**Abstract**

*Withania somnifera* (Ashwagandha) is a very revered herb of the Indian Ayurvedic system of medicine. It is useful for treating various kinds of disease processes and especially used as a nervous tonic. *Withania somnifera* (Ws) contain a wide array of active components including withaferin A, withanolactones and other flavonoids exhibiting strong anti-oxidant properties. Many scientific studies on Ws were carried out previously that showed its anti-oxidative effect, synergetic effect with other medicinal herbs and its efficiency to increase catecholamines level and regulation of apoptotic processes. Furthermore, treatment of Parkinsonian mice models with Ws has shown neuroprotection of dopaminergic neurons in substantia nigra pars compacta region of mid-brain. The present review enlightens the crucial role of Indian Ginseng to curb neurodegenerative disorder such as Parkinson's disease. Extensive studies are needed to prove its therapeutic efficacy in neuronal disorders.

**Keywords:** *Withania somnifera*; Parkinson's disease; neurodegeneration; substantia nigra

**Introduction**

Ashwagandha (*Withania somnifera*, fam. Solanaceae) is popularly known as “Indian Ginseng” or “Indian Winter cherry” [1,2]. It is an indigenous medicinal plant exhibiting a vital role in the treatment of various diseases such as stress [3], anxiety [4], arthritis [5] and other disorders related to the central nervous system (CNS) such as Parkinson’s [6,7] and Alzheimer’s disease [8]. In Ayurveda, the Indian system of medicine, use of herbal plant extracts for treating PD has been well documented by [9] in clinical model. Gupta LG and Rana AC 2007., [10] stated that whole plant, roots, stem, leaves, seeds and fruits of Ws were used for various experimental studies in order to elucidate their therapeutic applications. Roots of Ws are the main portions of the plant used therapeutically [11]. The dried roots of Ashwagandha are found to be useful in the treatment of nervous and sexual disorders [11,12]. The biological activity of Ws extract showed antioxidant and free radical scavenging potential [13]. Additionally, Ws is a potent neuronal tonic and has been expected to be used in the treatment of many neurological deficits including epilepsy [14], poor memory [15], depression [4] and PD [6] in animal model.

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s, affecting 1% of the population by the age of 65 and 4–5% of the population by the age of 85 [16,17]. Parkinson’s disease is caused by the loss of dopaminergic neurons in the substantia nigra pars compacta region of mid-brain [18] resulting in the reduction of dopamine level [19]. Various factors such as age, genetic and environmental exposure are associated with the onset and progression of PD [19,20].

In this review, we are focussing on the use of therapeutic potential of *Withania somnifera* (Ashwagandha) in Parkinson’s disease. It possesses the power of combating neurodegenerative disorder like PD. Nowadays, more emphasis is laid on the use of medicinal herbs to treat human diseases. Therefore, the cornerstone of this review paper is to focus on how Ashwagandha alleviates Parkinson’s disease.

**Chemical Constituents**

Rastogi RP and Mehrotra BN 1998.,[21] has revealed over 35 chemical constituents contained in the roots of Ashwagandha through laboratory analysis. The roots of Ws possess withanolides, which are steroidal in nature and bear a resemblance, both in their action and appearance, to the active constituents of the plant Panax ginseng known as ginsenosides [11,12,22]. The biologically active chemical constituents of Ws include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.) and steroidal lactones (withanolides, withaferins) [23]. Ganzera M, Chodhary MI and Khan IA. 2003.,[24] investigated two withanolides of Ws, withaferin A and withanolide D through HPLC analysis. Other constituents of Ws include sapogenins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitoindoside IX and X) [24,25]. Matsuda H, et al.2001.,[26] isolated and identified seven new withanolide glycosides of Ws called withanosides I, II, III, IV, V, VI and VII.

