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Nature's Neuroprotectors: Mucuna Pruriens, Brahmi, Ashwagandha In Parkinson's Therapy

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Abstract

The neurological condition known as Parkinson's disease, named after Dr. James Parkinson, whose original documentation dates back to 1817, is a degenerative and chronic condition that greatly affects movement. Motor symptoms including bradykinesia, stiffness, tremors, and postural instability are characteristic of this disease. These symptoms are caused by the degeneration of dopamine-producing neurons in the brain's substantia nigra. In addition to motor symptoms, people may suffer from autonomic dysfunction, emotional disorders, sleep abnormalities, and cognitive impairment. Medicinal plants have served as a constant source of medicaments, which have a great efficacy and demand for the treatment of Parkinson. Medicinal Plants, that deserve attention are Mucuna pruriens, Brahmi, Ashwagandha which have shown neuroprotective effect, anti-oxidant activity along with various pharmacological activity. M.pruriens has been of keen interest in phytochemical and Ayurvedic research due to its excellent medicinal values. The seeds of Mucuna pruriens contain alkaloids, glycosides, reducing sugars, saponins, tannins, terpenoids, calcium, phosphorus and potassium, polyphenolic substances, protease inhibitor, phytic acid, and L-dopa is a major constituent present in whole herb which act as a precursor of dopamine. The present review is an attempt to provide reported details of information on these herbs and phytoconstituents and pharmacological activities. It is an attempt to provide a direction for further research.

Keyword: Parkinson, Medicinal plant, Mucuna pruriens, Brahmi, Ashwagandha, Neuroprotective

Introduction

Parkinson's disease is a neurodegenerative condition brought on by increasing destruction to the brain's nigrostriatal tract's dopaminergic neurons. Dopamine from terminals in the striatum important in controlling smooth movement is depleted when dopaminergic neurons in this area of the brain are damaged or lost. The illness often affects people between the ages of 55 and 64, though it can also strike those considerably younger. Although the exact causes of the degeneration of dopaminergic neurons in

Parkinson's disease are unknown, new research indicates that neurotoxins produced by environmental, dietary, and lifestyle factors, as well as by normal metabolism influenced by genetic factors, may interact adversely over time to cause degeneration in dopaminergic neurons. Oxidative stress brought on by an excess of reactive oxygen species, or free radicals, is one of the common modes of action of these neurotoxins. Superoxide anions, peroxides, and hydroxyl radicals are created within dopaminergic neurons during the oxidative metabolism of dopamine. Even while effective antioxidant mechanisms have been created to detoxify these reactive species, pathological situations may exacerbate their creation or deplete the body's supply of antioxidants, which could result in damage. Reactive oxygen species cause harm to DNA, mitochondria, protein structures, and the cell membrane, which disrupts dopaminergic neurons' normal function and eventually kills the cells. The primary components of the antioxidant defence system are ingested antioxidant molecules, produced antioxidants, and antioxidant enzymes. Levodopa is regarded as the gold standard for treating Parkinson's disease symptoms, while other medications have also been utilized. Levodopa, however, has a lot of negative consequences. Mucuna pruriens endocarp is 2-3 times more effective than levodopa at reducing motor symptoms in an animal model of Parkinson's disease and is non-toxic in animal safety trials. In an animal model with Parkinson's disease, Mucuna pruriens dramatically restored norepinephrine in the nigrostriatal tract and dopamine in the substantia nigra, demonstrating a neuroprotective effect.

Figure 1 Parkinson Disease Symptoms

Patients with Parkinson's disease responded favourably to a clinical trial using Mucuna pruriens (HP-200, a commercially available Mucuna pruriens formulation). Although the mechanism of action of Mucuna pruriens in Parkinson’s disease is not fully understood it appears to have multiple pharmacological effects at more than one site in the central nervous system. Hence, understanding the mechanisms of action of Mucuna pruriens will provide important new insight into which mechanisms are most likely responsible for its therapeutic effect. This will help further to develop Mucuna pruriens as a botanical therapy for patients with Parkinson’s disease with dual benefits of immediate symptomatic relief and long-term neuroprotection to delay the progression of the disease [1].

1.Mucuna Pruriens

M. pruriens is a tropical twining herb commonly known as Velvet bean belongs to the family Fabaceae. The plant is famous for the extreme itchiness it produces on contact, particularly with the young foliage and the seed pods due to the presence of 5- hydroxytryptamine (5-HT). The plant is an annual, climbing shrub with long vines that can reach over 15 m in length. It is grown predominantly in Asia, Africa, and many parts of America. The beans of the M. pruriens are known to produce the unusual non protein amino acid L-dopa, a potent neurotransmitter. From the ancient times Cowhage has been used in Ayurvedic medicine for the treatment of Parkinson's disease associated with progressive degeneration of dopaminergic neurons in specific areas in the brain which is a common age-related neurodegenerative disorder. It affects more than four million people worldwide or for nervous system disorders as of the high concentration of L-dopa in the seeds [2].

It is also used in many other diseases such as for treating arthritis, anxiety, cancer, cough, diarrhoea, dysentery, diabetes, dysmenorrhea, delirium, gonorrhoea, gout, impotence, muscular pain, parasitic infections, rheumatic disorders, as analgesic and antipyretic, to induce vomiting, to treat snakebite and scorpion stings, sexual debility, sterility, tuberculosis and its direct application on skin can help to stimulate surface blood flow in conditions that involve paralysis. In India, it is considered an aphrodisiac, diuretic, emmenagogue, nerve tonic and uterine stimulant. In Central America, it is known as Nescafe as the seeds are roasted and ground to make a coffee substitute for decades [2]. Ayurveda, considered as the oldest ‘Science of Life’ describes various diseases and its treatment with herbs, minerals, and parts of animals. The Ayurveda describes various neurological diseases such as kampavat (Parkinson’s disease), apasmar (epilepsy), Unmad (schizophrenia), smrutinash (dementia), avsaada (depression), manas mandata (mental retardation), etc. Kampavata, (meaning tremors caused by excess of vata), is characterized in Ayurveda by tremors, rigidity, akinesia, dyskinesia, loss of olfaction, uncontrollable body movements, difficulty in step initiation, difficulty in maintenance of posture, etc. Mucuna pruriens is the most commonly used herb in treatment of Kampavat, either alone or with other herbs. The incidence of Parkinson’s disease (PD) is very high in aged population and levodopa is still the gold standard in management of PD. Prolonged use of levodopa leads to dyskinesias, toxicity, and diminishing efficacy. Despite of several advancements in drug developments, the control over progression of neurological damage is inadequate [3]. The velvet bean has traditionally used as a food source by certain ethnic groups in a number of countries. It is cultivated in Asia, America, Africa, and the Pacific Islands, where its pods are used as a vegetable for human consumption, and its young leaves are used as animal fodder. The plant has long, slender branches; alternate, lanceolate leaves; and white flowers with a bluish-purple, butterfly-shaped corolla. The pods or legumes are hairy, thick, and leathery; averaging 4 inches long; are shaped like violin sound holes; and contain four to six seeds. They are of a rich dark brown colour, and thickly covered with stiff hairs. In India, the mature seeds of Mucuna bean are traditionally consumed by a South Indian hill tribe, the Kanikkars, after repeated boiling to remove anti-nutritional factors. Most Mucuna spp. exhibit reasonable tolerance to a number of abiotic stresses, including drought, low soil fertility, and high soil acidity, although they are sensitive to frost and grow poorly in cold, wet soils.[4]

The genus thrives best under warm, moist conditions, below 1500 m above sea level, and in areas with plentiful rainfall. Like most legumes, the velvet bean has the potential to fix atmospheric nitrogen via a symbiotic relationship with soil microorganisms. Mucuna spp. have been reported to contain the toxic compounds L-dopa and hallucinogenic tryptamines, and anti-nutritional factors such as phenols and tannins. Due to the high concentrations of L-dopa (4–7%), velvet bean is a commercial source of this substance, used in the treatment of Parkinson disease [4]. The seeds of velvet bean are rich in protein (20-29%), lipids (6- 7%), dietary fibre (8-10%), ash (3%), carbohydrates (50-60%) and minerals. Also, they are extremely rich in alkaloids, saponins and sterols. It is recognized as an aphrodisiac in Ayurveda and helps to increase testosterone levels leading to deposition of protein in the muscles and increased muscle mass and strength. Besides its medicinal uses, M. pruriens L. is used as an important fallow and green manure crop [5].

Distribution

In India, it is one of the most popular medicinal plants. Cultivated in Uttar Pradesh, Madhya Pradesh and Andaman and Nicobar Islands etc. It is widespread over most of the subcontinent and found in forms of bushes, hedges, in dry-deciduous low forests types throughout the plains of India. It grows naturally grown right from lower Himalayan range to entire tropical plains of India and also cover the tropical regions, especially Africa, West Indies, tropical America, the Pacific Islands and the United State [2]

Taxonomy of Mucuna Pruriens [6]

Kingdom: Plantae, Planta, Planter, Plants, Vegetal

Sub Kingdom: Tracheobionta, Vascular Plants.

