Herbal Moieties and its effect on Parkinsonism: A New Prospective

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Abstract

Parkinson's disease is a brain disease that leads to stiffness, shaking, and problems with walking, balance of coordination, and brain injury. It occurs when nerve cells or neurons that produce an important brain channel known as dopamine and control the movements in an area of the brain is impaired and die. Parkinson's symptoms usually begin gradually and get worse over times. Age is the one clear risk factor for this disease. A person with Parkinson's disease may have clumps of proteins known as alpha synuclein or Lewy bodies in their brain. There is no cure for Parkinson's disease, the aim of medical management of Parkinson's disease to restore the proper balance of dopaminergic and cholinergic activities in the brain in order to relieve symptoms. This review presents a brief overview of scientific basis that support the plant derived natural products and their constituents for the treatment of underlying neuronal degeneration observed in Parkinson's disease. The neuroprotective effects exhibited by these medicinal plants and their constituents are considered to be due to their ability to modulate; glutathione, superoxide dismutase and catalase in the brain, which all are disrupted in the PD brain.

Keywords: PD, Indian Herbs

Introduction:

Parkinson's disease is named after James Parkinson who in 1817 wrote a classic "shaking palsy". Parkinson disease is an extra pyramidaldisorder. Parkinson's disease leads to stiffness, shaking, and problems with walking, balance of coordination, and brain injury. Symptoms of Parkinson's usually start progressively and can get worse over time. People can have trouble walking and talking as the disease progresses.1they can also have mental and behavioural changes, problems with sleep, depression, problems with memory and exhaustion. The disease affects about 50% more in women. Parkinson's disease can occur both in men and women. Age is the clear one factor for Parkinson's disease. While most individuals with Parkinson's first develop the disease at about 60 years of age, about 5 to 10 percent of individuals with Parkinson's have an "early-onset" disease that

starts before 50 years of age. Sometimes, but not always, early-onset forms of Parkinson's are hereditary, and certain forms have been related to particular gene mutations.2

PARKINSON DISEASE CAUSE

Parkinson's disease occurs when nerve cells, or neurons, become damaged and/or die in a region of the brain that regulates movement. These neurons normally generate an important brain chemical known as dopamine.3 They produce less dopamine when the neurons die or become impaired, which causes the movement problems of Parkinson's. The nerve endings that create nor epinephrine, the main chemical messenger of the sympathetic nervous system, which regulates many automatic body functions, such as heart rate and blood pressure, are also missing in people with Parkinson's. Loss of nor epinephrine can help to explain some of Parkinson's non-motional characteristics, such as fatigue, irregular blood pressure, reduced food movement through the digestive tract, and sudden drops in blood pressure when a person stands up from a sitting or lying position. Abnormal bodies, irregular clumps of protein alpha-synuclein, are present in many brain cells in people with Parkinson's. Scientists are seeking to better understand alpha-natural syncline's and abnormal functions and its relation to genetic defects causing Parkinson's disease and progressive dementia.Although some forms of Parkinson's tend to be congenital and some can be attributed to particular genetic defects, the condition develops spontaneously in most cases and does not appear to be hereditary.4 A combination of genetic factors and environmental factors, such as exposure to toxins, results in Parkinson's disease. Main disease symptoms such as tremor (trembling) in the hands, arms, legs, jaw, or head, limb and trunk stiffness, slow motion, poor balance and coordination, often causing falls. Depression and other emotional changes can include other symptoms. Difficulty swallowing, chewing, and speaking; issues with urination or constipation; problems with skin and sleep disturbances. Parkinson's symptoms and the rate of progression vary among people.5sometimes; individuals ignore early Parkinson's symptoms as the results of natural aging. There are no diagnostic tests to identify the disease definitively in most cases, so it can be hard to diagnose accurately. There are subtle early signs of Parkinson's disease and they occur progressively.Affected individuals, for instance, may experience slight tremors or have trouble getting out of a chair. They may note that their handwriting is slow and looks cramped or thin, or that they talk too softly. The first to note alterations in those with early Parkinson's might be friends or family members. They can see that the face of the individual lack's speech and animation, or that the person usually does not move an arm or leg. Parkinson's individuals often develop a Parkinson an gait that involves a tendency to lean forward, short fast steps as if hurrying forward, and decreased arms swinging. They may also have difficulties initiating or maintaining movements. Symptoms frequently begin on one side of the body, or on one side of the body, sometimes in one limb. When the disease progresses, both sides are gradually affected by it. The symptoms on one hand, however, may still be more severe than on the other. Many individuals with Parkinson's remember that they had sleep issues, constipation, diminished ability to smell, and restless legs prior to developing stiffness and tremor.6

PARKINSON'S DISEASE DIAGNOSIS

Symptoms similar to those of Parkinson's disease may be caused by a variety of disorders. Although these conditions can initially be misdiagnosed as Parkinson's, some diagnostic tests may help to differentiate them from Parkinson's, as well as their reaction to drug treatment.7because many other diseases have similar characteristics but need multiple therapies, it is important to make a correct diagnosis as soon as possible. No blood or laboratory tests are currently performed to detect non-genetic cases of Parkinson's disease. Diagnosis is based on the medical history of an individual and a neurological exam. Another significant characteristic of Parkinson's disease is the change after initiating treatment.8

PATHOPHYSIOLOGY

In basal ganglia, the dopaminergic activity is balanced by the cholinergic system. Parkinson disease is caused by the depletion of dopamine in relation to cholinergic activity. We can also say that the anti-dopaminergic drugs i.e., Phenothiazines, Haloperidol, Methyldopa etc cause Parkinson.9We can also say that it is imbalance primarily between the excitatory neurotransmitter Acetylcholine and inhibitory neurotransmitter dopamine in the basal ganglia. The most prominent pathological findings in Parkinson’s disease are degeneration of the darkly pigmented dopamine neurons in the substantia nigra (is a basal ganglia structure located in the midbrain)pars compacta (portion of the substantia nigra located in the mid brain) {SN-PC}, loss of dopamine in the neostriatum and the presence of intracellular inclusion bodies known as Lewy bodies.10

TREATMENT

It can be done by giving different medicaments to the patients like dopamine promoter, Anti-depressant, Anti-tremor. Or surgical process is also done like pallidotomy which is surgical procedure to destroy the small area of brain cells.Deep brain stimulation in which surgery is done to implant a device that sends electrical signals to brain areas responsible for body movement. Neural transplantation is potential treatment for Parkinson disease, because the most significant neuronal degeneration is site and type specific (i.e., dopaminergic); the target area is well defined (i.e., striatum); postsynaptic receptors are relatively intact; and the neurons provide tonic stimulation of the receptors and appear to serve a modulatory function.11