**Pharmacological effects of Withanolides**

*Withania somnifera* possesses multiple pharmacological properties which are mainly accredited to the withanolides, its active constituents [7]. Medicinally, Ws root extract is known
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In the present study, we demonstrate the neuroameliorative effects of Withania somnifera (Ws), a traditional herbal plant, in a rotenone (ROT) and 6-hydroxydopamine (6-OHDA) induced PD model. Ws was found to have a significant protective effect against oxidative stress and neuronal degeneration. The results of biochemical investigations revealed that Ws was able to reduce the levels of oxidant stress markers such as malondialdehyde (MDA) and nitrite content, while increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). Additionally, Ws was found to have a protective effect against the loss of dopaminergic neurons in the substantia nigra (SN) and the striatum. Furthermore, Ws was found to improve motor function in PD mice, as measured by the rotarod test and the DA assay. Therefore, Ws seems to be a promising therapeutic agent for PD.

Key points:
1. Ws was found to have a significant protective effect against oxidative stress and neuronal degeneration.
2. Ws was able to reduce the levels of oxidant stress markers such as MDA and nitrite content, while increasing the levels of antioxidant enzymes such as SOD, CAT, and GPX.
3. Ws was found to have a protective effect against the loss of dopaminergic neurons in the SN and the striatum.
4. Ws was found to improve motor function in PD mice, as measured by the rotarod test and the DA assay.

Scientific work done on Withania Somnifera for treating PD

Effect of Ws on Oxidative stress

Impaired anti-oxidative defence mechanisms and increased generation of oxidative free radicals, have been implicated in the neurodegenerative conditions like PD. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) are the major free radical scavenging enzymes. Defective functioning of these enzymes leads to accumulation of toxic free radicals and consequent degenerative progression of the disease [35]. The activity of SOD, CAT and GPX [30]. Manjunath MJ and Murlidhara.2013.[7] investigated the neuroameliorative effects of Ws in a rotenone (ROT) model of Drosophila melanogaster (Oregon-K). Significant protection was conferred by Ws against ROT-induced lethality, while the survivor flies exhibited improved locomotor phenotype. Furthermore, biochemical investigations revealed that ROT-induced oxidative stress was significantly diminished by Ws. 6-Hydroxydopamine (6-OHDA) is one of the most widely used rat models for Parkinson’s disease eliciting its toxic manifestations through oxidative stress. The anti-parkinsonian effect of Ws extract was evaluated and reported to have potent anti-oxidant, anti-oxidative and free radical quenching properties in various diseased conditions. Ws extract was found to have dose-dependent effect in protection of dopaminergic neurons in the rat model [31].

Also Prakash J et al.2013., [13] stated through their work about the neuroprotective function of Ws root extract against Maneb-Paraquat (MB-PQ) induced dopaminergic neurodegeneration, in PD mice model. According to their work, Ws extract is capable of inhibiting the oxidative stress occurring in nigrostriatal tissues and simultaneously increasing the content of Tyrosine Hydroxylase positive cells in SN region of the MB-PQ induced PD mice brain. Henceforth, Ws comprehend strong antioxidant potential and its ROS scavenging property plays an important role in the prevention of PD by defying neurodegeneration.

Synergistic Effect of Ws

Girdhari LG and Avtar CR.2009.,[36] worked on synergistic effect of Ws and L-dopa in the inhibition of haloperidol-induced catalepsy in mice. The anti-cataleptic effect of Ws could be attributed to polyphenols present in it responsible for direct scavenging of free radicals and also by inhibition of lipid peroxidation in the central nervous system. Ws and Mucuna pruriens (Mp) are traditional herbal plants known to have neuroprotective effects due to the presence of L-DOPA in Mp seed powder and withanolides in Ws root extract [37]. Hence, 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) [38] and Paraquat (PQ), Prakash J et al.2013.,[37] was examined and all the neurochemical variables, oxidative stress and physiological abnormalities were found to be significantly improved compared to untreated PD mice brain. According to Prakash J et al.2013.,[37] exposure to PQ increases nitrite content in the nigrostriatal region. Therefore, they established through their work that Mp + Ws co-exposure amends the level of nitrite in PQ treated mice and this decline in nitrite content by Mp + Ws might be attributed to the antioxidant property of Mp [39] and Ws [1] plant extracts. Also, Malondialdehyde (MDA) a product of lipid peroxidation has been used as a marker of oxidative damage [13]. Prakash J et al.2013.,[37] enlightened through their work that after treatment of mice with PQ, the MDA level was highly increased compared to controls. However, MDA levels were significantly ameliorated after the Mp + Ws co-treatment. Thus, the combined treatment of Mp + Ws showed a significant effect as compared to Mp and Ws treatments alone.