Division: Magnoliophyta. (Angiospeens)

Class: Magnoliopsida (Dicote, Dicotyledon)

Sub class: Rosidae.

Order: Fabales

Family: Leguminoseae

Sub Family: Fabaceae

Genus: Mucuna

Species: pruriens

Figure 2 Mucuna Pruriens

Synonyms: Carpopogon pruriens, Dolichos pruriens, Mucuna aterrima, M. atropurpurea, M. cochinchinensis, M. cyanosperma, M. deeringiana, M. esquirolii, M. prurita, M. utilis, Stizolobium aterrimum, S. deeringianum, S. pruriens, S. pruritum, S. niveum, Negretia pruriens Common Names: Cowitch, Cowhage, Velvet Bean, Cow-itch, Buffalo bean,velvet bean, mucuna, nescafe, pode mico, fava-coceira, cabeca-de-frade, cowage, cowhage, cow-itch, bengal bean, mauritius bean, itchy bean, krame, picapica, chiporro, buffalo bean[2].

Vernacular names Hindi- Kiwach, Daunch, Goncha, Bengali- Alkushi, bichchoti, Marathi- Kavacha, Kuhili, Kanchkuri, Gujarathi- Kivanch, Kavatch, Kannada- Nasukunni, Malayalam- Naicorna, OriyaKaincho[6].

Cultivation

It is a kharif season crop grown on plains, where the seeds are sowed as soon as the first shower occurs (June–July). Delays in sowing might have a negative impact on yield. Since it is a leguminous crop, it needs less nitrogen and phosphorus in the soil. During the rainy season, the soil has enough moisture, so it doesn't require any external watering. During the plant's growth and development phase, its vines require external support in order to climb and creep.

December marks the completion of the pods' development, and they are harvested in January. Pods are threshed to remove seeds after being dried in the sun for four to five days [2].

Botanical Description

Roots: The roots consist of many long, softly woody, somewhat flexible roots with a diameter of 7mm or more. The outer surface is dark brown to black in colour and somewhat rough due to the presence of many oblongs slightly protruding conspicuous lenticels and a few rootlets.

Leaf: leaves are fairly large, alternate, stipulate, pinnately and trifoliate. Stipules are deciduous about 1/5th inches in length. Stipels are three to five inch long and are minute and osculate, rachises leaflets are three to four inch long, by two to three inch wide, on short, thick, sparingly defexed hairy stalks, ovate-rhomboid acute or sub-acute, mucronate, membranous, glabrous or glabresent above and densely covered with fine lustures or silvery grey ad pressed hairs beneath. The shapes of terminal leaflets are rhomboid oval and smaller, while the lateral ones are varied unequal sided with their lower halves much broader

Flower: The heads of the flower are in form of axially arrayed panicles. They are 15 to 32 cm long and have two or three, or many flowers. The leaves accompanying with them are about 12.5 mm long, the stand axes of the flower are from 2.5 to 5 mm. The bell is 7.5 to 9 mm long and silky. The length of sepals is either longer or of the same as that of shuttles. The colour of crown is purplish or white. The flag is 1.5 mm long. The wings are 2.5 to 3.8 cm long

Pods: The pods are, 2 to 3 or 4 inch in length and half an inch broad. These are turgid explosively dehiscing pod, their shapes are like the letters blunt at either end, slightly covered at both ends and somewhat longitudinally ridged. The pod is compactly covered with numerous pointed hairs which are short, stiff or rigid, weak but not easily detached; initially they are of a pale yellowish brown or somewhat light rusty brown in colour but later changes into steel grey. The number of seeds present in the pods is 4 to 6 or sometimes more with septa or partitions between the seeds

Seed: The seed are 15-20 mm long and 7-15 mm broad and 4 to 6.5 cm thick reniform or ovoid in shape. The seed coat is hard, thick and glossy occasionally mottled. Seed Embryo fills up the seed and is made up of two large cotyledons. The hilum, the base of the funiculus (connection between placenta and plant seeds) is a surrounded by a significant arillus (fleshy seeds shell) [2].

Traditional Uses of Different Parts of the Plant

Root: Used as a blood purifier, diuretic, emmenagogue, for asthma, cholera, dropsy, delirium, elephantiasis, fevers, gout, kidney stones rheumatism, to relieve dysmenorrhea, in catarrh and dropsy.

Leaf: Used as an aphrodisiac, diuretic, nerve tonic, uterine stimulant, for scorpion stings and in dysentery.

Pods: Used in dropsy

Seed: It cures night dreams and impotency and to promote fertility, for sexual debility, seminal weakness and spermatorrhoea, as an aphrodisiac to increase seminal fluid and manly vigour, emmenagogue, antivenin, nervine, for abortion, diarrhoea, diabetes, gonorrhoea, muscular pain, persistent coughs, pulmonary tuberculosis, rheumatic disorders, scorpion stings and snakebite, worm infestation, sterility and general debility.[2]

Phytochemistry

Major chemical constituents

Leaf: Bufotenine (Indole Alkaloid), Choline (Alkaloid-misc), Dopa, L (Proteid), Dopamine, Genistein, Genistein, hydroxy, Harman, 6-methoxy Tryptamine, 5-hydroxy Tryptamine, n-ndimethyl, Tryptamine, n-n-dimethyl: 5-methoxy (Indole Alkaloid)

Figure 3 Mucuna Pruriens seeds

Pod: 5-Hydroxytryptamine, Bufotenine, Tryptamine 5-hydroxy Tryptamine, n-n-dimethyl, Tryptamine, n-n-dimethyl: methoxy, Tryptamine, n-n-dimethyl: n-oxide (Indole Alkaloid).

Seed: 1-Methyl-3-carboxy-6,7 -dihydroxy-1-,2, 3,-4Tetrahydroisoquinolone, 5-oxyindole-3- alkylamine, Alanine (Amino acid) , Alkylamine, 5-oxyindole-3 Alkylamine, indole-3 Amino acid analysis (Proteid) , Arachidic acid, Arginine (Amino acid), Aspartic acid, Behenic acid, Beta carboline, Calcium, Carbohydrates, Carboline, beta, Cis-12,13-epoxyoctadec-trans-9- cis- acid, Cis-12,13-epoxyoctadec-trans-9-enoic acid, Chymotrypsin Inhibitor, Cystine (Amino acid), DOPA- L (Proteid), Fat, Fatty acids, unsaturated, Flavone, 4'-5-6-trihydroxy3'-7-8-trimethoxy4'-O-beta-d-xylopyranosyl(1-2)-O-alpha-1-rhamnopyranoside) (Flavone), Galactose, D (Carbohydrate), Gallic acid, Glycine, Glutamic acid, Glutathione, Histidine (Amino acid), Iron (Inorganic), Indole-3-alkylamine, Isoleucine, Lecithin (Carbohydrate), Leucine (Amino acid), Leucine, iso, Linoleic acid, Linolenic acid (Lipid), Lysine (Amino acid), Mannose, D (Carbohydrate), Methionine (Amino acid), Mucunadine, Mucunain, Mucunine, Mucuna polysaccharide (Carbohydrate), Mucuna pruriens alkaloid P, Mucuna pruriens alkaloid Q Mucuna pruriens alkaloid R Mucuna pruriens alkaloid S, Mucuna pruriens alkaloid X (Alkaloid-misc), Myristic acid, Niacin (Inorganic), N,NDimethyltryptamine, N,N-Dimethyltryptamine-n-oxide, Nicotine, Oleic acid, Palmitic acid, Palmitoleic acid (Lipid), Phenyalanine (Amino acid), Phosphorus (Inorganic), Polysaccharide (Carbohydrate), Proline (Amino acid), Protein (Protein), Prurienidine, Prurieninine (Alkaloid misc), Quinoline, iso: 1-2-3-4-tetrahydro (Isoquinoline Alkaloid), Riboflavin (Inorganic), Saponins (Saponin), Serine (Amino acid), Serotonin, Sitosterol, (beta Sterol), Stearic acid, Stizolamine (Alkaloid), Thiamin

(Inorganic), Threonine (Amino acid), Trypsin, Tryptamine, Tyrosine (Amino acid), Valine, Vernolic acid (Lipid)[2].

