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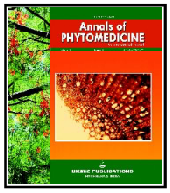

Review Article : Open Access

Therapeutic potential of Indian traditional medicines in Parkinson's disease

Shweta Sharma, K.P. Kochhar◆, Suman Jain, Rama Jayasundar* and M.R. Divya**

Department of Physiology, All India Institute of Medical Sciences, New Delhi-110029, India

**Department of NMR, All India Institute of Medical Sciences, New Delhi-110029, India*

***Department of Neurology, All India Institute of Medical Sciences, New Delhi-110029, India*

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Abstract

Parkinson's disease (PD) is second most common neurodegenerative disorder, which is a progressive motor disease that affects 10 million people worldwide and around 5.5 million Indian. The hallmark neuropathology in PD are damage to dopaminergic neurons located in the pars compacta of the substantia nigra (SN) that project to the striatum and alpha synuclein containing inclusion bodies in the surviving neurons, resulting in motor impairments, *e.g.*, tremors, bradykinesia (slow movement), poor balance, rigidity and difficulty in walking, as well as non-motor impairments including constipation, autonomic, psychiatric as well as cognitive impairments. The only pharmacology therapy for PD is levodopa but chronic use of this medicine has many side effects. Hence, these impairments are pressing issues that need to be addressed. This review article attempts to describe the usage of Indian traditional medicines to treat PD. In India, the references to the curative properties of dietary spices in the Rigveda and Atharvaveda arguably seem to be the earliest records of the use of herbs in medicine.

1. Introduction

Parkinson's disease is termed after Dr. James Parkinson, the surgeon who first defined it as "shaking paralysis" in 1817 (Houghton and Howes, 2005). It is only in last few decades that some breakthrough in development of specific therapies has been made to treat PD patients since the first patient was diagnosed with Parkinsonian syndrome. The aim of this review is to discuss the current therapeutic strategies, their limitations along with Indian traditional remedies used to treat PD.

The pathological hallmarks of PD are Lewy bodies whose main constituent is alpha-synuclein, a presynaptic neuronal protein. Interestingly, α-synuclein has a unique importance in aetiology of PD because it appears to link familial and sporadic forms of the disease. The proteostasis of alpha-synuclein is disturbed in PD suggested after investigating the presence of aggregates in patient brain (Fink, 2006; Lashuel *et al*., 2013). It was discovered in the 1960s that dopamine imbalance in the striatum is responsible for motor symptoms of PD. Dopamine connects the substantia nigra and the corpus striatum to regulate muscle activity. PD is characterized by progressive dopminergic neurons in pars compacta in the substantia nigra that leads to cardinal motor symptoms of PD, *i.e.*, rigidity, resting tremor and bradykinesia. The voluntary movements, gait coordination and postural maintenance, movement sequencing, habitual behaviours and autonomic activity are all affected through varying degrees of dopamine. Deterioration of the neurons that discharge dopamine causes a disparity of inhibitory (dopamine) and excitatory (acetylcholine) neurotransmitters in the region. This imbalance induces excessive repetitive uncontrollable movements, called dyskinesis, and absence of movement, known as gait freezing (Bloem *et al*., 2004; Olanow *et al*., 2009; and Devos *et al*., 2010).

As we know, PD is also an age-related neurodegenerative disorder where patients experience non-motor symptoms including fatigue, constipation, cognitive deficits, sleep disturbance, altered mood and pain. In this disease, over time the symptoms become worse, due to neuronal damage and emergence of interruptions in the blood brain barrier (BBB), caused by neurotoxic components released after the activation of glial cells. This loss of integrity of BBB generates a current of lymphocytes in the brain which ultimately leads to prolonged inflammatory reactions, responsible for neuronal damage (Dzamko *et al*., 2014).

The commonly used drug is levodopa for the treatment of PD. It suppresses some of the motor symptoms and compensates for dopaminergic cell loss by enhancing dopamine synthesis in the remaining terminals. Despite years of using levodopa (L-dopa), current treatment options for PD are largely ineffective to reverse or prevent pathological outcomes. Because longterm levo-dopa treatment often causes dyskinesis, motor fluctuations, and psychiatric disturbances (Schneider *et al*., 2003); alternatives in the form of herbal medicines and traditional system of medicines have also been explored (Nagashayana *et al*., 2000; Chen *et al*., 2007; and Li *et al*., 2011). Several reports have shown that a number of herbal remedies possess neurotrophic and neuroprotective properties in PD-related models (Kim *et al*., 2009; Hu *et al*., 2011; Mu *et al*., 2011; Xu *et al*., 2013; Gaur *et al*., 2013).

Corresponding author: Dr. K.P. Kochhar

Associate Professor, Department of Physiology, All India Institute of Medical Sciences, New Delhi-110029, India

E-mail: kpkochhar06@gmail.com

Tel.: +91-9871859100

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In this context, traditional Indian medicines have been revisited to determine whether their primary or adjunct form is more effective and/or less toxic.