Benefits of natural compounds

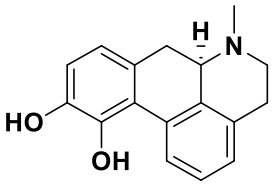
Plant is an important source of medicine and plays a key role in world health. Medicinal herbs or plants have been known to be an important potential source of therapeutics or healing support. The use of medicinal plants has obtained by a commanding role in health system all over the world. This involves the use of medicinal plants not only for the treatment of diseases but also as potential material for maintaining good health and conditions. Many countries in the world, that is, two-third of the world’s population depends on herbal medicine for primary health care. The reasons for this are because of their better cultural acceptability, better compatibility and adaptability with the human body and pose lesser side effects.12 From records, most of the used drugs contain plant extracts. Some contain active

ingredients (bioactive components or substances) obtained from plants. Through recent researches, plant-derived drugs were discovered from the study of curative, therapeutic, traditional cures and most especially the folk knowledge of indigenous people and some of these claims and believe of people are incomparable in spite of the recent advancement in science and technology.13

Medicinal plants may be defined as those plants that are commonly used in treating and preventing specific ailments and diseases and that are generally considered to be harmful to humans .These plants are either “wild plant species” those growing spontaneously in self-maintaining populations in natural or semi-natural ecosystems and could exist independently of direct human actions or the contrasting “Domesticated plants species” those that have arisen through human actions such as selection or breeding and depend on management for their existence 14 .Herbal medicines proved to be the major remedy in traditional system of medicine. They have been used extensively in medical practices since ancient times. This prompts the development in the practices of medicinal plants. The reasons are because of their biomedical benefits as well as place in cultural beliefs in many parts of world in the development of potent therapeutic agents.15

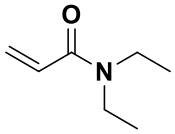
LIST OF FDA APPROVED DRUGS FOR PARKINSON’S DISEASES

1.**Apokyn(Apomorphine hydrochloride): -** Apomorphine hydrochloride acts by stimulating dopamine receptors in the nigrostriatal system, hypothalamus, limbic system, pituitary gland, and blood vessels. Thisenhances motor function, suppresses prolactin release, and causes vasodilation and behavioural effects.

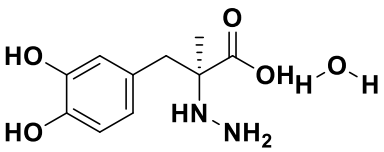


Apomorphine hydrochloride

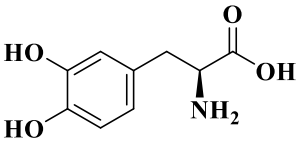
2.Comtan(N, N-diethyl-2-propenamide): - its ability to inhibit COMT in peripheral tissues, altering the plasma pharmacokinetics of levodopa.



3. Duopa entrnal suspension (Carbidopa and levodopa): -Duopa is an enteralsuspension of carbidopa and levodopa. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopamaking more levodopa available for delivery to the brain. Duopa is specifically indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

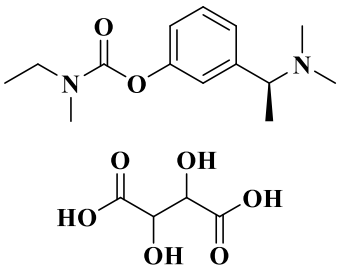


N-amino-a-methyl-3-hydroxy-L-tyrosine monohydrate

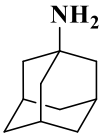


3-hydroxy-L-tyrosine

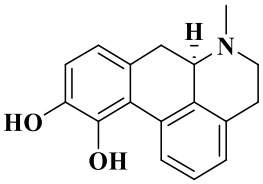
4. Exelon (rivastigmine tartrate): - The accurate mechanism of rivastigmine's action is unspecified, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase.



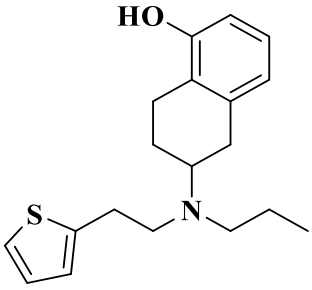
5. Gocoveris(Amantadine): - It will use to increase dopamine release and block dopamine re-uptake, thereby increasing dopamine levels in the brain.



6.Kynmobi(Apomorphine hydrochloride): -kynmobi is a non-ergoline dopamine agonist with high in vitro binding affinity for the dopamine D4 receptor, and moderate affinity for the dopamine D2, D3, and D5, and adrenergic α1D, α2B, α2C receptors. The precise mechanism of action of KYNMOBI as a treatment for "off" episodes associated with Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.

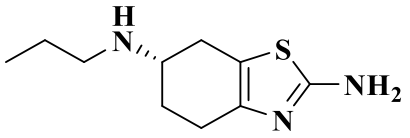


7. Neupro(Rotigotine): - Neupro is a transdermal delivery system that provides rotigotine, a non-ergolineD3/D2/D1 dopamineagonist, continuously over a 24-hour period. The exact mechanismofaction of rotigotine in the treatment of Parkinson's disease is unknown.



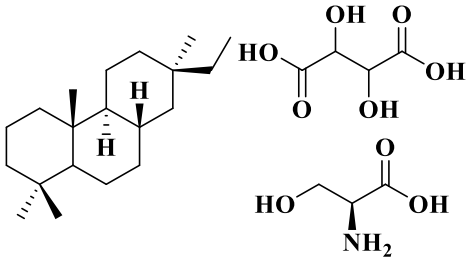
1-Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]

8. Mirapex (pramipexole): -Pramipexole stimulates dopamine receptors in the brain. Treatment benefits are thought to be related to the stimulation of dopamine receptors in the area of the brain known as the striatum.



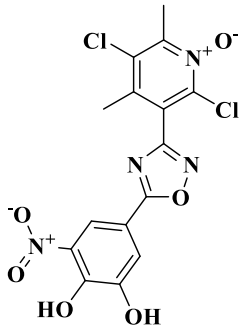
pramipexole

9. Nuplazid(Pimavanserin) : -The mechanism of action of Nuplazid in the treatment of hallucinations and delusions associated with PD psychosis.