Biological Activities

Anti-Parkinson's activity

The Parkinsonism was treated by the administration of powdered seed of M. pruriens containing 4 to 6% of levodopa. In a clinical study, the contribution of L-DOPA in the recovery of PD followed by Ayurveda medication. It was revealed that 30g Mucuna seed powder preparation has considerable faster action in treating PD patients than conventional standard drugs namely, Levo-dopa or Carbi-dopa and suggested that natural source of L-DOPA might possess advantages over conventional drugs in long term management of PD. Mucuna pruriens cotyledon powder significantly increased the brain mitochondrial complex-I activity but did not affect the total monoamine oxidase activity (in vitro) as having Nicotine adenine dinucleotide (NADH) and coenzyme Q-10 in the cotyledon powder which are shown to have a therapeutic benefit in Parkinson's disease. Unlike synthetic levodopa treatment, M. pruriens cotyledon powder treatment significantly restored the endogenous levodopa, dopamine, norepinephrine and serotonin content in the substantianigra. Clinical study confirmed the efficacy of the M. pruriens seeds in the management of Parkinson's disease by virtue of their LDOPA content. M. pruriens has been shown to increase testosterone levels Seeds of M. pruriens contain high levels (1–6%) of L-dopa (L-3,4-dihydroxyphenylalanine; a precursor of dopamine used in the treatment of Parkinson's disease. The effects of M. pruriens were studied in the 6- hydroxydopamine (6-OHDA) lesioned rat model of Parkinson's Disease. It has also studied Mucuna pruriens by the MPTP treated monkey Parkinson's Disease model. The comparison between levo-dopa (LD) kinetic dynamic profile of a dose of LD/aromatic amino acid decarboxylase peripheral inhibitors versus a nominally equivalent dose of a commercial Mucuna pruriens (Mucuna) seeds extract in 2 patients with Parkinson disease chronically taking LD standard combined with self-prescribed Mucuna [7].

M. Pruriens in Parkinson's disease: a double blind clinical and pharmacological study

A randomised, controlled, double blind crossover trial was carried out on 8 Parkinson disease patients with a short duration L-dopa response and on period dyskinesias completed. Patients were challenged with single doses of 200/50 mg LD/CD, and 15 and 30 g of Mucuna preparation in randomised order at weekly intervals. On Compared with standard LD/CD, the 30 g Mucuna preparation led to a considerably faster onset of effect (34.6 v 68.5 min; p=0.021), reflected in shorter latencies to peak L-dopa plasma concentrations. Mean on time was 21.9% (37 min) longer with 30 g Mucuna than with LD/CD (p=0.021); peak L-dopa plasma concentrations were 110% higher and the area under the plasma concentration v time curve (area under curve) was 165.3% larger (p=0.012). No significant differences in dyskinesias or tolerability occurred. So, study proves that this natural source of L-dopa might possess advantages over conventional L-dopa preparations in the long-term management of PD [2].

Antioxidant effect

The antioxidant activity on in vivo models of lipid peroxidation concluded that the seed ethanolic extract of Mucuna pruriens has an anti-lipid peroxidation property which is mediated through the removal of super

oxides and hydroxyl radicals. Experiment on in vitro lipid peroxidation of M. pruriens seeds revealed the inhibition of ascorbate/FeSO4 induced peroxidation by methanolic extract of M. pruriens which was monitored by the changes in optical density of the prepared concentrations (10-320 µg/ml). The inhibition increased with increase in concentration of the extract. The antioxidant effect on methanolic extract of Mucuna pruriens seed against Erlich Acites Carcinoma (EAC) bearing Swiss albino mice were studied by the following parameters; to estimate the liver biochemical parameters such as LPO, GSH and antioxidant enzymes like SOD, catalase etc. Treatment with extract decreased the levels of lipid peroxidation and increased the levels of glutathione, superoxide dismutase and catalase. Results suggest that the methanolic extract of Mucuna pruriens seeds exhibit significant antioxidant effects in EAC bearing mice. In vitro assays indicated that a whole plant of ethyl acetate and methanolic extract of Mucuna pruriens, containing large amounts of phenolic compounds, exhibited high antioxidant and free radical scavenging activities. These plant extracts served as a significant source of natural antioxidant, which might be helpful in preventing the progress of various oxidative stresses. Due to the high concentration of phenolic compounds, it is expected that Mucuna pruriens seeds have high antioxidant capacity. The various parts of this plant contain total phenols which might have antioxidant activity. The similar findings were observed for this plant where free radical scavenging activity was evaluated via nitric oxide scavenging method. The alcohol extract showed significant antioxidant activity which was comparable with standard ascorbate and total phenol content. The methanol extract of Mucuna pruriens seeds showed significant invitro antioxidant activity while it has also been indicated that the methanol extract of Mucuna pruriens can be a potential source of natural anti-oxidant [7].

Clinical Research

HP-200, which is a first liquid levodopa contains Mucuna pruriens endocarp, has been shown to be effective in the treatment of Parkinson's disease. The long-term effect of Mucuna pruriens endocarp in HP-200 on monoaminergic neurotransmitters and its metabolite in various regions of the rat brain was studied. HP-200 at oral administration of Mucuna pruriens endocarp in the form of HP-200 had a significant effect on dopamine content in the cortex with no significant effect on levodopa, norepinephrine or dopamine, serotonin, and their metabolites- HVA, DOPAC and 5-HIAA in the nigrostriatal tract. The failure of Mucuna pruriens endocarp to significantly affect dopamine metabolism in the striatonigral tract along with its ability to improve Parkinsonian symptoms in the 6-hydorxydopamine animal model and humans may suggest that its antiparkinsonian effect may be due to components other than levodopa or that it has a levodopa enhancing effect. In a clinical trial, Eight Parkinson’s disease patients with a short duration L-dopa response and on period dyskinesias completed a randomised, controlled, double blind crossover trial. Mucuna preparation led to a considerably faster onset of effect, reflected in shorter latencies to peak L-dopa plasma concentrations. Peak L-dopa plasma concentrations were 110 % higher and the area under the plasma concentration v time curve (area under curve) was 165.3% larger. No significant differences in dyskinesias or tolerability occurred.[6]

Traditional Uses [8]

Table 1 Worldwide Ethnobotanical Uses.

Country	Use
Brazil	Anthelmintic, aphrodisiac, diuretic, food, hydropsy, intestinal worms, nerve tonic, poison
Germany	Carminative, cholesterol, hypotensive, hypoglycemic, muscle pain, rheumatism, rubefacient, worms
India	Abortion, alterative, anthelmintic, antivenin, aphrodisiac, cancer, catarrh, cholera, cough, debility, delirium, diabetes, diarrhoea, diuretic, dropsy, dysentery, dysmenorrhea, emmenagogue, fertility, gout, impotency, irritant, lithiasis, nerve tonic, nervine, night dreams, scorpion sting, snakebite, spermatorrhoea, sterility, tuberculosis, uterine stimulant, worms
Nigeria	Snakebite
Pakistan	Aphrodisiac, diabetes
Elsewhere	Anasarca, anodyne, anthelmintic, antidote, aphrodisiac, asthma, burns, cancer, cholera, cough, cuts, diarrhoea, diuretic, dog bite, dropsy, emmenagogue, insanity, intestinal parasites, mumps, nervine, paralysis, pleuritis, resolvent, ringworm, rubefacient, snakebite, sores, syphilis, tumours, vermifuge, wind-burns, worms

2.Brahmi (Bacopa Monnieri)

Introduction

Indian ayurvedic system has described several natural products and herbs for CNS disorders. For nearly three millennia, Ayurvedic doctors in India employed BM widely as a "nerve tonic." The herb's therapeutic qualities were documented in the ancient Indian scriptures Sushruta Samhita (2300 B.C.) and Charaka Samhita (2500 B.C.). One of the most well-known nootropics is Bacopa monnieri (BM), sometimes referred to as Herpestis monnieri, brahmi, water hyssop, and Indian pennywort[9]. Since the brain is the centre of creative activity in the human body and Brahmi is the name of the mythological founder of the Hindu pantheon, Brahmi refers to substances that promote brain health. The first direct mention of Brahmi's ability to improve memory can be found in the Charak Samhita where Brahmi is recommended as a treatment for mental disorders (retardation) that result in madness. According to Charak, worry, a lack of intelligence, and difficulty concentrating are the root causes of the

