confers resistance to stimuli that promote mitochondria-dependent apoptosis. *Parkin* can also confer protection against kainate-induced excitotoxicity in primary neuronal cultures, presumably by suppressing cyclin E accumulation [20]. Ubiquitin carboxy-terminal hydrolase-1 (UCH-L1) is a highly abundant, neuronspecific protein that belongs to a family of deubiquitinating enzymes that are responsible for hydrolyzing polymeric ubiquitin chains to free ubiquitin monomers. UCH-L1 might additionally function as a dimerization-dependent ubiquitin protein ligase and can apparently maintain ubiquitin homeostasis by promoting the stability of ubiquitin monomers the mechanism by which UCH-L1 mutations cause PD is poorly understood. UCH-L1 promotes the accumulation of α-synuclein in cultured cells and may be relevant to the pathogenesis of PD [21]. Studies suggested that PINK1 may afford some protection against mitochondrial dysfunction and apoptosis induced by proteosomal inhibition, although the mechanis for this action was not understood. It has been suggested that PINK1 phosphorylates mitochondrial proteins, in response to cellular stress, to prevent mitochondrial dysfunction, although alternatively an inability to normally phosphorylate mitochondrial proteins could actually lead to mitochondrial

dysfunction which perhaps suggested that the loss of PINK1 kinase activity directly causes PD [22]. The physiological function of DJ-1 is unclear although many lines of evidence suggest that DJ-1 may function as an anti-oxidant protein or as a sensor of oxidative stress. Over expression of DJ-1 protects against oxidative injury whereas knockdown of DJ-1 by short interfering RNA enhances the susceptibility to oxidative stress. Thus, DJ-1 may play a critical role in both sensing and conferring protection against a range of oxidative stressors. However, mutation in DJ-1 leads to development of the susceptibility towards oxidative stress and causes PD [23].

Pathway of pathogenesis of Parkinson disease
Impairment of the ubiquitin-proteasome system (UPS), mitochondrial dysfunction and oxidative stress along with environmental factors like pesticides may underlie the molecular pathogenesis of familial and sporadic PD.

Mutations in five genes encoding α-synuclein, parkin, UCH-L1, PINK1, and DJ-1 are associated with familial forms of PD through pathogenic pathways that may commonly lead to deficits in mitochondrial and UPS function. PINK1, parkin, and DJ-1 may play a role in normal mitochondrial function, whereas parkin, UCH-L1, and DJ-1 may be involved in normal UPS function. α-synuclein fibrillization and aggregation is promoted by pathogenic mutations, oxidative stress, and oxidation of cytosolic dopamine (DA), leading to impaired UPS function and possibly mitochondrial damage. α-synuclein may normally be degraded by the UPS. Some environmental toxins and pesticides can inhibit complex-I and lead to mitochondrial dysfunction, whereas alterations in mitochondrial DNA may influence mitochondrial function. Impaired mitochondrial function leads to oxidative stress, deficits in ATP synthesis, and α-synuclein aggregation, which may contribute to UPS dysfunction. Oxidative and nitrosative stress may also influence the antioxidant function of DJ-1, can impair parkin function through *S*-nitrosylation, and may promote dopamine oxidation. Excess dopamine metabolism may further promote oxidative stress. Mitochondrial and UPS dysfunction, oxidative stress, and α-synuclein aggregation ultimately contribute to the demise of dopaminergic neurons in PD.

Mitochondrial dysfunction
Much evidence suggests a major role for mitochondrial dysfunction in the pathogenesis of PD because mitochondria are exposed to a highly oxidative environment, and the process of oxidative phosphorylation is associated with the production of ROS and in particular, defects in mitochondrial complex-I (complex-I) of the respiratory chain. A complex-I defect could most obviously contribute to neuronal degeneration in PD through decreased ATP synthesis as well as damage caused by excess production of ROS [24].

Oxidative stress
Neurons are especially vulnerable to free radical attack and impaired defences, and exposure to excess free radicals can lead to neuronal death. Receptor and lipids containing polyunsaturated fatty acids are particularly sensitive to oxidative stress. Reactive oxygen metabolites affect binding of ligands to membrane receptors such as dopaminergic receptors, alpha and beta adrenergic receptors, muscarinic cholinergic receptors, adenosine receptors, histaminergic receptors, and serotonergic receptors[25].