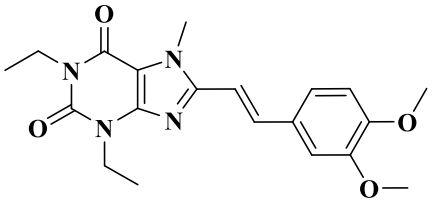
pimaranserin tartrate

10. Ongentys(Opicapone) : -Ongentys is an inhibitor of catechol-O-methyltransferase (COMT), which prevents breakdown of levodopa so that more of it enters the brain and transforms into dopamine. In Parkinson's disease, dopamine is the brain chemical that fuels normal activity and decreases**.**



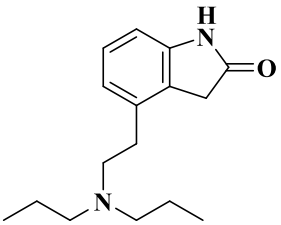
Opicapone

11. Nourianz tablets (istradefylline): - Nourianz (istradefylline) is an Adenosine A2A receptor antagonist.



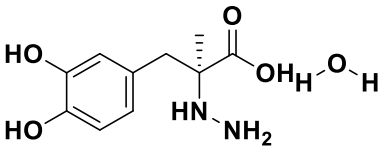
istradefylline

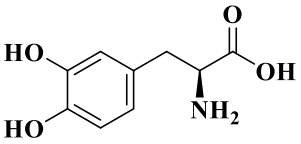
12. Requip(Ropinirole hydrochloride) : - Requip is a non-ergoline dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D2 and D3 dopamine receptor subtypes, binding with higher affinity to D3 than to D2 or D4 receptor subtypes.



4-(2-(dipropylamino)ethyl)indolin-2-one

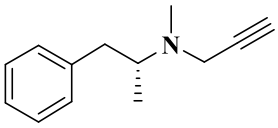
13. Rytary extended-release capsules(Carbidopa and levodopa): -Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for delivery to the brain. Levodopa: Levodopa is the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain.





N-amino-a-methyl-3-hydroxy-L-tyrosine monohydrate **3-hydroxy-L-tyrosine**

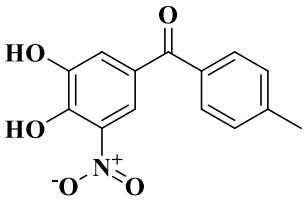
14. Selegiline tablets(L-deprenyl): -Selegiline is an irreversible inhibitor of monoamine oxidase (MAO), an enzyme that catabolizes norepinephrine, serotonin, and dopamine. The blockage of this enzyme prevents the reuptake of these neurotransmitters in the CNS, conferring increased levels of the biologically active monoamines at the synaptic cleft.



L-deprenyl

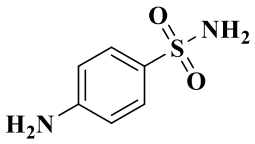
(R)-N-methyl-N-(1-phenylpropan-2-yl)prop-2-yn-1-amine

15. Tasmar(Tolcapone): -Tolcapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT). In mammals, COMT is distributed throughout various organs. The highest activities are in the liver and kidney.



Tolcapone

16. Xadago(Sufinamide): - XADAGO is an inhibitor of monoamine oxidase B (MAO-B). Inhibition of MAO-B activity, by blocking the catabolism of dopamine, is thought to result in an increase in dopamine levels and a subsequent increase in dopaminergic activity in the brain.



sulphanilamide

Different targets of Parkinson's disease

1. Type A Amyloidosis

In Parkinson's disease (PD), α-synuclein (α-syn) forms such aggregates called Lewy bodies (LBs). It has been reported that aggregates of α-syn with a cross-β structure are capable of propagating within the brain in a prion like manner. The presence of cross-β sheet-rich aggregates in LBs has not been experimentally demonstrated so far. Lewy bodies in thin sections of autopsy brains of patients with PD using microbeam X-ray diffraction (XRD) and found that some of them gave a diffraction pattern typical of a cross-β structure. This result confirms that LBs in the brain of PD patients contain amyloid fibrils with a cross-β structure and supports the validity of in vitro propagation experiments using artificially formed amyloid fibrils of α-syn. Notably, our finding supports the concept that PD is a type of amyloidosis, a disease featuring the accumulation of amyloid fibrils of α-syn.16

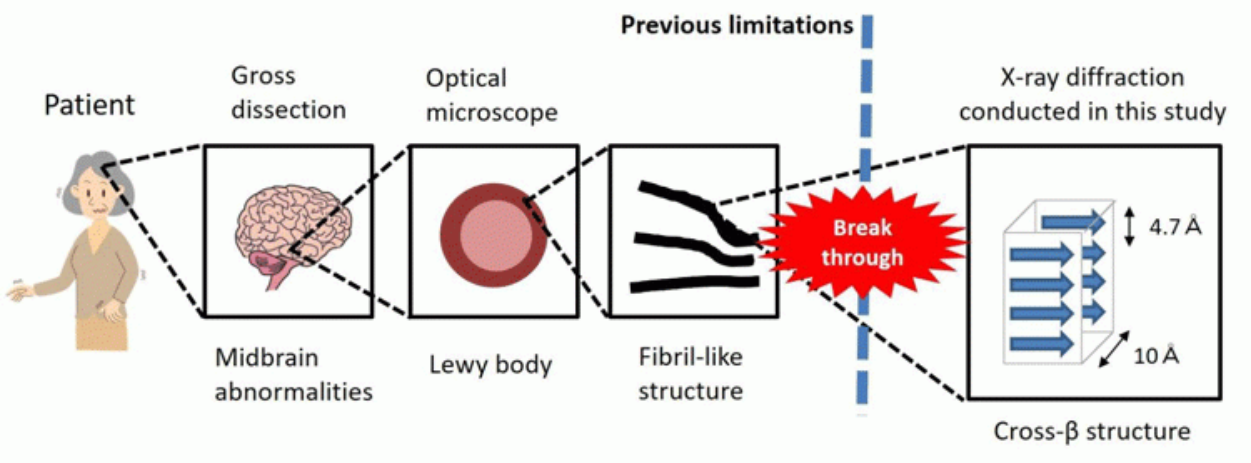


Figure 1. Abnormal changes in brain of the patients with Parkinson's disease

2. Glucose Metabolism Modification

The glycolytic rate in neurons is low in order to allow glucose to be metabolized through the pentose-phosphate pathway (PPP), which regenerates NADPH to preserve the glutathione redox status and survival. This is controlled by 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), the pro-glycolytic enzyme that forms fructose-2,6-bisphosphate, a powerful allosteric activator of 6-phosphofructo-1-kinase. In neurons, PFKFB3 protein is physiologically inactive due to its proteasomal degradation. However, upon an excitotoxic stimuli, PFKFB3 becomes stabilized to activate glycolysis, thus hampering PPP mediated protection of redox status leading to neurodegeneration.17

