



A Review On Ashwaganda In Brain Disorder

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ABSTRACT:

Ashwagandha (*Withania somnifera*), a well-known herb in traditional Ayurvedic medicine, has gained significant attention for its potential neuroprotective and therapeutic effects in managing various brain disorders. Research suggests that ashwagandha may offer benefits in conditions such as Alzheimer's disease, Parkinson's disease, depression, anxiety, and other neurodegenerative and neuropsychiatric disorders. The bioactive compounds in ashwagandha, including withanolides, are believed to exhibit anti-inflammatory, antioxidant, and adaptogenic properties, which help mitigate oxidative stress and neuroinflammation—key contributors to brain disorders. Studies have also indicated its potential role in modulating neurotransmitter systems, enhancing neuronal regeneration, and improving cognitive functions. Given its multifaceted mechanisms, ashwagandha holds promise as an adjunct therapy in brain disorders, although further rigorous clinical trials are needed to substantiate its efficacy and safety profile. This review critically examines the current literature on the therapeutic potential of ashwagandha in brain health and highlights areas for future research.

KEYWORDS : Ashwaganda , Phytoconstituents, Common brain disorders, Anxiety, Alzheimer's Disease, Parkinson's Disease , Recent patents.

INTRODUCTION :

The rise in brain disorders, encompassing neurodegenerative diseases (such as Alzheimer's and Parkinson's), mood disorders (like anxiety and depression), and age-related cognitive decline, has highlighted the urgent need for effective treatments and preventive strategies. Ashwagandha, often referred to as a "rasayana" (rejuvenator) in Ayurveda, has emerged as a candidate for brain health due to its adaptogenic and neuroprotective properties. Ashwagandha's bioactive compounds, particularly withanolides, are believed to counteract neurodegeneration, mitigate oxidative stress, modulate neurotransmitters, and reduce inflammation—properties that may help in the treatment and prevention of various brain disorders.

Mental health issues and neurological disorders are significant public health concerns globally, affecting over a billion individuals worldwide. Current treatments for neurological disorders in modern medicine primarily offer symptomatic relief, which can be costly and often accompanied by various side effects. Natural products have long been valued as a rich source for therapeutic agents, with many medicines derived from plant-based extractions and fractionations. These are increasingly recognized for their benefits in human health.

Today, medical practitioners are showing a growing interest in natural medicines, which are trusted for their cost-effectiveness and reduced side effect profiles. Ayurveda, a traditional Indian system of medicine, has developed specific protocols for managing and treating brain-related disorders. Ayurveda lists approximately 450 medicinal plants, including 56 key plants or their constituents used in treatments for neurological conditions (Balkrishna and Misra, 2018).

Table 1:

Marketed herbal formulation of Ashwagandha in brain disorders

SR. NO	Name of the formulation	Uses	Manufacture
1	Stresswin	Relieve stress, Antidepressant, Memory enhancement	Baidyanath Ayurved Bhawan
2	Stresscom	Relieve stress, Antidepressant	Dabur India Ltd.
3	Ashwagandharista	Memory enhancement, sleep induction Antistress	Baidyanath Ayurved Bhawan The Himalaya Drug Company
4	Himalaya Ashwagandha	Antistress	The Himalaya Drug Company
5	Brento	Nervine tonic	Zandu Pharmaceutical Works Lt
6	Stress Shield Antistress, Antianxiety Cureveda	Antistress, Antianxiety	Cureveda
7	Golden Milk	Memory enhancement	Gaia

• Phytoconstituents of Ashwagandha:

Ashwagandha contains a variety of non-nutritional compounds responsible for its medicinal properties. Over 35 phytochemicals have been isolated and identified in Ashwagandha. The primary chemical constituents are alkaloids and steroidal lactones. The alkaloids present in Ashwagandha include somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropine, cuscohygrine, and anaferine, with withanine being the predominant one. The main steroidal lactones are withaferin A, withanolides A-Y, withasomniferin-A, withasomidienone, withasomniferols A-C, and withanone. The major phytoconstituents of Ashwagandha are illustrated in and their respective properties in brain disorders are summarized in Table 2.

Table 2 :

Various neuroprotective properties of phytoconstituents of Ashwagandha in preclinical models.