2. Mode of action and disadvantage of the current pharmacolo-gical strategy

Conventional treatments for Parkinson's disease have included levodopa, dopamine agonists, and anticholinergics (Connolly and Lang, 2014). In the early stages of the disease, dopamine replacement therapy, using the dopamine precursor levodopa, is effective, but the dose response decreases with disease progression, and motor complications (dyskinesias) and other side effects (*e.g.*, mood disorders and sleep disturbances) arise after chronic treatment. These complications may be due to either the advanced stage of the disease (in which degenerating dopaminergic neurons cannot buffer the fluctuating plasma levels of levodopa, resulting in pulsatile stimulation of the dopamine receptors) or the further degeneration in non-dopaminergic regions (Cui *et al*., 2005). L-DOPA, however, carries several side effects, *viz*. It does not prevent dopaminergic neuron degeneration as well as it has no effects on non-motor symptoms (Olanow *et al*., 2006; Cenci, 2014; Tosi *et al*., 2016) and simultaneously prolonged use of levodopa can lead to levodopa-resistance ultimately leads to dyskinesia (Blasi *et al*., 2007). Levodopa is also responsible for PD-associated GI dysfunction in PD patients (Sun *et al*., 2008; Kango *et al*., 2013). Since the underlying mechanisms of neuronal loss in patients are not known, current therapies are mainly symptomatic and not curative or preventive (Poewe *et al*., 2010; Zhang *et al*., 2014). Levodopa significantly restored the cell proliferation (PCNA cells) in the SVZ of 6-OHDA-lesioned rats, again pointing to an important role of dopamine in increasing adult neurogenesis (Höglinger *et al*., 2004). Studies with dopamine receptor agonists and antagonists suggest that dopamine directly interacts with the neural precursor pool. Administration of the selective dopamine D2 receptor (D2L) agonist ropinirole increased the number of PCNA-expressing cells at both the lesioned and non-lesioned sides (Höglinger *et al*., 2004). However, this effect can be due to changes in the proliferation or the survival. In an elegant study, it was proven that intraventricular infusion of a D3 receptor agonist (7-hydroxy-N,N-di-npropyl-2-aminotetralin [7-OH-DPAT]) resulted in more BrdU labeled cells in SVZ and RMS of rats (Van *et al*., 2004). In mice, the same D3 receptor agonist failed to induce proliferation, pointing to species difference in dopamine receptor expression (Baker *et al*., 2005). However, the ability of these drugs to cross blood brain barrier and reach the brain for their action is still very low, hence traditional drugs with few side effects are of high priority and urgently needed. Currently, new therapeutic strategies have been introduced, which comprise traditional medicines and the use of new drug molecules and/or new delivery systems, increasing the therapeutic action while reducing adverse effects (Stayte and Vissel, 2014).

3. Indian traditional medicine

For centuries, the primary source of medicine are the agents derived from natural sources especially the plants because of their affordability, safety, long term use (Singh, 2007). All the evidences suggest that >70% of the current drugs are derived from plants (Newman and Cragg, 2012) and furthermore >50% of the worldwide population relies on plants for their healthcare. Plants have the ability to produce wide range of secondary metabolites which are useful in disease prevention and treatments purposes. These secondary metabolites include alkaloids, stilbenoids, saponins, glycosides, steroidal lactones, bilobalide, caffeine, xanthones, isoflavonoids, catechins, anthocyanins, thymocyanin, sallylcysteine, oligosaccharide esters, and some of these have neuroprotective potential due to which they can be used against PD (Singh *et al*., 2005; Hatti *et al*., 2014). Flavonoids (polyphenol group consists of aromatic rings with a phenolic hydroxyl group and a 3-OH), a group with strong antioxidant (scavenge free radicals and reactive oxygen species) and iron-chelating properties, are categorized into flavones, flavonones, isoflavones, flavonols and anthocyanidins based on their glycation, hydroxylation and alkylation patterns (Spencer, 2009). Along with their antioxidant properties, the feasible mechanism of action of flavanoids is the association of flavanoids with neuronal signaling cascades such as protein Kinase C, MAPK and PI3K/Akt, this association increase neuronal survival by decreasing apoptosis (Spencer, 2009). They can cause neurogenesis and angiogenesis and have the ability to function directly against neurotoxic agents and pro-inflammatory agents (Vafeiadou *et al*., 2007). Since oxidative stress is believed as major cause of dopaminergic neuronal failure in substantia nigra, so the molecules with antioxidative properties decrease the excitotoxicity, are of primary importance (Kedar, 2003; Dawson and Dawson, 2003; Schapira and Olanow, 2004).

Many medicinal plants contain constituents which have beneficial effects against PD. Across the world, phytomedicine, herbs and spices have long been recognized for their unique and beneficial advantages which are anticonvulsant, antidepressant, antianxiety, sedative, improving locomotor function, and memory enhancing effects (Kochhar, 2008; Kochhar, 2008; Kumar and Khanum, 2012). While most herbal products and their active ingredients have been examined *in vivo* for PD models; some have only been studied in cell models to date (Noelkar *et al*., 2005; Chan *et al*., 2009). In many neurodegenerative diseases, such as Parkinson's disease, dementia, stress, and fatigue, medicinal plants have also shown beneûcial effects (Gao *et al*., 2009; Kumar and Khanum, 2012; Al-Snafi, 2015). The available evidences of use of traditional medicines and their possible bioactivities are listed as follows:

3.1 *Azadirachta indica* L.

A. indica is also referred to as neem (Figure 1. A), which means it provides freedom from all diseases (Gupta *et al*., 2017), and it is used for thousands of years in Indian continent. All the parts of this plant, including leaves, bark, seeds and flowers have been used to treat both acute and chronic human diseases as an antimicrobial, larvicidal, antimalarial, antiviral, antibacterial, insecticide and spermicidal (Gupta *et al*., 2017). Neem belongs to Maliaceae/ Mahogany family and this plant can be used to cure multiple acute and chronic diseases.

1. (a) Chemistry of *A. indica*

Till date over 300 phytochemicals have been isolated from neem, hence it is considered as 'storehouse' of several phytochemicals, these phytochemicals are structurally complex and chemically diverse (Biswas *et al*., 2002; Subapriya and Nagini; 2005; Siddiqui *et al*., 2009). Majorly two classes of phytochemicals have been isolated from different parts of neem, *i.e.* (i) isoprenoids and (ii) non-isoprenoids. The most common isoprenoids are triterpenoids, vilasinins, linonoids, C-secomeliacins and diterpenoids and non-

isoprenoids are polysaccharides, polyphenolics, proteins, sulphur compounds, tannins, coumarin and aliphatic compounds (Biswas *et al*., 2002; Brahmachari, 2004). 0.13% essential oil is possessed by neem leaves which is responsible for the smell of leaves (Rex *et al*., 2019). Other phytochemicals derived from neem, which possess therapeutic roles are: azadirachtin, axadiradione, azadirone, nimbolide and gedunin.

