Review paper

Therapeutic potential of *Withania somnifera* in CNS disorders: A neuropharmacological review.

Abstract:

Context: According to the Ayurveda which is the oldest system of Medicine in the world defines the medicinal plant as Medhya Rasayana who shows the brain tissue specific properties. Medhya Rasayana can retard brain aging and can help in different central nervous system (CNS) disorders. *Withania somnifera* (Ashwagandha) is one of the medhya Rasayana and it has medicinal properties to treat several CNS disorders.

Objective: Research in the area of alternative medicine has come up with several options to treat the disorders of CNS. However, a comprehensive review of such a potent medicinal plant; *Withania somnifera* in different CNS disorders has been absent to date. The present review focuses on the effects of phytochemicals isolated from *Withania somnifera* on different types of central nervous system CNS disorders.

Materials and methods: Numerous animal and in vitro studies have been conducted on *Withania somnifera*, which advocates strong potential medicinal properties of this herbal drug. We reviewed the MEDLINE database to identify experimental studies conducted using *Withania somnifera* in several CNS disorders.

Results: Our present study has shown that *Withania Somnifera* has a very potent role in the treatment of CNS disorders i.e. Parkinson disease, Alzheimer's disease, Epilepsy, Anxiety, OCD, Hypoxia, Huntington's disease, Catalepsy and Bipolar disorder. *Withania somnifera* act on several neurotransmitters to treat these CNS disorders.

Discussion and conclusion: WS demonstrates remarkable potential in the amelioration of CNS disorders, with anticancer, anti-inflammatory, anti-stress, anti-depressant and anti-anxiety effects.

Key words

Withania Somnifera, CNS disorders, alternative therapy, Ashwagandha, herbal drug, phyto- therapy.

1. Introduction:

Withania somnifera (L.) dunal (Ashwagandha) used as a traditional Indian medicine since long. [1]–[3] also characterized as Rasayana (rejuvenation).[4]

The perennial shrub of Solanaceae family *W. somnifera*, have gained recognition as a treatment for mental disorders and various health conditions.[5] It has been used for treatment of anxiety,[6] neuronal degeneration,[7]–[11] epilepsy,[12-13] depression,[14] sleep,[15] memory[5,16,17] and many other CNS diseases.

The withanolides have been shown to have properties i.e anticancer, [18-20] anti-inflammatory,[21] anti-stress,[22] anti-depressant and anti-anxiety effect [23] antioxidant property,[24] memory enhancing,[25] anti-convulsant[26] and Immune-modulating.[27]

Ashwagandha is a natural source of alkaloids, steroidal lactones, saponins with an additional acyl group and withanolides with $C_6H_{12}O_6$ at C-27 position [24] and till now 35 chemical have been discovered, extracted and isolated from roots of WS.[28] The main component of *W. somnifera* is withanolide, derivative of steroids and rich of iron.[2]

2. Common name:

W. somnifera has several common names; Ashwagandha, winter cherry or Indian Ginseng.[2] This plant is known by different names in different part of India; Punir (in Hindi), Aksan (Punjab), Tilli (Marathi), Ashvaganda (Benagl, Bombay).[26] Other than this, withanolides in *W. somnifera* have structural resemblance with ginsenosides, active chemical compound present in 'Panax ginseng', therefore it is known as "Indian Ginseng."[29,30]

2.1 Classification of *W. somnifera*

Kingdom : Plantae
Division : Angiosperms
Class : Dicotiledoneae
Order : Tubiflorae
Family : Solanaceae
Genus : Withania
Species : somnifera

2.2 Biochemical constituents:

In commonly known form of *W. somnifera*, 35 chemicals have been identified and isolated from roots of shrub out of which withanolide A, withanoside IV, and withanoside VI are found to be most active [28] and withaferin A is the most studied component of *W. somnifera (fig.1).*