Peroxidation of membrane lipids may lead to a reduction of the receptor density and also alter the viscosity of the plasma membrane, thus affecting the receptor coupling mechanism. Reactive oxygen species may also interact with thiol / disulfide moieties on receptor proteins or on other factors in the receptor system, which are responsible for modulating receptor binding or coupling. Lipid peroxidation is also associated with an alteration in the phospholipase A_2 pathway, which might indirectly affect receptor function[25].

For several decades now, there has been a tremendous infatuation with the idea that oxidative stress causes or contributes to the pathophysiology of a variety of disorders of the central nervous system including PD. Post-mortem studies have consistently implicated oxidative damage in the pathogenesis of PD, and in particular, oxidative damage to lipids, proteins, and DNA has been observed in the SNc of sporadic PD brains [26].

Biochemical changes in Parkinson disease

The major neuropathological change in PD is the loss of the pigmented dopaminergic neurons in the substantia nigra with degeneration of the nigrostriatal tract. This neuronal loss leads to marked decreases in the concentrations of striatal Dopamine, the DA-synthesizing enzymes tyrosine hydroxylase and DOPA decarboxylase, and the DA metabolites homovanillic acid, dihydroxy phenylacetic acid and 3-methoxytyramine [27].

Post-mortem studies on brains from PD patients have also revealed changes in other neurotransmitters and neuromodulators. These include depletions of norepinephrine and serotonin, met-enkephalin and leu-enkephalin, substance P, cholecystokinin, bombesin and neurotensin and choline acetyltransferase. Whereas the concentration of gamma-aminobutyric acid (GABA) has been found to be elevated, its synthesizing enzyme glutamic acid decarboxylase is decreased. Despite the variety of changes in neurotransmitters / neuromodulators, the dopaminergic system has been investigated more extensively than any other[27].

Several groups have demonstrated evidence for increased free radical generation in the PD brain. Such changes include a decrease in reduced glutathione (GSH), an increase in the reduced and oxidised glutathione ratios (GSH/GSSG), increased activity of superoxide dismutase and increased levels of malondialdehyde and lipid hydroperoxides. Increased levels of protein carbonyls and of free radical damage to DNA further support free radical damage to proteins in PD. These changes appear to be most severe in the substantia nigra but can also be seen in some other areas of the PD brain. The presence of increased levels of iron will enhance the generation of hydroxyl radicals via the fenton reaction. The cause of increased free radical release in PD is not known. Enzymes involved in the metabolism of glutathione do not appear to be significantly affected [27].

LIST OF PLANTS USED IN PARKINSON DISEASE[28]

Table 3: List of plants with Anti-Parkinson's activity

Name of Plants	Family	Parts of the plants/extracts
Acanthopanax senticosus Harms	*Alariaceae*	Ethanolic and hot water extracts of stem bark
Withania somnifera	*Solanaceae*	Root extracts
Nardostachys jatamansi	*Valirenaceae*	Ethanolic extracts
Chrysanthemum morifolium Ramat	*Asteraceae*	Water extracts
Cassiae semen	*Leguminosae*	85% ethanolic extracts of seeds
Anemopaegma mirandu	*Bignoniaceae*	
Acorus calamus	*Araceae*	
Hypericum perforatum	*Hypericaceae*	Ethanolic extracts
Gastrodia elata Blume	*Orchidaceae*	Ethanolic extracts
Zingiber officinale	*Zingiberaceae*	
Centella asiatica	*Umbelliferae*	Aqueous extracts
Emblica officinalis	*Euphorbiaceae*	
Thuja orientalis	*Cupressaceae*	Ethanolic extracts
Ginkgo biloba	*Ginkgoaceae*	Crude extracts
Mucuna pruriens	*Fabaceae*	
Plumbago scandens	*Plumbaginaceae*	Crude ethanolic extracts and total acetone fraction
Bacopa monniera	*Scrophulariaceae*	Ethanolic extract of entire plants

CONCLUSION

Parkinson's disease is most common type of movement disorders and neurodegenerative disease. Pathophysiological hall mark is the depletion of neurotransmitter dopamine in substantia nigra par-compacta and others are combination of genetic and environmental factors is likely to be important in producing abnormal protein aggregation within select groups of neurones, leading to cell dysfunction and then cell death. Despite these causes other causes are the dopamine antagonists, oxidative stress, inflammation, mitochondrial dysfunction, viral infections also play a role in progression of illness. A numbers of drugs are available for treatment of illness although attention is being given to treatment of late complication and non motor complication of parkinson's disease. Herbal treatment approaches remain alternative way for providing the neuro-protection in Parkinson's disease.

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