Table 1: Neuroprotective effects of various medicinal plants extracts, their active constituents and mechanism of actions in various neurological disorders

Plants	Botanical name	Plant part	Bioactive compounds	Neurological disorders	Mechanism of action	Other biological role
Neem	*Azaradichta indica*		Deoxygedunin	Parkinson's disease	Improved the behavioral performance and reduced dopaminergic neurons loss in substantia nigra in Parkinson's disease models	Anti-proliferative, anti-inflammatory
		Leaf extract	Meliacin-nimbolide, quercitine, kaempferol	Parkinson's disease	Neem leaf extract suppresses radiation-induced NF-κB activation and increases caspase activity and cell death	
Karela	*Momordica charantia*	*Momordica charantia* Polysaccharides	Linolenic, momordicine, phenol, flavonoid and vitamin	Parkinson's disease	MCPs can regulate the activation state of the TLR4/MyD88/NF-κB pathway, exert protective effects, improve brain function	Antiviral, antioxidative
Ashwagandha	*Withania somnifera*	Root extract	Alkaloids, withanolides, sitoindosides Withanolide A and B, Sominone, Withanone, Witheferin A, Withanoside 4 and 5, Withanolide Q and Ashagand-hanolide	Parkinson's Disease	• Attenuated against 6-OHDA toxicity • Improved catecholamines in MPTP induced by parkinsonism • regulated D2 dop aminergicreceptor numbers instriatum • reduced oxidative impairments and restored mitochondrial respiratory chain enzymes	Antiplatelet aggregatory, anxiolytic, anticonculsive, anti-inflammatory
	Leaf extract			Parkinson's Disease	• Reduced the oxidative damage and modulated physiological abnormalities	
	Aqueous extract			Cognitive and motor coordination impairments	Regulated expression of synaptic proteins involved in synaptic plasticity and neuronal cell survival	
	Root powder extract			Parkinson's Disease	Decreased rotenone induced toxicity levels	
Pipalli	*Piper longum*	Seed extract	Alkaloids, Piperine, Pi-perluguminine	Parkinson's Disease	Showed neuroprotective effects in an MPTP induced chronic mouse model of PD	Antioxidative, anti-inflammatory, antianxiety

1. (b) Biological role of *A. indica*

It was demonstrated (Gupta *et al*., 2010) that the neem derived nimbolide possess potential to inhibit pro-inflammatory transcription factor, nuclear factor (NF)-κB signaling pathway, as it is well known that NF-κB regulate expression of genes that contribute to proliferation, angiogenesis *etc.* A comprehensive review of the molecular targets of neem components can be found in previous articles published by many researchers (Hao *et al*., 2014; Patel *et al*., 2016). One derivative of gedunin, *i.e.*, Deoxygedunin binds with TrkB receptor and activates TrkB and its downstream molecules in a brain-derived neurotrophic factor (BDNF)-independent manner. Both *in vivo* and *in vitro* studies have demonstrated neem's and its derivatives' neuroprotective effects. One study was aimed to examine the neuroprotective effects of deoxygedunin in 6-hydroxydopamine (6-OHDA)-lesioned rat model

and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mice model of Parkinson's disease. Deoxygedunin (5 mg/kg) was administered to the rats for one month intra-peritoneal. The treatment with deoxygedunin was started either two weeks before (pre-treatment) or two weeks after (post-treatment) in the 6-OHDA lesion. The isovolumetric vehicle was used as control and normal. Mice were given deoxygedunin (5 mg/kg, i.p.) for 2 weeks and with MPTP twice (20 mg/kg i.p.) on day 7. Deoxygedunin improved the behavioral performance and reduced dopaminergic neurons loss in substantia nigra in Parkinson's disease models. These observations were accompanied with the activation of TrkB receptors and associated signaling molecules such as phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK). These observations suggest the neuroprotective properties of deoxygedunin (Nie *et al*., 2015).

3.2 M. *charantia*

M. charantia (Figure 2), also known as bitter gourd or bitter melon, has long been regarded as a food and medicinal plant. It is an important edible plant with medicinal properties widely distributed throughout the Asia. *M. charantia* belongs to Cucurbitaceae family. Bitter gourd is a powerful nutrient-dense plant composed of a complex array of beneficial compounds. As a natural compound in daily food, *M. charantia* polysaccharides (MCPs) are famous for their antidiabetic, antioxidant, antitumor, anti-inflammatory, and hypoglycemic (Jia *et al*., 2017); however, little is known about its role from the perspective of neurogenesis regulation. Studies have been done and it is proved that MCPs can protect nerve damage following stroke *via* scavenging free radicals (Gong *et al*., 2015). It is also found (Gong *et al*., 2015) that MCPs can play a protective role in neurological diseases and injuries. In the view of potential use of bitter gourd fruit in the traditional medicine, its therapeutic benefits and bioactive compounds warrant further investigation.

2. (a) Chemistry of *Momordica charantia*

M. *charantia* include vitamins, minerals, antioxidants and bioactive chemicals, and these all contribute to its remarkable versatility in treating a wide range of illness and neurodegenerative diseases. Bitter gourd fruit contain high amounts of Vitamin B-complex, vitamin A, vitamin C as well as vitamin E due to which, they possess antioxidative, antiviral, antimicrobial activities, hence used as very popular traditional medicine in India for various diseases. All the medicinal value of bitter melon has been attributed to its high antioxidative properties due to presence of flavonoids, isoflavones, phenols, terpens, glucosinolates and anthroquinones, all of these also confer a bitter taste (Snee *et al*., 2011). It has also other very important health promoting substances such as charatine, polypeptide-p and vicin (Kumari *et al*., 2017). MCPs account for about 6% of *M. charantia* powder, which are heterosaccharides composed of glucose (Glu), rhamnose (Rha), mannose (Man), arabinose (Ara) and galactose (Gal) (Yan, 2021). Some scientist isolated acidic branched heteropolysaccharide, from bitter melon, which mainly consisted of Rha, Glu, Gal, xylose (Xyl), Man, Ara and galacturonic acid (GalA). It has antioxidant and inhibitory properties (Tan and Gan, 2016). Recently (Xu *et al*., 2015), a water-soluble polysaccharide is isolated from the fruit of bitter gourd, mainly composed of Gal, Rha, Ara and Xyl, have significant hypoglycemic effect.