Previous research demonstrated spectroscopic and physiochemical methods to isolate 5 new derivatives from roots of Ashwagandha.[31] Several reports have shown presence of alkaloids, steroidal lactones and saponins also present in minor quantity.[9,32] Apart from these, *Withania Somnifera* also contains starch, acylsteryl glucosides and amino acid, like tryptophan, alanine, glycine, and tyrosine, aspartic acid.[9]

Other than withanoilde, several alkaloids; choline, pseudo-withanine, somniferine, somnine, tropine, pseudotropine, 3-a-gloyloxytropane, isopelletierine and anaferine andanahydrine were also discovered.[33,34]

3. Complementary and Alternative medicine:

Despite of advancements in western medicines CAM appears to raise folk medicine towards modern pharmacology that may consider safer and more effective.[35,36] Chemically synthesized allopathic drugs showed adverse effects both physically and economically.[37] Although, many antiepileptic drugs present to treat epilepsy but many of them shows chronic toxicity and teratogenic effects on human brain.[38] Similarly, benzodiazepines prescribed in treatment of bipolar disorder and several psychotic diseases may cause anxiety and insomnia[39,40] if chronically used. Here, the use of alternative medicine comes in demand.

If we talk about CAM in CNS disorder, EEG and neuroimaging techniques detects the autoregulation and physiology of CAM in CNS and result shows similar structure involvement in different therapeutic approaches.[41] Herbal medications hope to overcome negative effects of synthetic drugs with curing the diseases by lowering the side effects and by focusing on the cause of disease instead of symptoms only.[37]

4. *W. somnifera* in CNS diseases:

To overcome the therapeutic limitations and side effects of western synthetic medicines,[37] herbal treatment was found to be effective in several CNS disorders. *Withania Somnifera* widely used to treat diseases from normal infection to cancer,[42] but their excessive use in nervous system disorder currently comes in limelight.[24] Neuromodulation of GABAergic[43,44] or cholinergic pathway[45] is considered in treatment of these types of CNS disorders via inhibiting excitotoxicity and oxidative damage conditions.[46]

4.1 Parkinson disease:

Parkinson's disease is most common neurodegenerative disorder in aged people.[47] Age, environmental and genetic factors cause loss of dopaminergic neuron leads to tremor, rigidity and postural instability in patients.[48-50] Several studies found that root extract of *W. somnifera* at pharmacological concentration enhance oxidative status by reducing lipid peroxidation level[51] or by increasing number of TH (Tyrosine hydrolase) positive cell in substantia nigra.[10] *W. somnifera*, 100mg/kg body weight for 7 or 28 days reduced the level of Catecholamines: dopamine (DA), 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA); antioxidants: glutathione (GSH)

and glutathione peroxidase (GPx); and lipid peroxidation marker (TBARS) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced model of PD.[11] In a clinical trail, 18 clinically diagnosed parkinsonian patients were traeted with a concoction in cow's milk of powdered *Mucuna pruriens* and *Hyoscyamus reticulatus* seeds and *W. somnifera* and *Sida cordifolia* roots for 28 days in cleansing therapy and for 56 days in palliative therapy. [52] This study also establishes the necessity of cleansing therapy in Ayurveda medication prior to palliative therapy. Hence *W. somnifera*, could be a promising CAM therapy for Parkinson's disease due to its potential anti-oxidant, anti-peroxidative and free radical quenching properties.

4.2 Alzheimer's disease:

Progressive neurodegenerative Alzheimer's disease (AD) is recognized to cause several abnormalities including memory loss, anxiety, language deficit, depression, mood disturbance and stress.[38] Significant causes of these impairments are cholinergic neuron degeneration, toxic β-Amyloid plaques, neurofibrillary tangles and neurochemical deficiencies.[53] Although, direct target molecule of *W. somnifera* has not been identified yet,[54] but root extract of *W. somnifera* shows potential neuroprotective effects against H2O2- and β-Amyloid cytotoxicity during Alzheimer's disease. Some researchers also believe that dried root abstract of *W. somnifera* enhances liver LRP (low density lipoprotein receptor- related protein) and decreases β-Amyloid formation by Aβ-degrading protease neprilysin (NEP) in brain.[55] There are lots of active ingredients of WS but few are very active like withanolide A, withanoside IV, and withanoside VI. Role of these ingredients in neurodegenerative diseases have been reported as they improves memory impairment, neurite atrophy, and synaptic loss in the cerebral cortex by restoring presynapses and postsynapses both In axons and dendrites in cortical neurons. The effect of herb has been found both in neurons as well as in glial cells. Further studies on Ashwagandha may lead to important leads which may help to solve urgent need in AD treatment.