Phytoconstituents	Type of study	Part used for isolation	Dose/IC50	Model/Method	Inference	Reference
Withaferin A (Glutathione conjugate CR-777)	In-vitro	Roots	27.1 μ M	Mesencephalic neurons exposed to MPP + injury, 6-OHDA injury and α -Synuclein injury	Neuroprotective, suppress oxidative stress (α -Syn aggregation via the induction of the cytoprotective PI3K/mTOR pathway)	Rabhi et al. (2019)
Withaferin A	In-vitro	—	2 μ M	SH-APP cells (a human neuroblastoma cell line) transfected with HIV-1 Tat (5–100 ng/ml) and coc (0.1–10 μ M) to induced neurotoxicity	Reduction in secreted A β and induced neurotoxicity in amyloid precursor protein (APP) plasmid transfected SHSY5Y cells (SHAPP)	Tiwari et al. (2018)
Withanolide A, withanolide B and withaferin A	In-vitro	Roots	In-vivo Roots 5, 10 and 20 mg/kg (intraperitoneally)	Nicotine (1mg/kg) Induced conditioned place preference in male albino mice	Anti-addictive (reversing nicotine induce conditioned place preference)	Dumore et al. (2019)
Withanolide (aqueous fraction)	In-vitro	Roots	12.5, 25, 50 and 100 mg/kg (orally)	Hypoxia time, antifatigue effect, swimming performance time, swimming induced gastric ulceration and hypothermia, immobilization induced gastric ulceration, autoanalgesia	Anti-stress activity in dose dependent manner	Singh et al. (2001)
Withanone	In-vitro	—	20 μ M	10 μ M retinoic induced neuronal distortion on Neuro2A (N2a) mouse neuroblastoma cell line followed by 3-mM NMDA	Neuroprotective effects of Withanone followed by reduction in oxidative stress and pro-apoptotic cytokines	Dar et al. (2017)

• Common brain disorders :

The term brain disorder extends beyond just conditions associated with insanity and severe mental derangement; it also encompasses various emotional disorders. When emotional factors exceed normal limits, they may develop into syndromes that are classified as mental disorders. The human brain contains approximately 100 billion neurons, each connecting with many others to form complex communication networks. These neurons are responsible for vital functions, such as thinking, learning, remembering, as well as processing sensory experiences like seeing, hearing, and smelling. Brain cells operate like tiny factories—they receive supplies, generate energy, build cellular structures, and eliminate waste. Additionally, brain cells are essential for processing and storing information. Brain cells process and store information to communicate with other cells, requiring large amounts of fuel and oxygen for optimal functioning and coordination. Common brain disorders are summarized in Fig. 1.

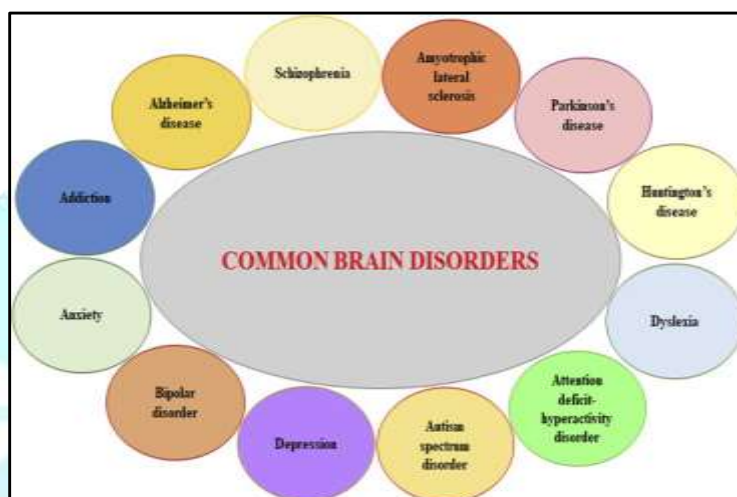


Fig 1 Common brain disorders

• Ashwagandha in Anxiety :

Anxiety is defined as "an emotion characterized by feelings of tension, worried thoughts, and physical changes." Overconsumption of highly palatable and calorie-dense foods contributes to a chronic positive energy balance, where energy intake exceeds expenditure, leading to increased body fat, weight gain, and ultimately, obesity (Dinh et al., 2015). Additionally, the consumption of high-calorie foods has been linked to various neuropsychiatric disorders, including anxiety, mood disorders, and binge eating (Castanon et al., 2014).

Studies on Ashwagandha leaf powder extract suggest that it possesses anti-anxiety, anti-inflammatory, and anti-apoptotic properties. These properties may be beneficial in preventing or slowing the adverse effects of obesity and related disorders (Kaur and Kaur, 2017).

The hydroalcoholic extract of Ashwagandha roots has demonstrated significant anti-stress activity (Singh et al., 2011). In one study, an alcoholic extract of Ashwagandha root and seed was administered to mice (100 mg/kg, intraperitoneally, as a single dose) and the impact on swimming performance was observed. Results showed that the swimming duration of Ashwagandha-treated mice doubled compared to the control group, indicating that Ashwagandha induced a state of nonspecific increased resistance to stress (Mishra et al., 2000; Singh et al., 2010).