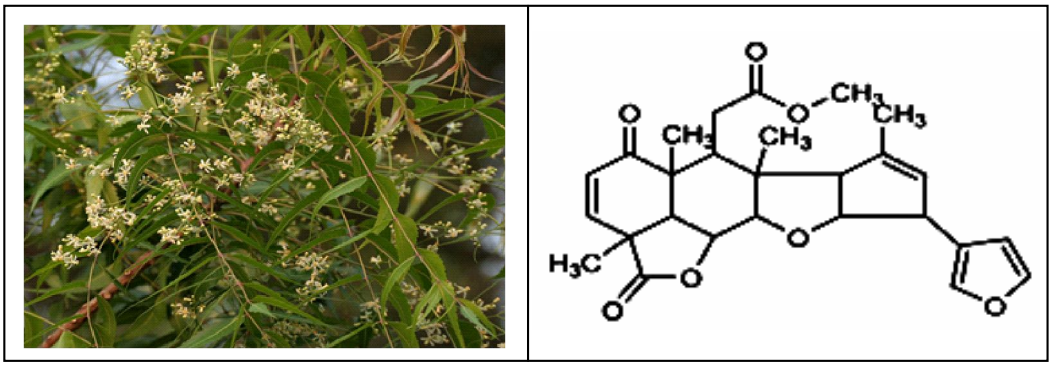

Figure 1: (A) Neem and (B) Nimbodine.

Figure 2: M. ***chrantia.***

2. (b) Biological role of M. *charantia*

The natural antioxidants of bitter gourd, polyphenolic compounds and phenols, have the ability of chain breaking antioxidants and proposed to protect against the damage caused by free radicals to cell membrane, cell component and DNA (Dziri *et al*., 2012). Bitter gourd is considered as one of the best diseased preventive foods, based on its potential and diversified effects (Amagase, 2006). Guo *et al*. (2021) recently investigated the potential role of MCPs in PD and reveal the molecular mechanism of its function *in vitro* and *in vivo*. In this study, it was found for the first time in animal and cell models of PD, those MCPs have antioxidant, anti-inflammatory, and antiapoptotic effects. In terms of anti-inflammatory response, this study detected the expression levels of inflammatory factors TNF-α and IL-1α in brain striatum tissue. In summary, this study found that in the PD model, MCPs can regulate the activation state of the TLR4/MyD88/NF-κB pathway, exert protective effects such as anti-inflammatory, antioxidative stress, and antiapoptosis, improve brain function, and provide a new method for the treatment of PD. This study confirmed that MCPs have protective effects on MPTP- and MPP+- induced PD models in mice and cells. It was found that MCPs can reduce the damage of MPTP to mice's coordination and exercise ability; it also inhibits the production of inflammatory factors and oxidative stress products in brain, thereby increasing the level of dopamine. In *in vivo* study, MCPs found to inhibit MPP+- induced apoptosis and oxidative stress, and also MCP exerts a protective effect by inhibiting the activation of the TLR4/MyD88/NF-κB pathway (Guo *et al*., 2021). It was proved that MCPs can improve oxidative stress, inflammation, apoptosis and hyperlipidemia during myocardial infarction by inhibiting the NF-κB signaling pathway (Raish, 2017). In a study (Kang *et al*., 2017), they concluded that MCPs also have the ability to increase total volatile fatty acid production, regulate rumen fermentation pathways, and hence affect the number of cellulose-decomposing bacteria. It is known that PD is related to oxidative stress, inflammation, and apoptosis (Dexter and Jenner, 2013). MPTP can induce the decrease of GSH and SOD levels in the mouse striatum and the increase of MDA levels. The treatment of MCPs can reverse the changes of these factors, suggesting that MCPs have antioxidant effects. It is also known that cytochrome C is a signal molecule necessary for the death of apoptotic cells. It was once found in alcoholic gastritis that MCPs can improve mucosal oxidative stress, apoptosis and inflammation by inhibiting the activation of the NF-κB signaling pathway (Raish *et al*., 2018).

3. *Withania somnifera* (L.) Dunal

Withania somnifera (L.) (Figure 3. A) Dunal is widely used in Indian systems of medicine (ISM) due to its exceptional pharmacological properties such as antistress, memory enhancer, nerve tonic and adaptogen with hypoglycemic and hypolipidemic effects. *W. somnifera* belongs to Solanaceae family. It is also lnown as "Indian Winter Cherry" or "Indian Ginseng" in English, as "Asgand" in Urdu and as "Ashwaghandha" in Sanskrit, it is an important herb in India (Amantea *et al*., 2009). It also used against insomnia, infertility, cognitive deficits, gout, infectious diseases and rheumatoid arthritis over thousands of years and it also has shown to be helpful in learning and memory (Van *et al*., 2004). The formulations of ashwaghandha are mainly used in Ayurvedic and Unani system of medicine due to its medicinal properties and is stated as an approved drug by Indian Pharacopoeia (1985) and it is a century old herbal Rasayana which is used to treat neuronal ailments (Singh *et al*., 2011; Uddin *et al*., 2012).