Figure 4 Bacopa Monnieri Leaves

mental illness. Sushruta Samhita, another genuine Ayurvedic text, has been described. Brahmi is effective in treating memory loss and cognitive decline. It is categorized as a "Medhya Rasayan" medication, which is used to enhance intelligence and memory (Medhya) [10]. Numerous inflammatory disorders such as rheumatism, asthma and bronchitis can also be managed by BM [9]. The major chemical entity present in BM is dammarane class triterpenoid saponin with jujubogenin, or pseudo-jujubogenin moieties, known as bacosides. The active ingredients responsible for neuropharmacological effects are bacoside A (comprising bacoside A3, bacopaside II, bacopasaponin C and bacopaside X), and bacoside B (comprising bacopaside N1, bacopaside N2, bacopaside IV and bacopaside V). Other identified chemical entities include bacogenin A4, bacopasaponins A-H, bacobitacin A-D, cucurbitacin E, monnieraside I and III, plantioside B, bacopasides I–XII, brahmine, herpestine, luteolin7-rutinoside, D-mannitol, hersaponin, monnierin, betulinic acid, stigmastanol, stigmasterol, β-sitosterol, wogonin and oroxindin. BM as well as its active constituents, has been explored against a wide variety of CNS disorders [9]. Active ingredients of Brahmi known as bacosides, which are responsible for improving memory, related disorders, and enhance efficiency of transmission of nerve impulse there by strengthening memory and cognition. The increasing demand of herbal medicine in recent years is observed which may be due to lesser side effect in comparison to recent synthetics drugs. To overcome this solution pharmaceutical industry develops in vitro system for production of medicinal plants and their extracts [10]. As revealed the importance of Brahmi (Bacopa monnieri Linn.) in enhancing memory and learning abilities. Since then, numerous investigations on animals have been carried out to ascertain the different characteristics displayed by the therapeutic herb. Numerous expanding investigations have also assessed Brahmi's capacity to protect neural structure and/or function. The well-known Ayurvedic herb brahmi is making a comeback in the treatment of memory-related illnesses. Its medicinal properties have been documented in traditional Chinese and Indian literature. Bacosides A and B are present in the active portions of Brahmi, a medicinal herb that has yielded several chemical compounds upon isolation. A variety of other phytochemicals, including saponins, glycosides, alkaloids, and flavonoids are the constituents of Brahmi. Research to date has shown that Brahmi exhibits antiparkinsonian, antistroke, and anticonvulsant potentials in addition to a variety of pharmacological actions, including memory enhancement in the treatment of schizophrenia and Alzheimer's disease [11]. The National Medicinal Plants Board study states that in 2000, the yearly market demand for Brahmi, or Bacopa monnieri, was approximately 1,000 tons. This demand surged significantly because of the plant's potential applications in Ayurvedic medicine for treating a wide range of illnesses. B. monnieri has drawn a lot of attention from all around the world lately because of its diverse range of pharmacological actions. Based on searches for "Bacopa" in the scientific literature from 2000 to 2015, the ScienceDirect, PubMed, and Google Scholar databases yielded, respectively, 529, 330, and 8,930 hits.[12]

Chemical Constituents

It is characterized by its typical chemical composition which predominantly includes compounds like dammarane-type triterpenoid saponins called as bacosides, with jujubogenin or pseudo-jujubogenin moieties as their aglycone units. Based on the structural similarity, 12 analogues from the family of

Bacosides have been elucidated. In the recent past, bacopasides I–XII, a different class of saponins have been identified as an important constituent of the herbal extract. Apart from hersaponin, apigenin, D-mannitol, monnierasides I-III, plantainoside B and cucurbitacin; the alkaloids brahmine, herpestine and nicotine have also been classified in the chemical constituents of Bacopa Monnieri. Bacoside A is the most studied and potent constituent of Bacopa, which is composed of bacoside A3, bacopasaponin C, bacopaside II and bacopaside X [11].

Active Components

The therapeutic effects of Bacopa monnieri are believed to be exerted through triterpenoid saponins present in the plant extract. Bacosides are the triterpenoid saponins of prime importance. They have been shown to enhance nerve impulse transmission. The bacosides promote the repair of damaged neurons by upregulating neuronal synthesis and kinase activity. The bacosides also aid in the restoration of synaptic activity, which ultimately leads to nerve impulse transmission. The nerve impulse transmission, plays a vital role in promoting healthy cognitive functions like attention span, focus, concentration, learning and memory. There is evidence which suggests that Bacopa, by the virtue of containing active constituents like bacosides, influences the synthesis and availability of the neurotransmitter, Serotonin; therefore, Bacopa helps to maintain neurotransmitter balance [11].

Taxonomical Classification: The taxonomy of B. monnieri is in the Kingdom (Plantae); Subkingdom (Viridiplantae); Infrakingdom (Streptophyta); Superdivision (Embryophyta); Division (Tracheophyta); Subdivision (Spermatophytina); Class (Magnoliopsida); Subclass (Asteridae); Superorder (Asteranae); Order (Lamiales); Family (Plantaginaceae); Genus (Bacopa); Species (B. monnieri) [12].

Nomenclature: B. monnieri is native in India, Bangladesh and Southern Asia, and also grows in Australia, Europe, and Africa. The vernacular name of B. monnieri is also known as Indian pennywort, water hyssop (English), farfakh (Arabic), brahmi (Assamese), aaghabini (Bengali), jia ma chi xian (Chinese), petite bacopa (French), kleine fettblatt (German), baam (Gujrati), psheta srua (Hebrew), adha birni (Hindi), bakopa (Japanese), jala brahmi (Kannada), barna (Malayalam), ghola (Marathi), medha giree (Nepalese), bakopa drobnolistna (Polish), brahmibuti (Punjabi), adha birni (Sanskrit), ahaznda poozndu (Tamil), neeri sambraani mokka (Telugu), phrommi (Thai), and rau dang bien (Vietnamese)[12].

Figure 5 Bacopa Monnieri Flower

Description: It is a member of the Scrophulariaceae family, is a small, creeping herb with numerous branches, small oblong leaves, and light purple flowers [10]. It grows to a height of 60-90 cm and its branches are 5-35 cm long. Roots are thin, wiry, small, branched creamish-yellow. Stem is thin, green or purplish green, about 1-2 mm thick, soft, nodes and internodes prominent, glabrous; taste, slightly bitter. Leaves are stalkless, simple, opposite, decussate, green, sessile, 8-15 mm long and 4 mm wide, ovate-oblong, taste slightly bitter. Flowers are small, axillary and solitary, five petaled white, purple, pink or pale violet in colour, pedicels 6-30 mm long, bracteoles shorter than pedicels. Fruits are capsules up to 5 mm

long, ovoid, glabrous and sharp at apex [12]. In India and the tropics, it grows naturally in wet soil, shallow water, and marshes. It is also found in Nepal, Sri Lanka, China, Taiwan, Vietnam, Florida and Southern states of USA. It is widely distributed in warmer parts of Asia, Australia, America and India commonly known as Brahmi or Indian water hyssop has been investigated. The herb can be found at elevations from sea level to altitudes of 4,400 feet, and is easily cultivated if adequate water is available. Flowers and fruit appear in summer and the entire plant is used for medicinal purpose [10].

Ethnopharmacology: It is bitter, astringent, and cooling; it is also said to sharpen the mind. It is frequently used to treat a variety of conditions, including epilepsy, dermatitis, anaemia, diabetes, heart problems, asthma, and insanity. It is also used to treat cataract issues and boils as a blood purifier. The entire plant is used medicinally; for example, children's bronchitis and diarrhoea can be treated with leaf juice; rheumatism can be treated with leaf paste; west Bengalis are said to eat the leaves and tender stalks; and cough disorders can be treated with leaf decoction. Additionally, it has been noted to be a safe heart tonic and to relieve anxiety neurosis in patients when combined with sugar, ginger juice and bark extracts of Moringa oleifera. It was reported as a potent antioxidant and bronco-vasodilator [10].

Pharmacological Properties:

The Effects of antiparkinsonian in addition to its memory-enhancing properties, Brahmi has been shown to be effective in treating Parkinson's disease, a neurodegenerative condition characterized by the death of dopamine-producing neurons in the substantia nigra and the accumulation of alpha-synuclein protein in inclusion bodies called Lewy bodies. Many experimental models have been used to investigate the mechanism behind the etiology of Parkinson's disease. There hasn't been much study done on how Brahmi and other plant extracts affect Parkinson's disease models, various research are conducted on the impact of CDRI-08 (KeenMind) on transgenic Drosophila fruit flies (PD model) that exhibit normal human alpha synuclein expression in their neurons. A variety of metrics, such as climbing skills, activity patterns, oxidative stress, and apoptosis, were assessed in order to examine the impact of Brahmi on fruit fly brain function. Research showed that when flies were exposed to Brahmi, there was a decrease in oxidative stress and apoptosis, as well as an improvement in climbing ability and activity pattern. These findings, which were dose dependent, imply that the herb lessens oxidative stress, neuronal cell death, and behavioural abnormalities in the brains of PD model flies. Similar findings were obtained in another research, also demonstrated the efficacy of Brahmi in alleviating the climbing activity of fruit flies compared to non-treated fruit flies. In keeping with other studies, a Caenorhabditis elegans model of Parkinson's disease used to examine this herb's effectiveness. According to the research, Brahmi supplementation decreased the build-up of alpha synuclein, stopped the death of dopaminergic cells, and increased the amount of lipids in the PD model. These findings support the idea that Brahmi might be used as an anti-Parkinsonian drug, although more investigation is needed into the possible use of herbal plants, chemicals, and extracts for the treatment of Parkinson's disease [11].Researchers have examined neuroprotective effect of B. monnieri in rotenone induced Parkinson's disease with particular reference to glutamate metabolism in different regions of rat brain. Glutamine content and activity levels of glutamate dehydrogenase, glutamine synthetase were significantly depleted and elevated glutaminase activity was found in different brain regions of rat during

rotenone induced Parkinson's disease when compared to control rats. Treatment with B. monnieri caused significant elevation in glutamine content and the activity levels of glutamate dehydrogenase, glutamine synthetase and depletion in glutaminase activity in different brain regions of rats when compared to induced Parkinson's disease rats. So, the results suggest the ability of B. monnieri extract to modulate glutamate metabolism in different brain regions of induced rodent model of Parkinson's disease [12].