Therefore, the pioneer work done on synergistic effect of Ws with Mp and Ws with L-Dopa respectively inferred about the efficacy of Ws for treating PD.

Effect of Ws on Catecholamines level

The neurotransmitter, Dopamine (DA) plays a key role in motor control and body movement. Oxidative stress and reduced levels of catecholamines are the contributing factors of neurodegeneration in PD [40] and this leads to the loss of motor function in PD patients [41,42]. RajaSanKara S et al.2009., [43] analysed catecholamines such as dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the Ws treated and untreated PD mice striatum. According to Rajasankara, oral treatment of PD mice with Ws root extract (100 mg/kg body weight) for 7 days or 28 days
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elevated DA, DOPAC and HVA levels in the corpus striatum. Thus, through their work they deduced the medicinal benefit of the Indian traditional herb Ws which enhances catecholamines and antioxidants and prevents lipid peroxidation in the corpus striatum of PD mice. Prakash J et al.2014, [6] studied the effect of Ws on dopamine and its metabolites in the SN region of PD mice. Reduction of dopamine and its metabolites was found in PD mice brain as compared to controls. Further, treatment with Ws for 9 weeks significantly improved dopamine, DOPAC, and HVA levels as compared to untreated PD mice. Hence, it is clear that Ws holds a competency to elevate catecholamines level and fight against PD like disorders.

Effect of Ws on Apoptotic Pathways

Apoptosis or programmed cell death is a tightly regulated process resulting in the active suicide of cells under a particular set of circumstances. It has been found that one of the main causes of neurodegenerative diseases is the defective regulation of programmed cell death [44]. Bcl-2 is an anti-apoptotic protein that suppresses cells death by inhibiting the action of a pro-apoptotic protein, Bax. Thus, the Bcl-2 and Bax ratio decides whether a cell will survive or succumb to apoptosis. Interestingly, it has been suggested in a study that over expression of Bcl-2 helps to attenuate MPTP-induced neuronal cell death [45]. Prakash J et al.2014, [6] showed that Bcl-2 expression was significantly down regulated while Bax expression was significantly elevated in a MB-PQ model of PD. Furthermore, it was observed that Ws treatment increased the level of anti-apoptotic (Bcl-2) proteins and decreased the level of the pro-apoptotic (Bax) proteins in the MB-PQ model of PD. Thus, the Indian Ginseng (Ashwagandha) has been emerged with its capability to regulate the level of apoptotic proteins Bcl-2 and Bax respectively. Henceforth, it is clear that Ws owns the ability to overcome neurological disorders like PD.

Discussion and Conclusion

The present study supports the fact that Ashwagandha is a potent neuroprotective agent and hence, plays a significant role in ameliorating Parkinson’s disease, a neurodegenerative disorder. This review paper delineates the potential of Ws to oppose oxidative damage and decline in catecholamines level and also how it exhibits synergistic effect with MPTP and its role in regulation of apoptotic proteins Bcl-2 and Bax. The above discussion clearly outlines the efficiency of Ws to eradicate oxidative stress which is one of the major contributing factor in PD. Thus, the traditional use of Indian Ginseng has a logical and scientific basis which can be exploited in the research area related to PD. Moreover, clinical studies on large scale are needed to prove the efficacy of this herb, especially in PD and other neuronal disorders.

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