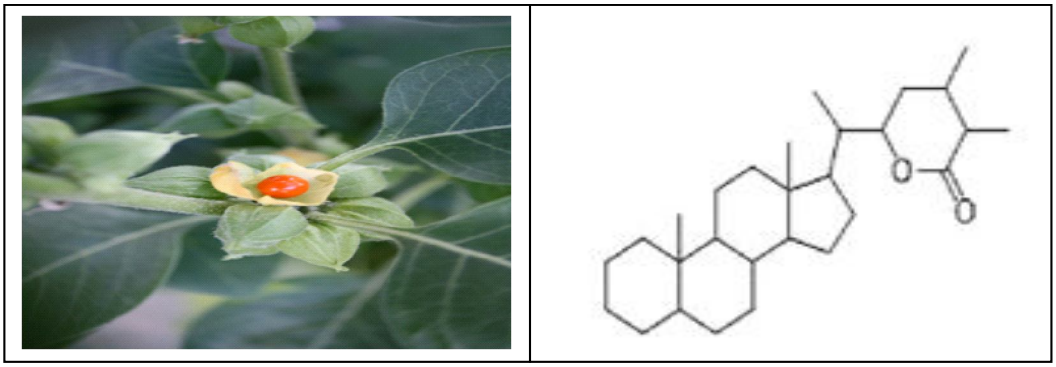

Figure 3: (A) *Withania somnifera* (B) Basic withanoid structure.

3. (a) Chemistry of *W. somnifera*

The extract of *W. somnifera* is a complex mixture composed of numerous phytochemicals including steroids, salts, flavonoids, alkaloids, steroidal lactones and nitrogen containing compounds. More than 40 withanolides (Figure 3 B), 12 alkaloids and several sitoindosides have been isolated and reported in this plant. Among these, phytochemicals the major pharmacological effects are ascribed to withanolides (Dar *et al*., 2015). The active constituents and metabolites of *W. somnifera* are: Withanolide A & B, sominone, withanone, witheferin A, withanoside 4 and 5, withanolide Q and ashwagandhanolide (Dar, 2020).

3. (b) Biological role of *Withania somnifera*

Different cellular and animal models study have demonstrated that the extract, constituents and the metabolites of *W. somnifera* possess antioxidant properties and rescue neuronal cells against toxic insults by modulating PI3K/MAPK/Akt signaling pathways. They also possess antiapoptotic cascades, hence has the potential to protect the neurons from degenerative conditions such as in diseases like Parkinson, Huntington and Alzheimer diseases. A big hurdle for its clinical use against these diseases is blood brain barrier permeability of its active constituents. Therefore, direct injections into brain or nanotechnological approaches can be done to achieve its clinical use (Dar, 2020). A lot of studies have been done with extract of different parts of this plant to cure Parkinson's disease

(Ahmad *et al*., 2005) used root extract and they found that root extract attenuated 6-OHDA neurotoxicity in rat model. Extract of active constituent of *W. somnifera* attenuated oxidative stress, restored level of dopamine, improved impaired cholinergic function and mitochondrial respiratory mechanisms, thereby reducing locomotors defects and lethality (Manjunath, 2015). In one study (Dar *et al*., 2017) it was proved that this plant work as an anti-platelet aggregatory, anxiolytic, anticonculsive, anti-inflammatory, and hence as neuroprotective agent. Ahmed *et al*. (2013) used active constituents in PD rat model and found that the number of surviving dopaminergic neurons increased and also pathology significantly reduced. The leaf extract reduced the oxidative stress and modulated physiological abnormalities whereas root extract improved catecholamines in MPTP induced PD rat model (Rajasankar *et al*., 2009; Rajasankar *et al*., 2009). Its root extract was found to regulate D2 dopaminergic receptor numbers also in striatum neurons, it also attenuated the apoptotic signals in the dopaminergic neurons also reduced oxidative impairments and restored mitochondrial respiratory chain enzymes and increased the expression of tyrosine hydroxylase (Nagashayana *et al*., 2000; Kumar *et al*., 2011; Prakash *et al*. 2014; Manjunath, 2015). Manjunath (2015) used root powder, extract of *W. somnifera* in rotenone induced PD rat model and found that after intervention of root powder the toxicity of rotenone decreased significantly.

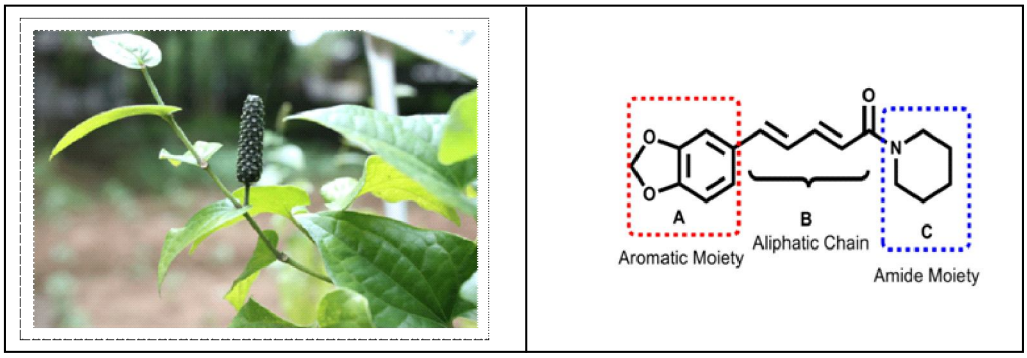

Figure 4: (A) *Piper longum* L. (B) Piperine.

4. *Piper longum* L.