Research conducted at the Department of Basic Medical Sciences, Calcutta University, also supports Ashwagandha's significant anti-stress adaptogenic effects. Their studies on rodents exposed to chronic stress (21-day electric foot shocks) confirmed its role in mitigating stress-induced hyperglycemic responses. Prolonged exposure to chronic stress in animals, such as repeated electric foot shocks over 21 days, has been shown to cause various adverse effects, including hyperglycemia, glucose intolerance, gastric ulcers, male sexual dysfunction, cognitive deficits, immunosuppression, and mental depression. Administering

Ashwagandha extract one hour before the shocks significantly reduced these stress-related effects (Singh et al., 2008). Ashwagandha was found to decrease neuronal activity and prevent nerve cells from excessive firing. Additionally, it exhibits GABA-like activity, which may contribute to its anti-anxiety effects (Singh et al., 2010).

Ashwagandha in Anxiety Management :

Anxiety is a mental health condition characterized by feelings of excessive worry, tension, and physical symptoms such as increased heart rate and muscle tension. Various lifestyle factors, including poor diet, stress, and lack of exercise, contribute to the onset and exacerbation of anxiety. Ashwagandha (*Withania somnifera*), a key herb in Ayurvedic medicine, has been traditionally used as an adaptogen—an agent that helps the body adapt to stress. Recent research supports Ashwagandha's effectiveness in managing anxiety through several mechanisms.

1. Anti-Anxiety and Adaptogenic Properties

Ashwagandha is known for its adaptogenic properties, meaning it enhances the body's resilience to stress. A study conducted on Ashwagandha leaf powder extract demonstrated significant anti-anxiety, anti-inflammatory, and anti-apoptotic effects (Kaur and Kaur, 2017). These properties are beneficial not only in reducing anxiety but also in managing other stress-related conditions like inflammation and cellular stress.

2. Anti-Stress Effects in Animal Studies

Studies on the root extract of Ashwagandha have demonstrated substantial anti-stress activity. For instance, an alcoholic extract of Ashwagandha root and seed administered to mice (100 mg/kg, intraperitoneally) improved their stress tolerance, as shown by an increase in swimming duration during forced swim tests. The swimming time of Ashwagandha-treated mice doubled compared to control mice, indicating that Ashwagandha may increase resistance to stress (Mishra et al., 2000; Singh et al., 2010).

Another study by Singh et al. (2011) on a hydroalcoholic root extract showed similar anti-stress effects, providing further evidence of Ashwagandha's role in stress resilience.

3. Impact on Chronic Stress-Induced Conditions

Research by the Department of Basic Medical Sciences at Calcutta University tested the effect of Ashwagandha on chronic stress in rodents subjected to electric foot shocks for 21 days. The chronic stress led to a range of physiological and behavioral disruptions, including hyperglycemia, glucose intolerance, gastric ulcers, cognitive impairment, immunosuppression, and depressive symptoms. Ashwagandha extract, administered an hour before each shock, significantly mitigated these effects, reducing stress-related responses and physiological changes (Singh et al., 2008).

4. Modulation of Neurotransmitter Activity

Ashwagandha's anti-anxiety effects may also be linked to its impact on neurotransmitter systems. It appears to have GABA-mimetic (gamma-aminobutyric acid) properties, which means it may enhance the calming effect of the GABA neurotransmitter, known for its inhibitory action in the central nervous system. This GABAergic activity may reduce excessive neuronal firing, thereby promoting a sense of calm and reducing anxiety (Singh et al., 2010).

5. Clinical Evidence of Anti-Anxiety Benefits

Clinical studies on humans have also supported Ashwagandha's role in managing anxiety. In a double-blind, placebo-controlled study, participants with a history of chronic stress who took Ashwagandha extract showed significant reductions in anxiety levels compared to those in the placebo group. They also experienced improved overall well-being, indicating Ashwagandha's potential as a natural anxiolytic.

• Ashwagandha in Alzheimer's Disease :

Alzheimer's disease is a neurodegenerative disorder primarily characterized by progressive memory loss and an irreversible decline in cognitive functions. Various in vitro and in vivo studies have highlighted the therapeutic effects of Ashwagandha and its phytoconstituents in managing Alzheimer's disease.

Recent research has investigated the anti-Alzheimer's potential of constituents in Ashwagandha root extract, identifying Withanone as particularly effective. Withanone significantly inhibits amyloid β -42, a key factor in Alzheimer's pathology, and enhances the activity of acetylcholine, glutathione, and β - and γ -secretase enzymes, while also reducing levels of pro-inflammatory cytokines (Pandey et al., 2018).

Another key compound, Withanolide-A, has been shown to inhibit human acetylcholinesterase, as demonstrated through high binding affinity in docking simulation studies (Grover et al., 2012). Acetylcholinesterase inhibition helps improve acetylcholine levels, which may benefit memory and cognition in Alzheimer's patients.