Antioxidant Effect

By preventing lipid peroxidation, the hexane and alcoholic extracts of BM exhibit antioxidant qualities. A more recent study investigated the antioxidant impact of BM through alternative mechanisms, such as the inhibition of glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD) activities. Additionally, the nitro blue assay revealed that the hydroalcoholic extract of the entire BM plant had an inhibitory impact on the superoxide produced from polymorphonuclear cells. Investigation has been done on hepato-protective activity of alcoholic extract BM on morphine-treated rats. It may be due to decreased brain mitochondrial enzyme activity in rats. Methanolic extract BM is able to directly inhibit the superoxide anion formation in a dose-dependent manner due to this it reduces concentrations of nitric oxide (NO), generated (enzymatic and nonenzymatic) by activated astrocytes, might be involved in a variety of neurodegenerative diseases, such as AD, ischemia and epilepsy [10].

Learning and memory: The neuropharmacological effects of plant extracts and isolated bacosides have been thoroughly studied in a number of laboratories, and numerous papers supporting their nootropic action are available. According to preliminary research, rats treated with plant or an alcoholic extract of BM plant had improved learning capacities. Further research revealed that the presence of Bacosides A and B in the ethanol extract was responsible for the impact that helped with cognition. In addition to improving learning and memory in healthy rats, these active ingredients prevented scopolamine, electroshock, and immobilization stress from causing amnesia. It is yet unclear how these pharmaceutical activities work. According to certain theories, bacosides cause membrane dephosphorylation in particular brain regions, which is followed by an increase in protein and RNA turnover. It has been demonstrated that BM increases hippocampal protein kinase activity, which may perhaps explain some of its nootropic effects. The two-week administration of BM also corrected the neurotoxin-induced acetyl cholinergic receptor depletion, acetyl cholinesterase activity reduction, and muscarinic cholinergic receptor binding in the frontal cortex and hippocampus. It has been suggested that the behavioural effects of cholinergic degeneration can be alleviated by a reduction in noradrenergic function. BM is known to lower nor epinephrine and increase 5-hydroxytryptamine levels in the hippocampus, hypothalamus and cerebral cortex, thus BM indirectly, modify Ach concentrations.[10]

Neuroprotective activity: The active constituents responsible for B. monnieri cognitive effects are bacosides A and B, moreover, triterpenoid saponins are responsible to enhance nerve impulse transmission. The bacosides also aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, restoration of synaptic activity, and nerve impulse transmission. It has been demonstrated that B. monnieri

suppresses acetylcholinesterase activity resulting in enhanced cholinergic function, which in turn enhances attention and memory processing and increases working memory in elderly people [12].

Molecular Mechanism of Bacopa Monnieri in Disorder Affecting the Brain

Bacoside A and B are reported to establish a healthy antioxidant environment in the brain by scavenging free radicals, reducing lipid peroxidation, and increasing the level of antioxidant enzymes, superoxide dismutase (SOD), glutathione (GSH)- peroxidase (GPx) and catalase (CAT) in the hippocampus and prefrontal cortex. Bacoside A has also shown anti-inflammatory activity by decreasing the level of proinflammatory cytokines, interleukin (IL)-6 and tumor necrosis factor (TNF)-α from the activated microglial cells. However, a recent study proposed that bacoside A might not be the only bioactive compound found in BM, and differences in extract efficacies could bring out new pharmaceutical lead compounds. Remarkably, BM was found to protect neuronal cells against glutamate associated oxidative stress, endoplasmic reticulum (ER) stress and mitochondrial stress; in an extract-dependent manner. By boosting the density of vesicular glutamate transporter 1 (VGLUT1) in the frontal cortex, striatum, and hippocampal CA1 areas, BM showed cognitive improvement in a rat model of schizophrenia. Moreover, BM demonstrated anti-aging and anti-apoptotic properties in human astrocytes by means of mitophagy's defensive function. Moreover, BM and bacoside A reduced the effects of hypoglycemia on changes in dopaminergic function and oxidative stress-related cell death by regulating the expression of the D1 and D2 dopamine receptors, cyclic adenosine monophosphate (Camp) signaling, Bax, and SOD. Considering the whole-system approach, the entirety of compounds rather than specific individual components might be synergistically acting to mediate beneficial effects. These might be mediated through multiple targets and signaling pathways, involving acetylcholine (Ach), γ-aminobutyric acid (GABA), glutamate, dopamine and serotonin (5-HT), as well as calcium channel. Further, BM may regulate different biological pathways related to transmembrane transport, Mrna translation and protein misfolding, to exert protective effects in the brain. Especially, BM can enhance cell proliferation and migration while acting to inhibit neuronal disease-associated pathways linked to oxidative stress, apoptosis, brain damage, and growth failure [9].

Table 2 Effects of oral administration of BM extract in Animal models of Parkinson's disease [9]

Model System	Dose	Evaluation	Findings
Rotenone induced PD in male Wistar rats	180 mg/kg	Ach & AchE levels	↓ Ach & ↑ AchE
Rotenone induced PD in male Wistar rats	180 mg/kg	Glutamine level, GDH & GS activity	↑ Glutamine, ↑ GDH & GS activity
Rotenone induced PD in male	180 mg/kg	EP, NE, DA & 5- HT levels	↑ NE, EP, DA & 5-HT

Wistar rats			
MPTP induced PD in male Swiss albino mice	40 mg/kg	SLA, SOD & CAT activity	↑ Locomotor activity, ↑ SOD & CAT activity
MPTP induced PD in male Swiss albino mice	40 mg/kg	Grip strength, SLA, SOD & CAT activity	↑ Grip strength, ↑ locomotor activity, ↑ SOD & catalase activity
MPTP induced PD in male Swiss albino mice	40 mg/kg	Rotarod, grip strength, foot printing, biochemical parameters, immunohistochemistry (TH), western blot	↑ Motor function, ↑ catalase, SOD, GR, GPx, dopamine, DOPAC and HVA, ↓ LPO & nitrite, ↓ TH immunoreactivity, ↓ Bax and caspase-3 & ↑ Bcl2 protein expression
Rotenone induced hemi-PD in male Wistar rats	50 mg/kg	T-maze, radial maze, rotarod, narrow beam	↑ Working & reference memory, ↑ motor co-ordination
Rotenone induced PD in male Wistar rats	40 mg/kg	rotarod, ELISA, biochemical analysis	↑ Motor function, ↓ α-synuclein, ↓ ROS, ↓ pro-inflammatory cytokines

AchE, Acetylcholine esterase; CAT, Catalase; DA, Dopamine; DOPAC, 3,4-Dihydroxyphenylacetic acid; EP, Epinephrine; GDH, Glutamate dehydrogenase; GPx, Glutathione peroxidase, GR, Glutathione reductase; GS, Glutamine synthetase; 5- HT, Serotonin; HVA, Homovanillic acid; LPO, Lipid peroxidation; MPTP, 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; NE, Nor-epinephrine; PD, Parkinson's disease; ROS, Reactive oxygen species; SLA, Spontaneous locomotor activity; SOD, Superoxide dismutase, TH, Tyrosine hydroxylase

3.Ashwagandha (Withania Somnifera)

Introduction

Medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments include their safety, economic feasibility, effectiveness, and ease of availability. Ashwagandha (Withania somnifera) is a perennial plant belonging to the family Solanaceae. Ashwagandha, A popular Ayurvedic herb, is