3.Sex-Related Differences

Less frequent incidence and a more congenial composition in women mainly in Western populations, which is thought to be mediated by oestrogens in particular in early stages of the Parkinson's disease. Not only motor symptoms seem to underlie gender effects, but also non-motor symptoms such as psychiatric and cognitive impairments, which can often precede motor manifestation. However, reliable results for gender differences in PD in particular of cognitive function and emotion processing, having a major impact on quality of life, are lacking.18

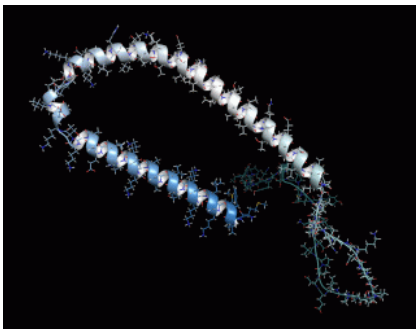


Figure 2. α-synuclein

4.Preventing Aggregation

α-synuclein from aggregating in the nerve tissue of Parkinson's patients.β-wrapins, can block α-synuclein aggregation. This is achieved by capturing the protein monomers and forming chemical complexes with them, which inhibits the elongation of amyloid fibrils. Protein homeostasis, or proteostasis, is the process of maintaining the conformational and functional integrity of the proteome. The failure of proteostasis can result in the accumulation of non-native proteins leading to their aggregation and deposition in cells and in tissues. The amyloid fibrillar aggregation of the protein α-synuclein into Lewy bodies and Lewy neuritis is associated with neurodegenerative diseases classified as α-synucleinopathies, which include Parkinson's disease and dementia with Lewy bodies**.**

The β-wrapins also stop seed fibrils from forming in the first place. Very small amounts of the wrapins are sufficient for this to happen, so a binding protein is not needed for every monomer.19

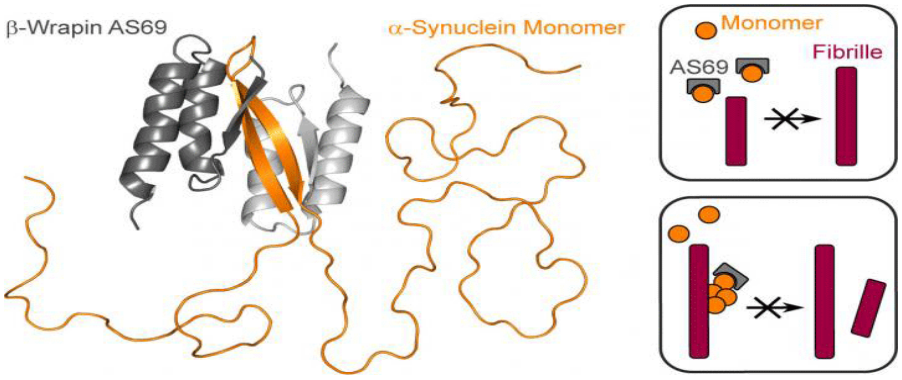


Figure 3. Aggregation inhibitor β-wrapin AS69(grey) binds a specific region in the otherwise disordered Parkinson's protein α-synuclein(orange), thus preventing elongation and formation of new protein fibils(red).

5. DNA Repair Mechanism

Alpha-synuclein is a presynaptic protein that forms abnormal cytoplasmic aggregates in Lewy body disorders. Although nuclear alpha-synuclein localization.alpha-synuclein modulates DNA repair. First, alpha-synuclein colocalizes with DNA damage response components within discrete foci in human cells and mouse brain. Removal of alpha-synuclein in human cells leads to increased DNA double-strand break (DSB) levels after bleomycin treatment and a reduced ability to repair these DSBs. Similarly, alpha-synuclein knock-out mice show increased neuronal DSBs that can be rescued by transgenic reintroduction of human alpha-synuclein. Alpha-synuclein binds double-stranded DNA and helps to facilitate the non-homologous end-joining reaction.20

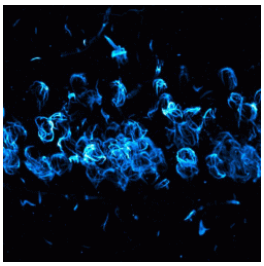
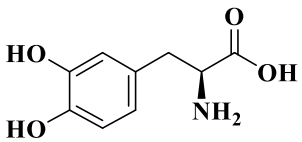
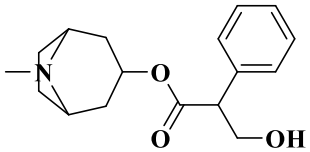
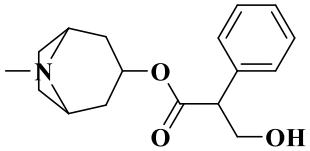
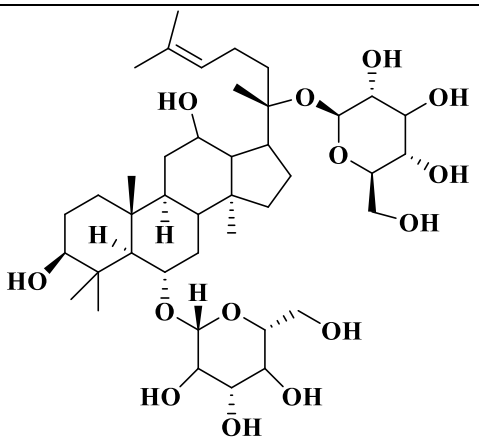
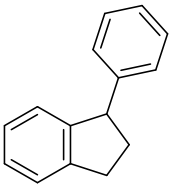
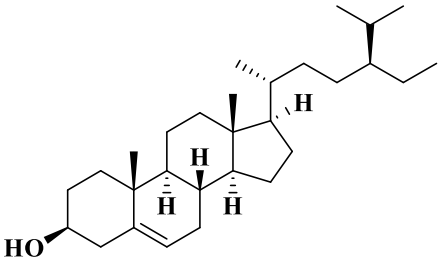
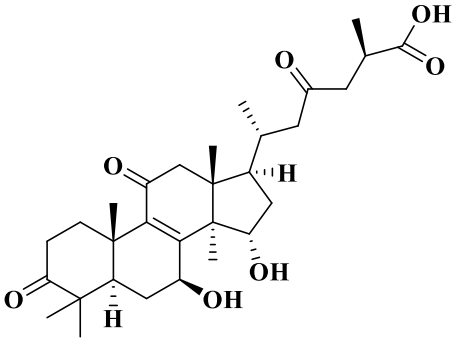
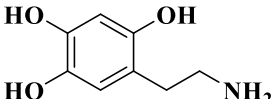
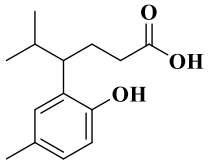
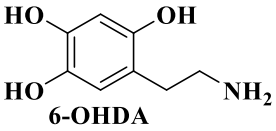
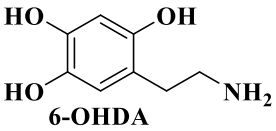
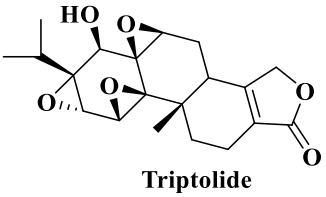
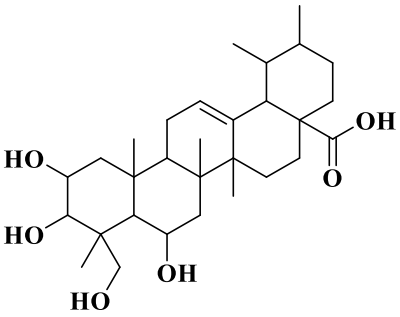
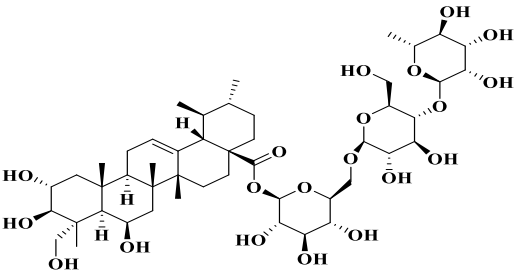
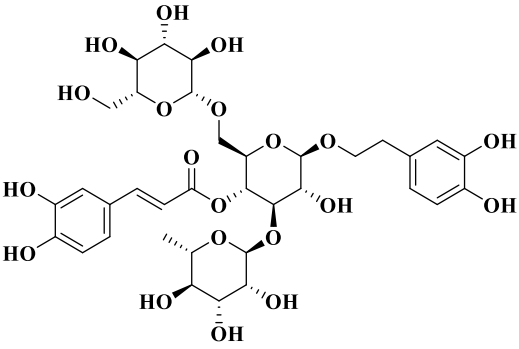