4.3 Epilepsy:

The metabolic profile of *W. somnifera* includes restoration of imbalance in GABA / glutamate modulation[56] and higher serum level of peptide hormone, Ghrelin.[57] Despite the availability of anti-epileptic drugs, either the cost or difficulty to access with physicians[58] or adverse side effect of AED[59] make allopathic drugs less concerned in epilepsy. *W. somnifera* acts as CAM in epilepsy treatment.[60] It shows antioxidative mechanism, increases GABA level & cortical muscarinic ACh and enhances neutrite regeneration in brain.[5] This inexpensive and culturally acceptable herbal therapy may open new doors for epileptic patients around the world.[60]

4.4 Anxiety:

It's a widespread psychopathological disorder associated with unpleasant emotional state shows lifetime prevalence leads to depression, somatic distress and low self-esteem.[6,61] Neurotonic effect of root withanoildes produces GABA-mimetic activity in treatment of anxiety.[43,62] Still, unidentified dosing of *W. somnifera* may cause intolerable side effects on human.[63]

4.5 OCD:

This mental disorder characterized by persistent and distressed thought (Obsessions) with repeated egoistic behavior (compulsion).[64] It causes impairment in serotonergic & dopaminergic system[65], [66] with pathological defects, observed in orbitofrontal cortex, dorsolateral PFC and ant. cingulate cortex.[67] WS poses anxiolytic & anti-depressent properties, therefore considered in OCD treatment.[64] Methanolic and aqueous root extract of Ashwagandha increases serotonergic transmission[14,64] via effecting $5HT_{2A/2C}$ receptors in brain.

4.6 Hypoxia:

Hypoxia is considered as generation of superoxide radicals in less availability of oxygen[68] which causes hippocampal neurodegeneration and cognitive dysfunction includes memory impairment.[69], [70] Withanolide A maintains balance of corticosterone level by increasing minerlocorticoid receptor expression and decreasing glucocorticoid expression in hippocampus. This signalling pathway plays a vital role in memory and neuronal survivability.[70]

4.6 Huntington's disease:

HD is also a neurodegenerative disease identified by neuronal destruction in basal ganglia [71] accompanied by progressive motor dysfunction, chorea, dystonia, emotional disturbances, memory, and weight loss.[72] HD can be induced by introducing oxidative stress factor (i.e. 3-Nitropropionic acid) in experimental animals. In pathophysiology of the HD; GABA and enkephalin neurons of basal ganglia plays an important role[38,73] along with molecular alteration in (NMDA) receptors.[74] Polyglutamine stretches formed by Cytosine-Adenine-Guanine (CAG) repeats with the increasing age is highly correlated with the HD.

W. somnifera act by GABAergic system aberrance of which is a major cause of most of the neurological disorder. WS root extract corrects the major imbalance in GABAergic system and improves cognitive function, acetyl cholinesterase enzyme activity and glutathione enzyme level in experimental animal model of HD. Treatment with *W. somnifera* restores impaired motor function and other cognitive deficits. The antioxidant property of the WS root extract makes it a potential leader to treat HD.[75]

4.7 Catalepsy:

Neuroleptic catalepsy can be reversed by D1 & D2 receptor agonist[76] and *W. somnifera* play important role in this as with combination of other drugs, NR-ANX-C (*Withania Somnifera*, *Ocimum sanctum, Camellia sinensis*, triphala and shilajit).[77]