Figure 6 Ashwagandha

commonly known as “Indian winter cherry.” The root smells like a horse, and that is why it is named Ashwagandha (on consuming it gives the power of a horse). The species name somnifera means “sleep-inducing” in Latin, indicating its sedating properties. Some herbalists refer to Ashwagandha as Indian ginseng, because it is used in Ayurvedic medicine in a way similar to Chinese ginseng (Panax ginseng) in traditional Chinese medicine (TCM). It has been used as an antibacterial, antioxidant, adaptogen, aphrodisiac, liver tonic, and an anti-inflammatory agent. W. somnifera has been used in different medicinal systems for centuries. Writings indicate that the therapeutic use of plants is as old as 4000–5000 BC and the Chinese used the first natural herbal preparations as medicines. In India, however, earliest references to the use of plants as medicine appear in Rigveda, which is said to have been written between 3500 and 1600 BC. Later, the properties and therapeutic uses of medicinal plants were studied in detail and recorded empirically by the ancient physicians in Ayurveda, which is a basic foundation of ancient medical science in India [13]. Ashwagandha belongs to the family Solanaceae. Other common names of Ashwagandha are Indian ginseng, poison gooseberry and winter cherry. Ashwagandha is cultivated in North western and other parts of India. In India Madhya Pradesh, Gujarat, Haryana, Maharashtra, Punjab, Rajasthan and Uttar Pradesh are the main producing state of Ashwagandha. It is also found in Nepal, China and Yemen. The climatic conditions required for the cultivation of Ashwagandha include an altitude of 1500 m above the sea level. The semi tropical regions which receive about 500–800 mm annual rainfall is the best suited for its cultivation. The crops require dry condition during growing periods and optimum temperature required for its cultivation is 20–38 °C. The sandy loam or light red soil and partial shade sun are other suitable factors for its growth. The extract of roots contains steroidal lactones with ergostane, which contain withanone, withaferin, withanolides, sitoindosides and about 0.2% alkaloids. Various studies have been conducted on active phytoconstituents which helps in providing a rationale background for drug design with upgraded and better pharmacological properties. The herb is reported to possess beneficial effects in a wide range of neurological disorders including stress, Parkinson’s disease, Huntington’s disease and Alzheimer’s disease etc. Ashwagandha modulates the brain oxidative stress makers, such as superoxide dismutase (SOD), catalase, lipid peroxidation (LPO), and non-enzymatic antioxidants like glutathione (GSH). The roots and its extract induce axon and dendrite outgrowth, proposing its possible effect on neuronal regeneration. Ashwagandha on the basis of Phyto-pharmacological studies proved potential as anti-inflammatory, anti-oxidant, anti-cancer, anti-microbial, anti-malarial, diuretic, sedative, immunomodulatory and cardioprotective properties [14].

Figure 7 Ashwagandha leaves

Historical Background

In many traditional medical systems, including Ayurveda, Unani, Siddha, homeopathy, Chinese, Tibetan, African, etc., Ashwagandha is a key plant. The Latin term “somnifera” in Withania somnifera means “sleep-

inducer," which explains why it is widely used as a neuroprotective. In different parts of India, it goes by different local names. The oldest medical systems include the Chinese medical system and the traditional Indian medical system, or Ayurveda. Further proof and evidence-based study on Ayurveda were needed. Because its roots resemble sweating horses, Ashwagandha, which means "odour of the horse," is the name given to it in Ayurveda. It has been widely utilized to cure a variety of ailments for the past thousand years. Traditionally, Ayurvedic practitioners would boil the fresh roots in milk. Another way to administer it is to grind the roots into a fine powder known as "churna" and mix it with liquids, primarily milk, honey, and water. Leaves, branches, seeds, and berries are among the other parts that have been utilized to extend life and promote health. It is categorized as "Rasayana" in the Ayurvedic system, which means "tonic" and primarily functions as a body rejuvenator, disease prevention, aging slowing agent, and memory enhancer. An ancient medical system known as Unani is practiced primarily in South Asian and Middle Eastern nations. It is founded on the idea of homeostasis, and treatments use physical methods to treat illnesses. It makes use of either the administration of a particular diet or the adjustment of food amount and quality. Ailments are treated with natural substances, either as single medications or as combinations of two or more medications. In the Unani system, Withania somnifera is referred to as Asgand and is discussed in the book "Kitab-ul-Hashaish" Asgand Nagori and Asgand Dakani are the two variants known in the Unani system, according to literature; nevertheless, Asgand Nagori is more recommended in terms of medicine. Polyarthritis, rheumatoid arthritis, lumbago, painful swellings, asthma, spermatorrhoea, general and sexual debility, anxiety, neurosis, scabies, ulcers, and leucorrhoea are among the conditions it is used to treat. One of the oldest known traditional medical systems in the world is the Tibetan System of Medicine (TSM). It is mostly practiced by Amchis, herbal healers, and is well-liked in the northern regions of India, specifically Ladakh, Lahul, and Spiti. It is also referred to as Sowa-Rigpa, which is the science of healing, and is based on the literature of the Indian Buddhist system. In TSM, Withania somnifera is referred to as Ba-dzigandha or Asgandnagori. It is primarily recommended for the treatment of respiratory conditions, hepatic disorders, body strengthening and maintaining haemoglobin level. African traditional healers recommend it for typhoid, diarrhoea, skin conditions, fever, colds, asthma, and venereal infections like syphilis. It is also recommended as a sedative, hypnotist, anthelmintic, and antirheumatic. Withania somnifera is utilized in African Zulu tradition to ward against sorcery. Additionally, it serves as an insect barrier [14].

Botany of W. Somnifera

W. somnifera, commonly known as Ashwagandha, is an important medicinal plant that has been used in Ayurvedic and indigenous medicine for more than 3,000 years. Ashwagandha (W. somnifera) belongs to the genus Withania and family Solanaceae. Two species, such as, Withania coagulans Dunal and W. somnifera Dunal, are found in India. W. coagulans is a rigid gray under shrub 60–120cm high. W. somnifera is an erect, evergreen, tomentose shrub 30–75cm in height. Its roots are stout, fleshy, cylindrical, 1–2cm in diameter, and whitish brown in colour. Leaves are simple, ovate, glabrous, and opposite. Flowers are bisexual, inconspicuous, greenish or dull yellow in colour, born on axillary umbellate cymes, and comprise five sepals, petals, and stamens each; the two celled ovary has a single style and a bilobed stigma. The petals are united and tubular. The stamens are attached to the corolla tube and bear erect anthers that form

a close column or cone around the style. Pollen production is poor. The fruit is a small, globose, orange-red berry when mature and is enclosed in a persistent calyx. The seeds are small, flat, yellow, and reniform in shape and very light in weight. The cultivated plants have sizeable differences from the wild forms not only in their morphological characteristics but also in their therapeutic action, although the alkaloids present are the same in both. The 23 known Withania species are widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region, Northern Africa, India, Sri Lanka, Afghanistan, Baluchistan, and Sindh. It is found in high altitudes, ascending to 5,500 feet in the Himalayas. It has various names, such as Kaknaj-e-Hindi (Arabic), winter cherry (English), Asgandh or Punir (Hindi), Kaknaj-e-Hindi or Asgand Nagaori (Persian, Urdu), and Ashwagandha (Sanskrit)[13].

Bioactive Molecules

The pharmacological effects of the roots of W. somnifera are attributed to the presence of withanolides, a group of steroidal lactones. This plant is commonly used in formulations for its wide range of health benefits. In Ayurveda, Withania is widely claimed to be a potent aphrodisiac, sedative, and rejuvenate, and to have life-prolonging properties. It is also used as a general energy-enhancing tonic known as Medharasayana, which means that "it promotes learning and a good memory." Laboratory analysis has revealed more than 35 chemical constituents contained in the roots of W. somnifera. The biologically active chemical constituents are alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitonidoside XI and X). W. somnifera is also rich in iron. The roots of W. somnifera consist primarily of withanolides, which are believed to account for its extraordinary medicinal properties. Withanolides are steroidal and bear a resemblance, both in their action and appearance, to the active constituents ginsenosides present in Asian ginseng (Panax ginseng). Ashwagandha's withanolides have been researched in a variety of animal studies examining their effect on numerous conditions, including immune function and even cancer. Chemical analysis of Ashwagandha shows its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropine, choline, cuscohygrine, isopelletierine, anaferine, and anahydrine. The withanolides within the leaves have C28 steroidal nucleus with C9 side chain and a six-member lactone ring. Twelve alkaloids, 35 withanolides, and several sitoindosides from W. somnifera have been isolated and studied. A sitoindoside is a withanolide containing a glucose molecule at carbon 27. Much of Ashwagandha's pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D [13].

Further chemical analysis has shown the presence of the following

Alkaloids: Anaferine, Anahygrine, Cuscohygrine, Scopoletin, Withanine, Withaninine, Somniferine, Tropeltigloate, Somniferinine, Somninine, Nicotine, Visamine, Withasomine, and Pseudotropine.

Salts: Cuscohygrine, Anahygrine, Tropine, Pseudotropine, and Anaferine.

Steroidal Lactones: Withaferin-A, Withanone, WS-1, Withanolide E, Withanolide F, Withanolide G, Withanolide H, Withanolide I, Withanolide J, Withanolide K, Withanolide L, and Withanolide M

Nitrogen containing compounds: Withanol, Somnisol, and Somnitol.

Steroids: Cholesterol, β-sitosterol, Stigmasterol, Diosgenin, Stigmastadien, Sitoinosides VII, Sitoinosides VIII, Sitoinosides IX, and Sitoinosides X.