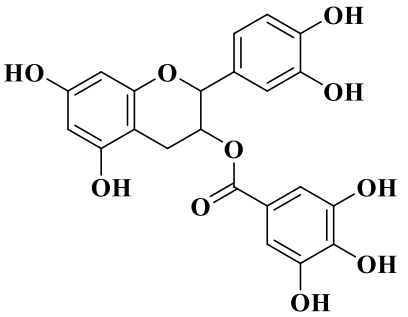
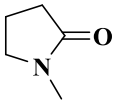
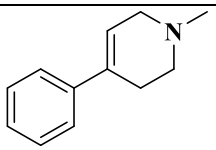
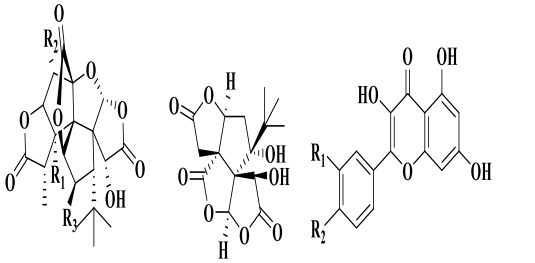
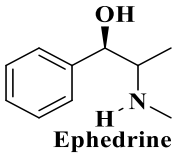
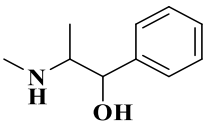
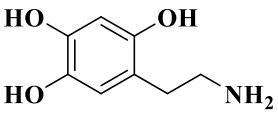
Figure 4. This picture shows abnormal aggregated alpha-synuclein Lewy pathology within neurons of brain's hippocampus in a mouse model of Parkinson's disease and delmentia with Lewy bodies. New research suggests that alpha-nuclein proteins repair DNA breaks within the nucleus of brain cells. When they cluster outside the nucleus as, shown here, it can lead to cellular dysfunction and death.

SOME NATURAL PRODUCTS USED FOR THE TREATMENT OFPARKINSON DISEASE

S.NO	BIOLOGICAL SOURCE	PLANT PART	CHEMICAL CONTITUENT	STRUCTURE
1.	*Mucuna pruriens*	Velvet Bean	Levodopa	 LEVODOPA
2.	*Atropa belladonna*	Leavesand Aerial	Atropine	 Atropine
3.	*Hyoscyamus niger*	Dried Leaves and Seed	Hyoscyamine	 Hyoscyamine

4.	*Ginseng*	Root of plants genus Panax	Ginsenoside	 Ginsenoside
5.	*Caffeine*	Cocoa Beans, Kola Nuts, Coffee Beans	Phenylindane	 phenylindane
6.	*Quercus infectoria*	dyer's oak	beta-sitosterol	 beta-Sitosterol
7.	*Ganoderma lucidum*	Perennial Fungus	Ganoderic Acid	 Ganoderic acid
8.	*Sterospermum Suaveolens*	Root Bark	6-OHDA	 6-OHDA
9.	*Alpinia oxyphylla*	Fruit	Oxyphylla A	 4-(2-hydroxy-5-methylphenyl)-5-methylhexanoic acid

10.	*Withania somnifera*	Dried Roots and Stem bases	6-OHDA [Hydroxy Dopamine]	 6-OHDA
11.	*Nardostachys jatamansi*	Flowering Buds	6-ODHA	 6-OHDA
12.	*Tripterygium wilfordii*	Roots	Triptolide	 Triptolide
13.	*Centella asiatica*	Flowering plant	Brahmoside, Masecassoside	 Brahmoside  Madecassoside
14.	*Cistanche salsa*	Stem	Echinacoside	 Echinacoside

15.	*Camelia sinesis (Green Tea)*	Leaf Bud	Epicatechin-3-gallate	 Epicatechin-3-gallate
16.	*Tinospora cordifolia*	Leaves	N-methyl -2-pyrrolidone	 1-methylpyrrolidin-2-one
17.	*Acantophanax senticosus*	Roots	(1-Methyl-4-Phenyl-1,2,3,6 Tertrahydro-Pyridine)	 MPTP
18.	*Gingko biloba*	Leaves	EGb761	 Ginkolides A: R1=OH R2,R3=H B:R1, R2,=OH, R3=H C: R1,R2,R3=OH Bilobadine Flavanoid Quercetin: R1, R2= OH Kaempferol: R1=H, R2= OH Isorhamnetin: R1= OCH3, R2=OH
19.	*Sida cordifolia*	Seeds	Ephedrineand Pseudoephedrine	 Ephedrine  Pseudoephedrine
20.	*Polygala*	Root extract	6-ODHA	 6OHDA