Piper longum (L.) (Figure 4. A), a native of the Indo-Malayan region, has been widely used in the traditional medicine in Asia and Pacific Islands as analgesic (Kumar *et al*., 2011). It is known as Pippali in Ayurveda (Soni *et al*., 2011). *P. longum* belongs to Piperaceae family. Piperine (Figure 4. B) is the major effective constituent of *P. longum*. Piperine possess a role that it can be used as potential bioavailibity enhancer of drugs used in the management of various diseases, bioenhancers are agents capable of increasing bioavailabilty when combined with a particular therapeutic agent without exerting any of its biological activity at the used dose. It might enhance the absorption and bioavailability of drugs probably by its effect on intestinal brush border morphologically (Han, 2011; Johnson *et al*., 2011). The term bioenhancer/biopotentiator was first defined by an Indian scientist Dr. C.K. Atal at Regional Research Laboratory (RRL, Jammu), currently known as the Indian Institute of Integrative Medicine, Jammu, India (Dudhatra *et al*., 2012). Bioenhancers are capable of increasing the absorption from the gastrointestinal tract or inhibiting enzymes involved in the biotransformation of the drug by preventing the drug transformation to metabolites and by decreasing the rate of elimination (Khatri *et al*., 2015; Prasad *et al*., 2016; Khatri and Awasthi, 2016). Along with the bioenhancing effect, it has multiple biological properties also, *e.g*., anti-inflammatory, antianxiety effects, antiHBV activity, anticancer, antioxidative. *P. longum* is well reported in Indian medicine for the treatment of diseases such as cancer, asthma, depression, rheumatoid arthritis, inflammation, pain management, depression, influenza, fever and infectious diseases (Pardeep and Kuttan, 2002; Parthasarathy , 2008; Correa *et al*., 2010; Jiang *et al*., 2013; Bi *et al*., 2015). It is widely used as an analgesic and it is reported that piperine can be used for the enhancement of stimulation of appetite, salivation and blood circulation (Meghwal *et al*., 2021). It also acts on many enzyme systems, *e.g*., p-glycoproteins (Li *et al*., 2011; Meghwal *et al*., 2021).

4. (a) Chemistry of *P. longum*

Alkaloids of *P. longum* called as PLA and it includes piperine and piper longuminine. These alkaloids have multiple biological properties such as antioxidative, anti-inflammatory, antianxiety, *etc*. Its fruit contains numerous alkaloids and related compounds among which, piperine is most abundant. PLA is extracted from seeds of *P. longum* which contain 4-5% piperine, the amount of piperine content can be influenced by alterations in conditions of cultivation such as drying conditions, climate and the place of origin (Sozzi *et al*., 2012). Piperine is basic (weak) in nature which upon hydrolysis converted into piperidine and piperic acid, IUPAC name of piperine is (2E, 4E)-5-(benzo[d] [1,3]dioxol-5-yl)1-(piperidin-1-yl)penta-2,4-dien-1- one (Pruthi, 1999). A conjugated aliphatic chain acts as a bridging connective structure between piperidine and 5-(3,4-methylenedioxyphenyl) moiety which makes piperine a unique and excellent molecule to offer optimum attributes for the tendency of the molecule to bind successfully to the CYP- 450 enzymes (Bang *et al*., 2009).

4. (b) Biological role of *P. longum*

It is indicated (Lee *et al*., 2006) that piperine attenuate viability loss of MPTP-induced PC12 cells by suppressing the mitochondrial membrane permeability transition, leading to the activation of caspase-3. A lot of studies have examined neuroprotective functions of PLA in PD models. An *in vivo* study with mouse model of PD was done to demonstrate the protective effects of PLA against MPTP-induced dopaminergic neuronal cell death. This study provided some evidences that PLA protected dopaminergic cells from MPTP neurotoxicity by ameliorating behavioral abnormalities, reducing

loss of TH-positive neurons in substantia nigra, increasing levels of DA and its associated metabolites, and enhancing antioxidative defence system by increasing enzymes activity, *e.g.*, GSH and SOD activity, resulted into decreased MDA levels. The phytochemicals of *P. longum*, *e.g.*, alkaloids possess protective effects in PD models including MPTP, 6-OHDA rat/mouse models (Zaveri *et al*., 2010; Subburaman *et al*., 2010; Liu *et al*., 2011). It was reported (Pal and Choudhary, 2012) the effect of piperine on 3T3-L1 cell lines by inhibiting the expression of PPAR-γ, thus it can be used in treatment of various diseases. Piperine have the ability to inhibit intestinal and hepatic hydroxylation and glucuronidation of aryl-hydrocarbon, thus preventing the degradation of drugs in the gut and improve their bioavailability. For example, co-administration of piperine enhances the bioavailability of curcumin *in vivo* by 2000% in humans and 154% in rats (Zaveri *et al*., 2010). Studies have shown that curuminderivatized with piperic acid (obtained by the base hydrolysis of piperine) forming di-piperoylcurcu-mindiester, showed improved protection against oxidative and nitrosative stress *in vitro* and against toxin induced cell death in dopaminergic cells (Harish *et al*., 2010; Mythri *et al*., 2011). Thus, the use of such pro-drugs with improved cellular uptake would be beneficial in targeting the degenerative processes involved in neurodegenerative diseases such as PD. Although, the neuroprotective applications of *P. longum* in isolation have not been patented; several formulations have been described which include the use of the dried seed powder of *P. longum* in combination with other natural products. US6106839 patent describes the use of *P. longum* powder (10-35% by weight) along with cowhage (55-99% by weight) and ginger (5-15% by weight) to treat PD (Pruthi and Pruthy, 2000).

Figure 5: (A) *Asparagus racemosus* L. and (B) Shatavarin.