4.8 Bipolar disorder:

Cognitive impairments with frequent mood fluctuations are easily observed in bipolar disorder.[78] Anxiety and insomnia are commonly observed symptoms[39,79] in this disorder. Limited treatment availability makes herbal medication an attractive tool.[80] Very few studies of *W. somnifera* on bipolar disorder reported functional recovery in patients.[81] A reduction in insomnic and anxiety

condition with auditiory-verbal working memory improvement also observed in *W. somnifera* treated subjects.[82]

5. Conclusion:

CNS disorders are one of the major threats of modern life and are considered as the most disabling disease which is a big burden on the society. Millions of people every year disable with different types of CNS disorders despite tremendous efforts to find methods of control and cure. Although great advances were made in modern medical science to control disease but many diseases like Autism are not yet curable fully. The underlying mechanism leading up to CNS disorders are still unknown and most of them remain a mystery disease. To find out newer, safe and effective therapeutics, scientists are evaluating some medicinal plants and herbs which are a rich source of a variety of chemicals with nutritive and therapeutic properties. World-over the pharmaceutical companies and research organizations are focusing on the vast untapped potential of herbals as potent drugs.

W. somnifera demonstrates remarkable potential in the amelioration of CNS disorders, with anticancer, anti-inflammatory, anti-stress, anti-depressant and anti-anxiety effects. The results of some powerful studies indicated that at least part of the chronic stress-induced pathology may be due to oxidative stress, which is mitigated by W. somnifera. [83] Use of alternative medicine is growing as the side effects of allopathic medicine increasing. In such a condition biomedical research on W. somnifera can open new gates towards the treatment of CNS and other disorders.

W. somnifera is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to increase energy, improve overall health and longevity, and prevent disease in athletes, the elderly, and during pregnancy [85]. WS is well known for its other biological activities like anti-parkinsonism [48-50], anti- Alzheimer's [54-55], anti-epileptic [59-60], anti-anxiety [43,62], anti-Huntington [73-74] and anti-catalepsy [77]. All the important studies using W. somnifera have been listed in the table no. 1 and the results of the studies described in table no. 1 shows its chemical ingredients are effective in prevention and treatment of different kinds of CNS disorder like Parkinson, epilepsy, Huntington and bipolar disorder (Fig. 2).

Therefore, the use of W. somnifera as multi-dimentional traditional medicine has resulted into several commercial drugs and therefore W. somnifera ranks a valuable plant in the pharmaceutical industries. this medicinal plant W. somnifera alone can be used as complementary and alternative medicine (CAM) in the treatment of CNS disorders. All the described studies shows that the W. somnifera work as adaptogen/ anti-stress agent, immunomodulator, antioxidant (reducing free radical damage, anabolic effect, improving resistance of body, reducing fatigue and detoxificant effects makes it the best complementary and alternative medicine (CAM). Although, the phyto-chemistry and pharmacology of W. somnifera has been widely investigated in several diseases, yet the studies on

protective effect of the extracts of the plant parts in different neurodevelopmental disorders are very few. Although it is required to identify the novel clinical properties of the plant in case of some neurodevelopmental disorders like autism spectrum disorder, the severe disorder in which the drug therapy is very limited.

Here, we are able to suggest that the other diseases which happens due to or result in imbalance in above said mechanism like autism spectrum disorder (ASD), W. somnifera may be very useful.

6. Future perspective:

Complexity of CNS disorders and many adverse effect of western medicine highly support herbal drug therapy in future. The use of *W. somnifera* as multi-dimentional traditional medicine has resulted into several commercial drugs and therefore W. somnifera ranks a valuable plant in the pharmaceutical industries. The phyto-chemicals and pharmacology of W. somnifera has been widely investigated in several diseases. Beside the CNS disorders we discussed in this review, there are numbers of CNS disorder on which the studies on protective effect of the extracts of the plant parts are not tested i.e. dementia, autism and other neurodevelopmental disorders. Although it is required to identify the novel clinical properties of the plant in case of some neurodevelopmental disorders like autism spectrum disorder, the severe disorder in which the drug therapy is very limited. Still lots of research are required to fully characterize the mechanism of action in CNS disorders of phyto-chemicals of *W. somnifera*.