1.MUCUNA PRURIENS

Kaunch beej is seed of Kapikacchu herb. *Mucuna pruriens* is a Latin word for *kaunch beej*.*Mucuna pruriens* is a produce tropically. This plant is indigenous to equatorial Asia and Africa extensively naturalized and cultivated from the family Fabaceae. Having the chemical constituents' lipids (6-7%), 3,4-Dihydroxyphenylalanine and alkaloid and Proteins (20-29%), fixed oil, carbohydrates (50-60%), fibre (8-10%), saponins, sterols and minerals, Fat, Fatty acids, 13-epoxyoctadec-trans-9-enoic acid, indole -3, Asparticacid, Beta carboline, Amino acid analysis Carbohydrates, Carboline, Cis-12,13-epoxyoctadec-trans-9-cis-acid, beta, Cis-12, Calcium, Chymotrypsin Inhibitor, Cystine (Amino acid), Thiamine (Inorganic), Behenic acid. The higher concentration of L-DOPA is present in M. pruriens seed. An atypical non protein amino acid and a candid predecessor to the neuro transmitter dopamine, an of great magnitude understanding compound complex in mood, movement and sexuality.21

Mucuna pruriens is aplant product from which we can isolate L-Dopa.Levodopa is converted to dopamine via the action of a naturally occurring enzyme called DOPA decarboxylase. This occurs both in the peripheral circulation and in the central nervous system after levodopa has crossed the blood brain barrier. Only 1-3% of levodopa actually enters brain unaltered.22

2. *HYOSCYAMUS NIGER*

This belongs to the family Solanaceae. It is commonly called as henbane, black henbane or stinking nightshade. It grows in many Mediterranean countries including Greece, and the generally the areas of Europe and Asia where there is a temperature climate. Botanicalname: Hyoscyamus Niger Linn. Family: Solanaceae Common names Khurasani-ajvayan (Hindi), Black henbane(French) Jasquiame(English); Bilsenkraut(German) 23

Chemical Constituents List of non-alkaloids constituents isolated from *Hyoscyamus niger* seeds.

S.No.	Secondary Metabolites	Name of Compound
1	Coumarinolignans	Cleomiscsin A, Cleomiscosin B, Hyosgerin, Venkatasin, Cleomiscosin A methyl ether.
2	Lignans	Hyosmin, Cannabisin D, CannabisinG, Gross amide, Hyoscyamine, Hyoscyamus, Balanophonin
3	Withanolides Glycerides	Hyoscyamilactol, 16 α-acetoxy-hyoscyamilactol, Daturalactone (1-O-octadecanoyl glycerol, 1-O-(9Z,12Z-octadecadienoyl) glycerol,1-O-(9Z,12Z-octadecadienoyl)-3-O-nonadecanoyl glycerol
4	Flavonoids	Rutin, Spiraeoside,3,5-Dihydroxy-3,4,5,6,7-pentamethoxy flavone
5	Flavonoid glycoside	Pongamoside C, Pongamoside D,
6	Steroidal glycoside	Atroposide A, Atroposide C, Atroposide E, Petunioside L.
7	Saponins	Hyoscyamoside A, B, B1, B2, B3, C, C1, C2, D, D1, E, E1, F, F1.J and J1

8	Phenolics	Vanillic acid, N-trans-feruloyl tyramine
9	Miscellaneous	5-(hydroxymethyl) furfural, Daucosterol, β-sitosterol, 1,2-4-tetracosanediol diferulate, Riboflavin.

Hyoscyamine is sometimes used to reduce tremors and rigid muscles in people with symptoms of Parkinson's disease.

3. ATROPA BELLADONNA

It is often known as belladonna deadly nightshade. It is poisonous perennial herbaceous plant belongs to the family Solanaceae. Common Names: Belladona (Spanish), belladonna (French), Devil's cherries (Hindi). It is containing chemical constituents Tropane alkaloids (0.2-0.5%): i. L-hyoscyamine ii.D, L- hyoscyamine (Atropine)iii. Scopolamine iv. Apoatropine, iv. Belladonnine Atropine act as competitive antagonists at muscarinic receptors and block the binding of acetylcholine to the central nervous system and parasympathetic postganglionic muscarinic receptors.24

4.GINSENG

Ginseng is the root of plants in the genus Panax, such as Korean ginseng, South China ginseng, and American ginseng, typically characterized by the presence of ginsenosides and gintonin.Botanical name: Panax ginseng, Panax quinquefolius (American ginseng, an endangered species), Panax repens.Synonyms: American ginseng, Chinese ginseng, Korean ginseng

Chemical constituents: Ginseng root contains 2–3% ginsenosides of which Rg1, Rc, Rd, Re, Rb1, Rb2, and Rb0 ginsenosidesginsengsaponins, are the major pharmacologically active ingredients of ginseng.25

a) *Ginsenoside*help to suppress the destruction of dopaminergic neurons.**b**) Ginsenosides could have effects on monoamine signalling. Total saponins extracted from *Panax notoginseng* increased the levels of 5-hydroxytryptamine, dopamine and noradrenaline, suggesting that it may have antidepressant effects by modulation of brain monoamine levels.26

5.CAFFEINE

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class. It is the world's most widely consumed psychoactive drug. Synonym of caffeine 1,3,7-Trimethyl-1H-purine- 2,6(3H,7H)-dione, 1,3,7-trimethylxanthine, 1,3,7-triméthylxanthine, 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione, Anhydrous Caffeine, Cafeina, Caféine, Caféine Anhydre, Caféine Benzodate de Sodium, Caffeine Sodium Benzoate, Caffeine Anhydrous, Caffeine Citrate, Caffeinum, CitratedeCaféine, Citrated Caffeine, Methylxanthine, Méthylxanthine, Trimethylxanthine, Triméthylxanthine.Phenylindane may elicit neuroprotective effects by inhibiting the aggregation of amyloid-beta (Aβ) and tau (AD) or α-synuclein (PD).27

6 QUERCUS INFECTORIA

It is Aleppo oak.it is species of oak. Manjakani is the name used in Malaysia for the galls; these have been used for centuries in softening leather and in making black dye and ink. Having chemical constituentsBeta-sitosterol, tannin (50-70%) and small amount of free gallic acid and ellagic acid. β-sitosterol is the death of motor neurons in the lumbar region of the spinal cord and loss of tyrosine hydroxylase-positive dopaminergic neurons in the substantia nigra. 28