Flavonoids: Kaempferol and Quercetin [13]

The plant contains carbohydrate-D-glucose, maltose, rhamnose, sucrose, and starch. It contains proteins, amino acids, and the alkaloid shankhpushpine (C17H25NO2), with a melting point of 162–164°C. The most notable constituents are tropine alkaloids. Only convolamine has been identified, but other alkaloids (convoline, convolidine, convolvine, confoline, convosine, etc.) found in other species from this family are most likely present as well. The fresh plant contains volatile oils, fatty acids, fatty alcohols, and hydrocarbons, such as myristic acid (30.9%), palmitic acid (66.8%), linoleic acid (2.3%), and straight chain hydrocarbon hextriacontane. A study was performed for a chemical examination of the whole plant (C. pluricaulis) and reported the presence of scopoletin, β-sitosterol, and ceryl alcohol. The chloroform fraction of this plant extract contains 20-oxodotriacontanol, tetratriacontanoic acid, and 29-oxodotriacontanol. The flavonoid kaempferol and steroids phytosterol and β-sitosterol were also found in significant amounts. An estimation of scopoletin content was determined by spectrofluorimetry and HPTLC. Ashwagandha roots contain alkaloids, starch, reducing sugar, hentriacontane, glycosides, dulcital, withaniol acid, and a neutral compound. Wide variation (0.13–0.31%) is observed in alkaloid content. Eight amorphous bases have been isolated (withanine, somniferine, somniferinine, somnine, withananine, withananinine, pseudowithanine, and withasomnine). Other alkaloids reported are nicotine, tropine, pseudotropine, 3, a-tigloyloxytropine, choline, cuscudohygrine, anaferine, anahygrine, and others. Free amino acids in the roots include aspartic acid, glycine, tyrosine, alanine, proline, tryptophan, glutamic acid, and cystine. The leaves contain 12 withanolides, alkaloids, glycosides, glucose, and free amino acids. The berries contain a milk-coagulating enzyme, two esterases, free amino acids, fatty oil, essential oils, and alkaloids. Methods for the analysis of alkaloid in Asgandh roots have also been reported [13].

Major Medicinal Value in Animals and Humans

Withaferin A and withanolide D are the two main withanolides that contribute to most of the biological actions of Withania. The active ingredients of WS are alkaloids (isopelletierine, anaferine, cuscohygrine, anahygrine, etc.), steroidal lactones (withanolides and withaferins), and saponins. Sitoindosides and acylsterylglucosides in Ashwagandha are antistress agents. Active principles of Ashwagandha, for instance, sitoindosides VII–X and Withaferin A, have been shown to have significant antistress activity against acute models of experimental stress. The arial parts of WS yield 5-dehydroxy withanolide-R and withasomniferin-A. The biological activities of W. somnifera are anxiolytic, antidepressant, antifungal, antimicrobial, antimalarial, apoptotic, chondroprotective, cardioprotective, immunomodulator and neuroprotective promote inhibition of COX-2 enzyme and promote learning and memory in Alzheimer's disease (AD). Numerous studies indicated that Ashwagandha possesses antioxidant, antitumor, antistress,

anti-inflammatory, immunomodulatory, hematopoietic, antiaging, anxiolytic, antidepressive, and rejuvenating properties, and that it also influences various neurotransmitter receptors in the central nervous system (CNS) [13].

Animals

Animals' Human civilization has long included the use of medicinal plants to treat a variety of illnesses. The majority of the time, humans discovered a plant's medicinal qualities by trial and error, but their belief systems also had an impact and frequently led to the plant becoming associated with mythical and religious traditions. The use of medicinal plants has developed into both an art and a science, with practitioners relying on their knowledge, customs, and understanding of sickness. Disease treatments for animals evolved concurrently with those for humans. This information was transmitted orally, by example, and occasionally in writing. In poor nations, ethnoveterinary medicine (EVM) plays a significant role in the provision of animal health care. Traditional veterinary theory, medications, surgical techniques, diagnostic procedures, and animal husbandry practices are all included in this now-recognized field of study. Evm encompasses the veterinary elements of ethnobotany.[13]

Humans

Astringent, bitter, acrid, somniferous, thermogenic, stimulant, aphrodisiac, diuretic, and tonic are some of the properties of roots. The leaves have anti-inflammatory, antitumorous, antihepatotoxic, and antibacterial qualities. The seed has diuretic, hypnotic, and milk-coagulating qualities. W. somnifera has been utilized as an antibacterial, antioxidant, adaptogen, aphrodisiac, liver tonic, and anti-inflammatory substance. In ethnomedicine, it is a well-known health food and herbal tonic used to treat cardiovascular disorders. It can be used by humans as a single herb or as a component of formulations that contain polyherbal or herbomineral substances. It is generally believed that ashwagandha doses for humans are safe and nontoxic, ranging from 4 to 6 grams per day. Stress activates the hypothalamic pituitary adrenal (HPA) axis and produces oxidative stress, which is a key cardiovascular risk factor. With its strong antistressor capabilities, ashwagandha has been shown to mitigate stress-induced alterations and offer cardio protection in ischemic rats, which is comparable to the benefits associated with adaptogens like Panax ginseng. Additionally, it lengthens the duration of contractility and improves coagulation time. It also raises heart weight and glycogen levels in the liver and myocardium, indicating an acceleration of the anabolic process [13].

Pharmacological Effects

Withania somnifera has a variety of pharmacological characteristics, the majority of which are attributed to its active components, withanolides. Ws root extract has been shown in studies to be anti-aging, anti-oxidant, and anti-cancerous. Ws roots are a possible source of hypoglycemic, diuretic, and hypocholesterolemic drugs. Sitoindosides VII-X and Withaferin-A, Ashwagandha's two active principles, have been demonstrated to have considerable antistress efficacy when evaluated in a wide range of stress-induced paradigmsi, as well as strong anti-oxidant activity in a rat model. Withanolides act as hormone precursors, which can be transformed into human physiologic hormones as needed. Pretreatment with Ws extract prevented all changes in antioxidant enzyme activities, catecholamine content, dopaminergic D2

receptor binding, and tyrosine hydroxylase expression in PD rat model (Parkinson's induced by 6-hydroxydopamine (6-OHDA)) in a dose-dependent manner. Thus, Ws appears to perform its pharmacological impact by occupying receptors on the cell membrane, inhibiting the binding of real hormone in a concentration-dependent way. The demonstration of the therapeutic potential of withanolide A isolated from the root of Ws, which can regenerate neurites and reestablish synapses in severely injured neurons in mice. Withaferin A, a significant component of physiologically active steroids, shown potent anti-inflammatory and anti-cancer activity. Thus, the study highlighted Ws' pharmacological potential, which may be used in the future to develop treatment approaches for Parkinson's disease[15].

Antioxidant Effect

The brain and nervous system are more vulnerable to free radical damage than other tissues due to their high concentration of lipids and iron, both of which are known to impair the generation of reactive oxygen species. The brain also consumes roughly 20% of the total oxygen supply. Free radical damage to nerve tissue may contribute to neuronal loss during cerebral ischemia, as well as normal aging and neurodegenerative illnesses such as epilepsy, schizophrenia, Parkinson's, Alzheimer's, and others. Because traditional Ayurvedic use of WS has encompassed numerous disorders related with free radical oxidative damage, it is believed that the effects are attributable to some kind of antioxidant action. The active principles of WS, sitoindosides VII-X and withaferin A (glycowithanolides), were tested for antioxidant activity using the major free-radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) levels in the rat brain frontal cortex and striatum. Decreased activity of these enzymes causes an accumulation of harmful reactive free radicals, which has degenerative effects. An increase in these enzymes would indicate more antioxidant activity and a protective effect on neural tissue. Active glycowithanolides of WS (10 or 20 mg/kg intraperitoneally) were administered once daily for 21 days to groups of six rats. All enzymes showed dose-related increases, which were equivalent to those reported with deprenyl (a recognized antioxidant) treatment (2 g/kg/day intraperitoneal). This suggests that WS has an antioxidant impact in the brain, which may account for its various pharmacological characteristics. Further research into other areas of the brain (for example, the cerebellum, medulla, and hypothalamus) may shed light on the impact of WS on cognitive behaviour and other brain functions in both healthy and ill persons. Another study investigated the effect of an aqueous suspension of WS root extract on stress-induced lipid peroxidation (LPO) in mice and rabbits. LPO blood levels were raised by administering 0.2 mg/kg of lipopolysaccharides (LPS) from Klebsiella pneumoniae and 100 mg/kg of peptidoglycans (PGN) from Staphylococcus aureus. The simultaneous oral treatment of WS extract (100 mg/kg) prevented a rise in LPO. The authors highlighted that the almost harmless amounts of LPS and PGN utilized in this investigation that generated higher levels of LPO were akin to a mild bacteremia that may result from tooth extraction, streptococcal angina, etc[16].

Ws' neuroameliorative effects were examined in a rotenone (ROT) model of Drosophila melanogaster. Ws provided significant protection against ROT-induced lethality, and the survivor flies displayed an enhanced locomotor phenotype. Furthermore, biochemical studies demonstrated that ROT-induced oxidative stress was greatly reduced by W. 6-Hydroxydopamine (6-OHDA) is one of the most commonly

used rat models for Parkinson's disease, inducing toxic symptoms via oxidative stress. The anti-Parkinsonian impact of Ws extract was tested and reported to have potent anti-oxidant and anti-Peroxidative and free radical quenching characteristics in a variety of pathological states. Ws extract was observed to reverse levels of reduced glutathione, GPX, SOD, and CAT considerably in a dose-dependent manner as compared to the 6-OHDA rat model. Also, it has been reported on the neuroprotective activity of Ws root extract against ManebParaquat (MB-PQ)-induced dopaminergic neurotoxicity in a PD mouse model. According to the findings, Ws extract can decrease oxidative stress in nigrostriatal tissues while also boosting the number of Tyrosine Hydroxylase positive cells in the SN area of the MB-PQ-induced PD mouse brains. Ws has a considerable antioxidant capability, and its ROS scavenging property plays a crucial part in the prevention of Parkinson's disease by opposing neurodegeneration [15].