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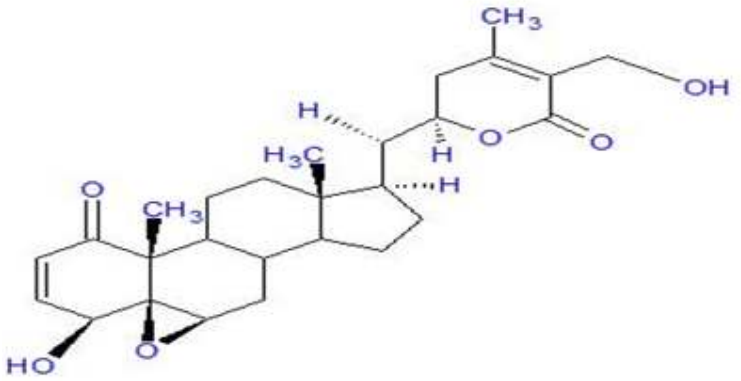

Fig 1: Structure of an important withanolide of *withania somnifera* (withaferin A).

Fig 2: *Withania somnifera* acts on different molecular parameters to treat several CNS disorders.

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S. No.	Disease	Inducer	Treatment	Dose	Treatment Duration	Evaluated parameters	Result	Ref.
1.	PD	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Withania somnifera root extract	100mg/kg body weight	7 or 28 days	DA, DOPAC, HVA, GSH and GPx	Reduced levels of DA, DOPAC, HVA, GSH and GPx.	11
2.	PD	6-Hydroxydopamine (6-OHDA)	Withania somnifera extract	100, 200 and 300 mg/kg body weight	3 weeks	lipidperoxidation, reduced glutathione content, activities of glutathione-S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression	Reverse all the parameters significantly.	83
3.	PD	1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP; i.p, 20 mg/kg body weight for 4 days),	Withania somnifera (Ws) root extract	100 mg/kg body weight	4 weeks	thiobarbituric acid reactive substance (TBARS), and increased activities of superoxide dismutase (SOD) and catalase (CAT)	Significant improvement in the mice's behavior and antioxidant status, along with a significant reduction in the level of lipid peroxidation.	51
4.	Alzheimer's disease	APP/PS1 Alzheimer's disease transgenic mice.	WS extract	1 g/kg	7-30 days	plasma and brain Aβ, Behavioral Deficits and Plaque Pathology	Reversed behavioral deficits, plaque pathology, accumulation of β-amyloid peptides (Aβ) and oligomers in the brains of middle-aged and old APP/PS1 Alzheimer's disease transgenic mice.	55
5.	Epilepsy	PTZ	WS extract	100 or 200 mg/kg,	-	seizure threshold	increased the seizure threshold	5
6.	Hypoxia	simulated altitude of 25,000 ft	*Withania somnifera* root extract	10 µmol/kg	21 days pre-exposure and during 07 days of exposure to a simulated altitude of 25,000 ft	expression of GCLC and Nuclear factor (erythroid-derived 2)–related factor 2 (Nrf2) and glutathione (GSH) level .	suppressed Nrf2 and GCLC expression whereas inhibition of corticosterone synthesis upregulated Nrf2 as well as GCLC	70
7.	obsessive compulsive disorder	marble-burying behavior	methanolic extract W. somnifera	10, 25, 50, 100 mg/kg	30 min. prior to the assessment	marble burying behavior	successively decreased the marble burying behavior activity without affecting motor activity	64
8.	Catalepsy	haloperidol (1mg/kg)	NR-ANX-C, a polyherbal formulation containing bioactives of Withania somnifera Ocimum sanctum, Camellia sinensis, triphala and shilajit	25 mg/kg		The superoxide dismutase (SOD) level in brain tissue	Significant (P<0.01) reduction in the cataleptic scores and reduction in SOD activity was observed in NR-ANX-C (25 and 50 mg/kg) treated groups	77

454 Table 1. Important studies on few of CNS disorders, their model, type of treatment, doses, time of
455 treatment, evaluated parameters and results.

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