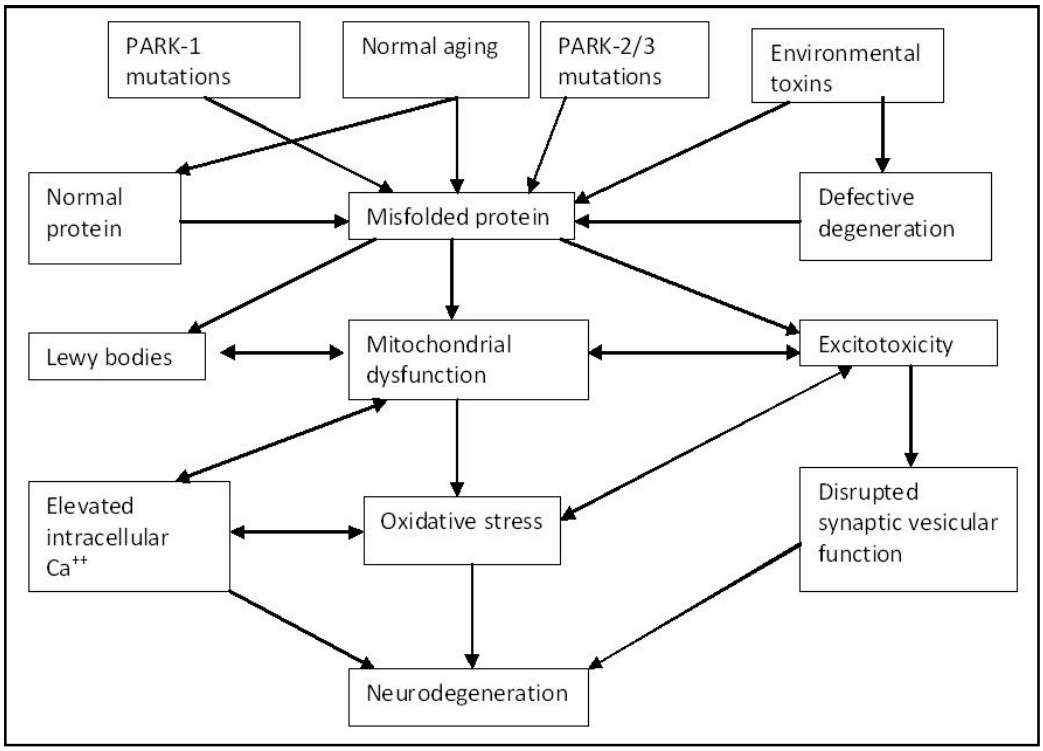

Figure 6: The putative pathomechanism of Parkinson's disease. Both environmental and genetic factors can initiate a cascade of molecular steps, which lead to excitotoxicity, mitochondrial dysfunction, oxidative stress and ultimately cell death.

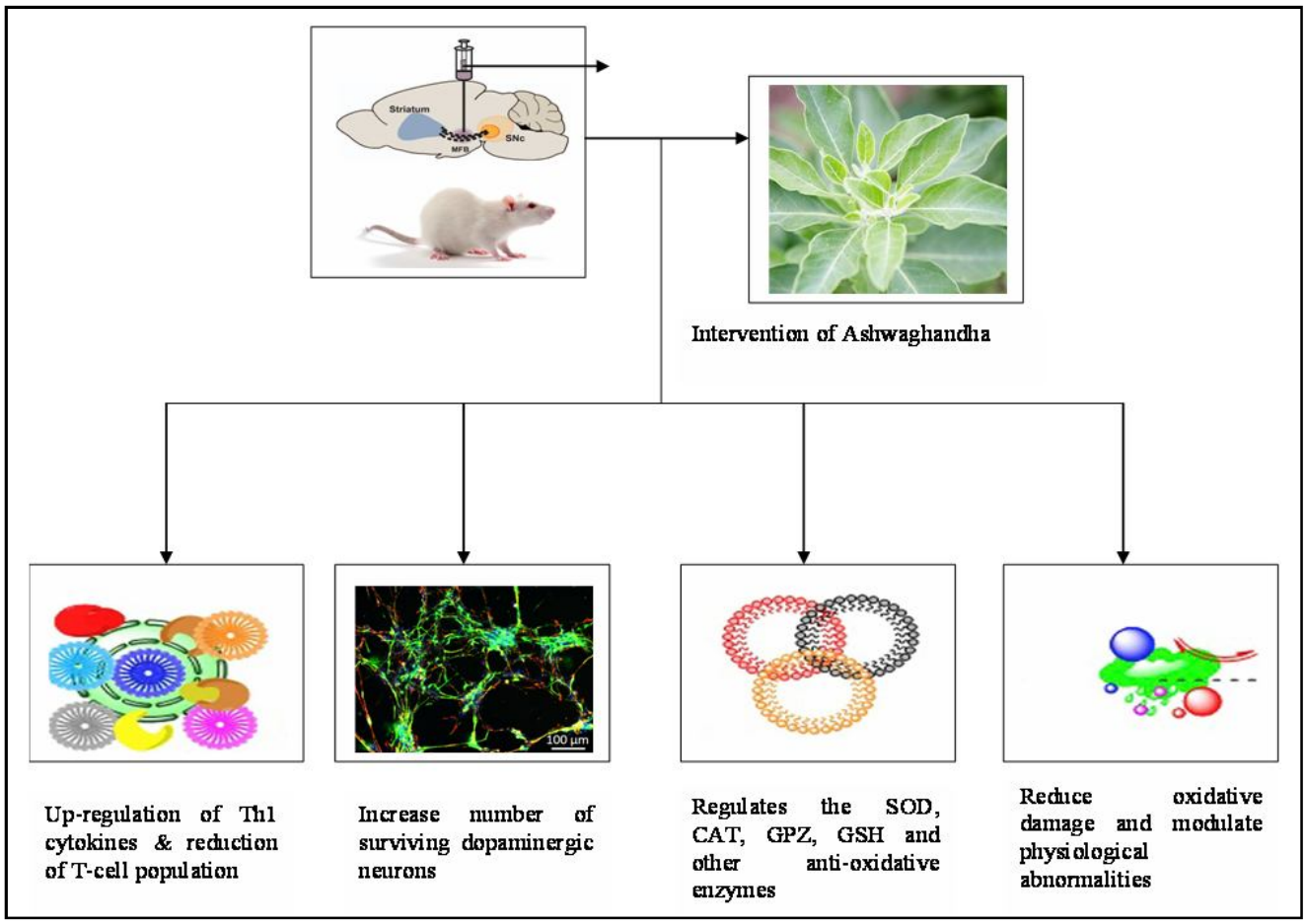

Figure 7: Graphical depiction of neuroprotective effects of *W. somnifera* (L.): *W. somnifera* extracts and its active constituents have demonstrated to possess antioxidant properties, rescue of neuronal cells against toxic insults, by regulating different antioxidant enzymes, lipid-peroxidation processes in Parkinson's disease.