Antiparkinsonian Effect

In several research, ashwagandha has been shown to improve Parkinson's disease. Ashwagandha ethanolic root extract has been shown to prevent Parkinsonian symptoms in Balb/c mice induced with MPTP. Ashwagandha suppressed oxidative stress and mitochondrial dysfunctions in the rotenone model of Drosophila melanogaster, resulting in decreased cholinergic function and dopamine depletion. Mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine showed changes in catecholamines, antioxidants, and lipid peroxidation markers. Treatment with 100 mg/kg Ashwagandha normalizes dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, anti-oxidants (glutathione and glutathione peroxidase), and thiobarbituric acid reactive substance levels in striatum, as well as improves motor functions. Another study found that Parkinson's caused mice showed improved behaviour, antioxidant status, and lipid peroxidation levels in their brains. It has been found that Ashwagandha root extract improved motor movements and gripping ability in a Maneb-Paraquat (MB-PQ)-induced Parkinsonian mice model. Furthermore, catalase levels decreased while nitrite and lipid peroxidation levels increased, balancing prooxidants and oxidative stress in Parkinson's disease. A study found that ethanolic root extract of Ashwagandha alleviated Parkinson's disease by inhibiting the apoptotic pathway and oxidative stress in dopaminergic neurons. The reduction of Inos and Bax expression, as well as the induction of Bcl-2 protein expression, resulted in a significant improvement in oxidative stress and apoptotic state in an MB-PQ-induced Parkinsonian mice model. As a result of these findings, Ashwagandha appears to have a neuromodulatory effect. Further research is needed to determine the specific mechanism to support the plant's therapeutic application as an anti-parkinsonian medication [14].

Synergistic Effect of Ws synergistic effect of Ws and L-dopa in the inhibition of haloperidolinduced catalepsy in mice. Ws' anti-cataleptic activity could be linked to its polyphenols, which are responsible for direct free radical scavenging as well as suppression of lipid peroxidation in the central nervous system. Ws and Mucuna pruriens (Mp) are traditional herbal herbs renowned for their neuroprotective properties due to the presence of L-DOPA in Mp seed powder and withanoloides in Ws root extract. As a result, the synergistic effect of Ws and Mp in Parkinsonian mice induced by chronic exposure to 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) and Paraquat (PQ), it was investigated, and all neurochemical variables, oxidative stress, and physiological abnormalities were found to be significantly improved when

compared to untreated PD mice brain, according to the research, exposure to PQ increases nitrite content in the nigrostriatal region. As a result of the research, it was discovered that Mp + Ws co exposure alters the level of nitrite in PQ-treated mice, and that this decrease in nitrite content may be attributable to the antioxidant properties of Mp and Ws plant extracts. Malondialdehyde (MDA), a lipid peroxidation product, has also been utilized to detect oxidative damage. Experiment showed that mice treated with PQ had significantly higher MDA levels than controls. However, MDA levels were dramatically reduced following the Mp + Ws co-treatment. Thus, the combined treatment of Mp + Ws had a substantial effect when compared to Mp and Ws therapies alone. As a result, the pioneering study on the synergistic effect of Ws with Mp and Ws with L-Dopa shed light on Ws' efficacy in the treatment of Parkinson's disease [15].

Effect of Ws on Catecholamines level

Dopamine (DA) is a neurotransmitter that regulates motor control and body movement. Oxidative stress and low catecholamine levels contribute to neurodegeneration in Parkinson's disease resulting in the loss of motor function in PD patients. The examination of catecholamines such as dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the striatum of Ws-treated and untreated PD mice. According to study, oral treatment of PD mice with Ws root extract (100 mg/kg body weight) for 7 or 28 days increased DA, DOPAC, and HVA levels in the corpus striatum. Thus, through studies, it was determined the medical effect of the Indian traditional plant Ws, which promotes catecholamines and antioxidants while preventing lipid peroxidation in the corpus striatum of PD mice. Investigation has been done on the effect of Ws on dopamine and its metabolites in the SN area of PD mice. Dopamine and its metabolites were discovered to be reduced in the brains of Parkinson's disease mice compared to controls. Furthermore, Ws therapy for 9 weeks dramatically enhanced dopamine, DOPAC, and HVA levels as compared to untreated PD animals. As a result, it is obvious that Ws has the ability to increase catecholamine levels and combat Parkinson's disease-like diseases [15].

Effect of Ws on Apoptotic Pathways

Apoptosis, also known as programmed cell death, is a closely regulated process that results in active suicide of cells under certain conditions. It has been discovered that one of the primary causes of neurodegenerative diseases is improper regulation of programmed cell death. Bcl-2 is an anti-apoptotic protein that prevents cell death by blocking the activity of the proapoptotic protein Bax. Thus, the Bcl-2 and Bax ratio determines whether a cell will survive or die from apoptosis. Interestingly, a study found that overexpression of Bcl-2 helps to reduce MPTP-induced neuronal cell death. In an MB-PQ model of Parkinson's disease, Bcl-2 expression was considerably down regulated while Bax expression was significantly raised. Furthermore, it was discovered that Ws therapy enhanced the level of anti-apoptotic (Bcl-2) proteins while decreasing the level of pro-apoptotic (Bax) proteins in the MB-PQ model of PD. Thus, Indian Ginseng (Ashwagandha) has emerged with the ability to regulate the levels of the apoptotic proteins Bcl-2 and Bax, respectively. It is now obvious that Ws is capable of overcoming neurological disorders such as Parkinson's disease [15].

Experimental Studies Supporting Medicinal Value of W.Somnifera

The leaves and roots of this plant are used as an abortifacient, aphrodisiac, diuretic, nerve tonic, narcotic, sedative, astringent, growth promoter, and anthelmintic. It has antiarthritic, antibacterial, antistress, antitumor, and anticancer activities. It is an antidote for scorpion stings. It is used for toning the uterus, consumption, dropsy, impotence, rheumatism, debility from old age, ulcer, sexual and genital weakness, assumption, rheumatic swelling, loss of memory, loss of muscular energy, spermatorrhea, syphilis, sterility of women, blood discharge, leucorrhea, anemia with emaciation, multiple sclerosis, neoplasia, cancer, and fatigue. Fruits and seeds are diuretics and are used in the coagulation of milk. Asgand (W. somnifera) has been recommended for the treatment of various ailments, which include polyarthritis (Waja-ul-Mafasil), rheumatoid arthritis (Hudar), lumbago (Wajaul- Qutn), painful swellings (Tawwarum-eAlami), spermatorrhea (Jaryan-e-Mani), asthma (Zeeq-unNafas), general debility (Zof-e-Aam), sexual debility (Zof-e-Bah), amnesia (Nisyan), anxiety neurosis (Qalaq-e-Usabi), scabies (Jarb), ulcers (Qurooh), marasmus (Saghal), and leucorrhea (Sailan-ur-Rahem) [13].

Conclusion

This combined analysis of multiple review and research findings demonstrates that herbal plants, particularly Mucuna pruriens, brahmi, and ashwagandha, have the ability to control and manage Parkinson's disease while also providing many other pharmacological activities such as neuroprotective and antioxidant effects. Research suggests that combining these medications together can improve their effectiveness in controlling and managing Parkinson's disease, as well as their neuroprotective and antioxidant properties, leading to fewer symptoms. They can also be administered independently; Mucuna pruriens alone produce 5-6% L-dopa, a precursor to dopamine, but it is preferable to utilize them together for a synergistic effect. This review only supports earlier research on medicinal plants for their intended treatment. More studies are required for further investigation. The present review is an attempt to provide reported details of information on these herbs and phytoconstituents and pharmacological activities. It is an attempt to provide a direction for further research.

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17) Parkinson disease symptoms photo Figure 1 **https://images.app.goo.gl/zQyxwZLRc9z3pT1z711**

18) Figure 2 **https://images.app.goo.gl/2qHhybACMUzRsvTa8**

19) figure 3 **https://images.app.goo.gl/mniRjRx97fXBBARKA**

20) figure 4 **https://images.app.goo.gl/4KfBzcf7xbE89FES**

21) figure 5 **https://images.app.goo.gl/tZut8ULropqFV2c47**

22) figure 6 **https://images.app.goo.gl/KbmxjiKNw93boJqu6**

23) figure 7 **https://images.app.goo.gl/DdW3vdhavxny7u9WA**