7 GANODERMA LUCIDUM

Ganoderma lucidum is a reddish laccate species of *Ganoderma* with a limited distribution in Europe and parts of China, where it grows on decaying hardwood trees.Family: Ganodermataceae

Neuroprotection targeting mitochondrial dysfunction has been proposed as an important therapeutic strategy for Parkinson's disease. *Ganoderma lucidum* (GL) has emerged as a novel agent that protects neurons from oxidative stress.29

8 STEROSPERMUM SUAVEOLENS

*Stereospermum suaveolens*from the family Bignoniaceae, popularly known as "Padiri", is a large deciduous tree found throughout the moist parts of India.*Stereospermum suaveolens* is also known 'Patala'.*Stereospermum suaveolens* have two varieties mentioned by Bhavaprakasha as Patala and Sitapatala. Patala is identified as *Stereospermum suaveolens* and Sitapatala as *Stereospermum chelonoides.*Other namesPadhal, Podal(Hindi Name) Kaligottu, Padiri(Telugu Name) Rose Flower Fragrant (English Name) Padiri(Malayalam Name)Methanolic extract of *Stereospermum suaveolens* can give to the patient in which Parkinson's is introduced by 6-ODHA.30

9 WITHANIA SOMNIFERA

Withania somnifera commonly known asashwagandha. It is obtained from the family Solanaceae commonly known as ajagandha, amangura, amukkirag, asan, asana.

The root extract is rich in steroidal lactones including withanone, withaferin, withanolides, withasomidienone, and withanolide. These compounds have been reported to inhibit metastasis and quinone reductase activity, preferentially affect the cholinergic signal transduction cascade of the cortical and basal forebrain, and thus may be beneficial for the treatment of PD. Withanolides are potent suppressors of NF-κB activation mediated by a number of inflammatory agents, and that this suppression occurs through inhibition of IκBα kinase (IKK) complex consisting of IKK-α, IKK-β, IKK-γ (also called NEMO), IKK-associated protein 1, FIP-3 , heat shock protein 90, and glutamic acid, leucine, lysine, and serine–abundant protein.31

10 *GINKGO BILOBA*

Ginkgo biloba has Ginkgolides and bilobalides compounds as chief constituents. EGb761, a well-defined mixture of active compounds such as Ginkgolides and bilobalides extracted from leaves, exerts a protective effect against oxidative stress induced by MPTP. EGb761

recovered striatal DA levels and tyrosine hydroxylase in the striatum and substantia nigra pars compacta. The neuroprotective effect of EGb761 against MPTP neurotoxicity is associated with its free radical scavenging activity, blockade of lipid peroxidation, and reduction of superoxide radical production. 32

11*CAMELIA SINESIS*

The common namesare“tea plant”, “tea shrub”, “tea tree”. It belongs to the family Theaceae. whose leaves and leaf buds are used to produced tea. The plant originated near the southwest region of China as an evergreen forest shrub. the leaves of this plant are similar to the bay leaf.Chemical constituents of *Camelia sinesis*like catechin, epigallocatechin gallate, flavan-3-ol, theanine, polyphenol oxidase, theaflavin digallate, gallocatechin gallate, and oleanane. 33 Epicatechin-3-gallate (EGCG) is the tea’s most abundant polyphenol which offers antioxidant and neurogenerative effects for the prevention of Parkinson symptoms.MPTP-induced parkinsonian mice have shown that green tea extract can attenuate DA depletion and dopaminergic neuronal survival in the substantia nigra region of the brain. The catechol-like structure of EGCG exerts an inhibitory effect on DA uptake by blocking uptake of the neurotoxin MPP+ (1-methyl-4-phenylpyridinium) and protecting dopaminergic neurons against MPP+ injury. Moreover, EGCG regulates extracellular signaling kinases (ERK1/2 and mitogen activated protein kinases), the major impediment to neuronal damage and oxidative stress.34

12. ALPINIA OXYPHYLLA

Alpinia oxyphylla is traditional Chinese medicine.Widely used for treating diarrhea, ulceration, and enuresis. Moreover, A. oxyphylla is effective for cognitive function improvement and nerve regeneration. *Alpinia oxyphylla(*General name/Botanical name)Chinese black cardamon(English name) Yi Zhi, Yi Zhi Ren(Chinese name)Fruit of this plant is used .From the familyZingiberaceae.The principal component of Lewy bodies is alpha-synuclein (alpha-syn) and its accumulation in neurons is a crucial pathological event in PD pathogenesis.It is suggested from the different study that Oxyphylla A is a novel compound obtained from the fruit of Alpinia oxyphylla, promoting in particular alpha-syn degradation in a cellular PD model.35

Conclusion:

Parkinson is a lifelong condition that involving the neurological changes in the body. The cause of PD still remain a mystery. The management of neurodegenerative diseases is a great challenge in modern system of medicine due to their complicated pathogenesis. Nature has given a number of medicinal plants, the importance of plant-based traditional medicine systems in neurodegenerative diseases is increasing day by day due to their less side effects and low cost. The strength of this extensive and up-to-date study is to provide the compiled information from a large number of meta-analyses of preclinical studies related to the impact of natural bioactive compounds in PD.

Reference:

1. Lang AE, Lozano IS. Parkinson's disease. New England Journal of Medicine. 1998 Oct 15; 339(16):1130-43.
2. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003 Sep 11; 39(6):889-909.
3. De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. The Lancet Neurology. 2006 Jun 1; 5(6):525-35.
4. Tysnes OB, Storstein A. Epidemiology of Parkinson’s disease. Journal of Neural Transmission. 2017 Aug; 124(8):901-5.
5. Gray P, Hildebrand K. Fall risk factors in Parkinson's disease. Journal of Neuroscience Nursing. 2000 Aug 1; 32(4):222.
6. Hubble JP, Cao T, Hassanein RE, Neuberger JS, Roller WC. Risk factors for Parkinson's disease. Neurology. 1993 Sep 1; 43(9):1693-.
7. Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. The Lancet Neurology. 2006 Jan 1; 5(1):75-86.
8. Factor SA, Weiner W. Parkinson's disease: diagnosis and clinical management.
9. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain. 2001 Nov 1; 124(11):2131-46.
10. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, Olanow CW. Pathophysiology of the basal ganglia in Parkinson's disease. Trends in neurosciences. 2000 Oct 1; 23:S8-19.
11. Calne DB. Treatment of Parkinson's disease. New England Journal of Medicine. 1993 Sep 30; 329(14):1021-7.
12. Albarracin SL, Stab B, Casas Z, Sutachan JJ, Samudio I, Gonzalez J, Gonzalo L, Capani F, Morales L, Barreto GE. Effects of natural antioxidants in neurodegenerative disease. Nutritional neuroscience. 2012 Jan 1; 15(1):1-9.
13. Sarrafchi A, Bahmani M, Shirzad H, Rafieian-Kopaei M. Oxidative stress and Parkinson’s disease: new hopes in treatment with herbal antioxidants. Current pharmaceutical design. 2016 Jan 1; 22(2):238-46.
14. Pathak-Gandhi N, Vaidya AD. Management of Parkinson's disease in Ayurveda: Medicinal plants and adjuvant measures. Journal of ethno pharmacology. 2017 Feb 2; 197:46-51.
15. Mazo NA, Echeverria V, Cabezas R, Avila-Rodriguez M, Tarasov VV, Yarla NS, Aliev G, Barreto GE. Medicinal plants as protective strategies against Parkinson's disease. Current pharmaceutical design. 2017 Aug 1; 23(28):4180-8.
16. Rane P, Sarmah D, Bhute S, Kaur H, Goswami A, Kalia K, Borah A, Dave KR, Sharma N, Bhattacharya P. Novel targets for Parkinson’s Disease: Addressing different therapeutic paradigms and conundrums. ACS chemical neuroscience. 2018 Jun 29; 10(1):44-57.
17. Peppard RF, Martin WW, Carr GD, Grochowski E, Schulzer M, Guttman M, McGeer PL, Phillips AG, Tsui JK, Calne DB. Cerebral glucose metabolism in Parkinson's disease with and without dementia. Archives of neurology. 1992 Dec 1; 49(12):1262-8.
18. Cerri S, Mus L, Blandini F. Parkinson’s disease in women and men: what’s the difference? Journal of Parkinson's disease. 2019 Jan 1; 9(3):501-15.

19. Olanow CW, McNaught KS. Ubiquitin–proteasome system and Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2006 Nov; 21(11):1806-23.
20. Gencer M, Dasdemir S, Cakmakoglu B, Cetinkaya Y, Varlibas F, Tireli H, Kucukali CI, Ozkok E, Aydin M. DNA repair genes in Parkinson's disease. Genetic testing and molecular biomarkers. 2012 Jun 1; 16(6):504-7.
21. Katzenschlager R, Evans A, Manson A, Patsalos PN, Ratnaraj N, Watt H, Timmermann L, Van der Giessen R, Lees AJ. Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study. Journal of Neurology, Neurosurgery & Psychiatry. 2004 Dec 1; 75(12):1672-7.
22. Cilia R, Laguna J, Cassani E, Cereda E, Pozzi NG, Isaias IU, Contin M, Barichella M, Pezzoli G. Mucuna pruriens in Parkinson disease: a double-blind, randomized, controlled crossover study. Neurology. 2017 Aug 1; 89(5):432-8.
23. Zhang L, Ding R, Chai Y, Bonfill M, Moyano E, Oksman-Caldentey KM, Xu T, Pi Y, Wang Z, Zhang H, Kai G. Engineering tropane biosynthetic pathway in Hyoscyamus niger hairy root cultures. Proceedings of the National Academy of Sciences. 2004 Apr 27; 101(17):6786-91.
24. Yun DJ, Hashimoto T, Yamada Y. Metabolic engineering of medicinal plants: transgenic Atropa belladonna with an improved alkaloid composition. Proceedings of the National Academy of Sciences. 1992 Dec 15; 89(24):11799-803.
25. Lui JH, Staba EJ. The ginsenosides of various ginseng plants and selected products. Journal of Natural Products. 1980 May; 43(3):340-6.
26. Ren FC, Liu TC, Liu HQ, Hu BY. Influence of zinc on the growth, distribution of elements, and metabolism of one-year old American ginseng plants. Journal of plant nutrition. 1993 Feb 1; 16(2):393-405.
27. Ashihara H, Suzuki T. Distribution and biosynthesis of caffeine in plants. Front Biosci. 2004 May 1; 9(2):1864-76.
28. Umachigi SP, Jayaveera KN, Kumar CA, Kumar GS, Kumar DK. Studies on wound healing properties of Quercus infectoria. Tropical journal of Pharmaceutical research. 2008 Apr 3; 7(1):913-9.
29. Ren ZL, Wang CD, Wang T, Ding H, Zhou M, Yang N, Liu YY, Chan P. Ganoderma lucidum extract ameliorates MPTP-induced parkinsonism and protects dopaminergic neurons from oxidative stress via regulating mitochondrial function, autophagy, and apoptosis. Acta Pharmacologica Sinica. 2019 Apr; 40(4):441-50.
30. Shalavadi MH, Chandrashekhar VM, Avinash SP, Sowmya C, Ramkishan A. Neuroprotective activity of Stereospermum suaveolens DC against 6-OHDA induced Parkinson's disease model. Indian journal of pharmacology. 2012 Nov; 44(6):737.
31. RajaSankar S, Manivasagam T, Sankar V, Prakash S, Muthusamy R, Krishnamurti A, Surendran S. Withania somnifera root extract improves catecholamines and physiological abnormalities seen in a Parkinson's disease model mouse. Journal of Ethno pharmacology. 2009 Sep 25; 125(3):369-73.
32. Kim MS, Lee JI, Lee WY, Kim SE. Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease. Phytotherapy Research: An International Journal Devoted to

Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2004 Aug; 18(8):663-6.

33. Malar DS, Prasanth MI, Brimson JM, Sharika R, Sivamaruthi BS, Chaiyasut C, Tencomnao T. Neuroprotective properties of green tea (Camellia sinensis) in Parkinson's disease: a review. Molecules. 2020 Jan; 25(17):3926.
34. Bitu Pinto N, da Silva Alexandre B, Neves KR, Silva AH, Leal LK, Viana GS. Neuroprotective properties of the standardized extract from Camellia sinensis (green tea) and its main bioactive components, epicatechin and epigallocatechin gallate, in the 6-OHDA model of Parkinson's disease. Evidence-Based Complementary and Alternative Medicine. 2015 Oct; 2015.
35. Li G, Zhang Z, Quan Q, Jiang R, Szeto SS, Yuan S, Wong WT, Lam HH, Lee SM, Chu IK. Discovery, synthesis, and functional characterization of a novel neuroprotective natural product from the fruit of alpinia oxyphylla for use in Parkinson's disease through LC/MS-based multivariate data analysis-guided fractionation. Journal of proteome research. 2016 Aug 5; 15(8):2595-606