5. *Asparagus racemosus*

Asparagus racemosus (Figure 4. A) traditionally known as "Shatavari"- a herb which is highly effective in curing the problems related with female reproductive system and is found at low altitude throughtout India (Hasan *et al*., 2016). The two main texts on Ayurvedic medicines, *i.e*., Charak Samhita and Ashtang Hridyam, written by Charak and Vagbhata, respectively, lists *A. racemosus* as part of various formulas used to treat disorders affecting women's health (Thorne, 2000). It belongs to Asparagaceae family. *A. racemosus* used as medicine in Ayurveda, Siddha and Unani system and in modern Ayurveda its roots are used as drug and considered to be effective in night blindness, blood purifying, kidney problems, throat complaints, nervous disorder and it acts as antidysentriric, anti-inflammatory, antidiarrheal, antitubercular, antiepileptic, antispasmodic, laxative, appetizer and as a female tonic also (Thakur *et al*., 2018). *A. racemosus* is mentioned as medhya-the plants which promote learning and memory also increase intelligence (Ojha *et al*., 2010) and as rejuvenator herbs which improve health by increasing viability, resistance and immunity, also imparting longevity as well as protection against stress.

5. (a) Chemistry of *A. racemosus*

Approximately 300 species of Asparagus are distributed around the world, and among these, 22 species have been recorded in India where, *A. racemosus* is most commonly used as a medicinal plant in traditional medicine (Bopana and Saxena, 2007). The content of Shatavari (Figure 5. B) are flavonoids (quercetin, rutin and kaempferol), sapgenin, sarsasapogenins and polyphenols and these polyphenols are the precursor of many pharmacologically active steroids. Its various parts possess a wide range of phytochemical constituent, *e.g*., Shatavari roots contain four steroids saponin known as shatvarins (shatvarin I to IV). Shatvarin I is the major glycoside with rhamnose and 3-glucose moieties attached to sarsapogenin, wherein shatvarin IV one rhamanose and two glucose moieties are attached. Shatavarin V, curillins, curillosides, asparosides and Asparginins have also been reported recently (Patricia *et al*., 2006). The oligo-spirostanoside is also present which is refrred to as immunoside (Handa *et al*., 2003) and polycyclic alkaloid - aspargamine A. (a cage type pyrrolizidine alkaloid) are also present. *A. racemosus* has various components such as furan compound- racemofuran (Kamat *et al*., 2000), isoflavones-8-methoxy- 5, 6, 4-trihydroxy isoflavone-7-0-beta-D-glucopyranoside (Saxena and Chaurasia, 2001), cyclic hydrocarbon-racemosol (Wiboonpun *et al*., 2004), carbohydrates-polysaccharides, mucilage and in flower and fruits flavanoids (glycosides of rutin, hyperoside and quercitin) are present (Singh, 2007). Essential fatty acids such as gamma linolenic acids, diosgenin, glucourbnides, quercetin and vitamin A are found in it, and its woody portion of tuberous roots

have kaepfrol along with sarsapogenin. Its roots have various sterols, *e.g.*, benzaldehyde, sitosterol and undecanylcetanoate and also trace minerals, *e.g.*, manganeese, copper, cobalt, zinc along with potassium, selenium and magnesium (Mohanat *et al*., 2003; Gadade and Patil, 2019).

5. (b) Biological role of *A. racemosus*

A. racemosus inhibited acetylcholinesterase enzyme in specific brain regions (prefrontal cortex, hippocampus and hypothalamus). Thus, it shows antiamnesic and nootropic activities in the models tested and these effects may be mediated through augmentation of cholinergic system due to its anticholinesterase activity and *A. racemosus* extract verified that significant decrease in latency time during retention trials. Hippocampal regions associated with the learning and memory functions and show dose dependent increase in acetylecholinstrase activity in carbonic anhydrase-1 with *A. racemosus* (Ojha *et al*., 2010, Sharma *et al*., 2010). Parihar and Hemnani (2004) conducted a study to investigate the potential of methanolic extract of *A. racemosus* roots against kainic acid (KA)-induced hippocampal and striatal neuronal damage in mice. Intra-hippocampal and intra-striatal injections of KA to anesthetized mice resulted in the production of excitotoxic lesions in the brain. After KA injection, impairment of hippocampus and striatal regions of brain was observed accompanied by increased lipid peroxidation, increased protein carbonyl content, decreased glutathione peroxidase (GPx) activity and reduced glutathione hormone (GSH) content. GSH is an important antioxidant which acts as a nucleophilic scavenger of toxic compounds and as a substrate in the GPx-mediated destruction of hydroperoxides which would otherwise accumulate to toxic levels in brain tissues. The mice treated with *A.racemosus* extract showed an enhancement in GPx activity and GSH content, and reduction in membranal lipid peroxidation and protein carbonyl. It is concluded that the plant extract plays the role of an antioxidant by attenuating free radical induced oxidative damage (Bhattacharya *et al*., 2002).

6. Conclusion

Currently, the CNS diseases, in particular the neurodegenerative disorders, constitute a serious health problem increasingly affecting the global population, involving a great morbidity and mortality. The current treatments available in clinics alleviate symptoms, but do not minimize the pathological conditions associated to these diseases. For example, the neuronal cells degeneration and the loss of dopamine production, in Parkinson's disease, thereby, for this disorder, there is a decrease of neurons, which are related to the loss of physiological, cognitive and intellectual functions, originating dementia. The complex organization and structure of the brain, as well as the existence of physiological barriers, such as the BBB and the blood-CSF barrier, difficult the delivery of drugs directly to the CNS, also these drugs have several side effects, along with lack of therapeutic efficacy. To overcome these drawbacks, several alternatives to conventional treatments have been developed. Among these, the most promising is the use of traditional medicines (*e.g.*, Neem, Karela, Pipalli, *etc.*). The progresses that have been made in this area outline the possibility of this application for the treatment of Parkinson's disease, in a near future, although more studies are needed.

Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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