In studies by Sehgal et al., a semi-purified Ashwagandha root extract rich in withanolides and withanosides demonstrated neuroprotective effects. This extract countered β -amyloid and hydrogen peroxide-induced cytotoxicity in Alzheimer's disease models (APP/PS1 transgenic mice and APPSwInd mice, line J20) by upregulating the lipoprotein receptor-related protein in the liver, which is involved in clearing amyloid beta (Sehgal et al., 2012).

Ashwagandha at a dose of 100 mg/kg has also shown protective effects against acetylcholinesterase (AChE) inhibition and cognitive impairment, particularly in cases of propoxur-induced cognitive deficits in rats (Yadav et al., 2010). Additionally, methanolic chloroform extract of Ashwagandha has demonstrated high cell viability and enhanced PPAR- γ levels, as well as restored cellular morphology in β -amyloid-infected SK-N-MC cell lines (Kurapati et al., 2013).

Further studies have shown that an aqueous extract of Ashwagandha containing Withanolide derivatives, including Withaferin A, protects differentiated PC12 cells from β -amyloid and hydrogen peroxide-induced cytotoxicity (Kumar et al., 2010).

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, primarily marked by memory loss and cognitive decline, which is attributed to the accumulation of amyloid-beta ($A\beta$) plaques, tau protein tangles, oxidative stress, inflammation, and neuronal damage. Ashwagandha (*Withania somnifera*), a well-known adaptogen in traditional Ayurvedic medicine, has gained attention for its neuroprotective properties that could benefit Alzheimer's treatment.

1. Key Bioactive Compounds in Ashwagandha

The neuroprotective effects of Ashwagandha are largely attributed to its bioactive constituents, including withanolides, withanosides, withaferin A, and withanone. These compounds interact with key biochemical pathways implicated in Alzheimer's, making them promising for therapeutic use.

2. Amyloid-Beta ($A\beta$) Plaque Inhibition

One of the central mechanisms in Alzheimer's is the accumulation of amyloid-beta plaques, which disrupt neuronal function. Research has identified Withanone, a component of Ashwagandha root extract, as effective in inhibiting $A\beta$ -42 peptide, a major contributor to plaque formation. By reducing $A\beta$ -42 levels, Withanone may help protect against the toxic effects of amyloid-beta accumulation (Pandey et al., 2018).

Study Insight: In a study by Pandey et al. (2018), Ashwagandha root extract was found to not only inhibit $A\beta$ -42 but also boost the activity of enzymes like acetylcholine and glutathione, known for their roles in cognition and cellular protection, respectively. It also increased levels of β - and γ -secretase enzymes, which assist in the breakdown of amyloid-beta, thereby potentially mitigating plaque formation.

3. Cholinergic System Support

Alzheimer's disease is associated with a decline in acetylcholine (ACh) levels, a neurotransmitter essential for learning and memory. Ashwagandha has shown cholinergic activity by increasing acetylcholine levels through acetylcholinesterase (AChE) inhibition, which slows down acetylcholine breakdown.

Study Insight: Withanolide-A, another active compound in Ashwagandha, was shown to inhibit human AChE with high binding affinity in docking simulation studies (Grover et al., 2012). This suggests that Withanolide-A may enhance acetylcholine levels, thereby improving cognitive function in Alzheimer's patients.

4. Neuroprotection Against Oxidative Stress and Inflammation

Oxidative stress and inflammation are significant factors contributing to Alzheimer's disease. Ashwagandha has demonstrated antioxidant and anti-inflammatory properties, primarily due to withanolides, which protect neurons from oxidative damage and reduce pro-inflammatory cytokines that contribute to neuronal death.

Study Insight: In experiments conducted by Sehgal et al. (2012), a semi-purified root extract of Ashwagandha containing withanolides and withanosides produced neuroprotective effects in Alzheimer's models. The extract mitigated cytotoxicity induced by both hydrogen peroxide (H₂O₂) and amyloid-beta in APP/PS1 transgenic mice and APPSwInd mice (line J20). Ashwagandha was found to upregulate the expression of liver lipoprotein receptor-related protein, aiding in amyloid clearance.

5. Protection Against Acetylcholinesterase (AChE) Inhibition

Studies have also shown that Ashwagandha protects against AChE inhibition, which is associated with reduced cognitive impairment and neurotoxicity.

Study Insight: Yadav et al. (2010) found that Ashwagandha administered at a dose of 100 mg/kg in rats showed protective effects against cognitive impairment caused by exposure to propoxur, a pesticide known to inhibit AChE. This effect highlights Ashwagandha's potential in preserving cognitive function.

6. Cellular Protection and PPAR- γ Modulation

Ashwagandha has shown protective effects in cellular models of Alzheimer's by maintaining cell viability, modulating PPAR- γ (a receptor involved in inflammation and cellular energy balance), and restoring cell morphology.

Study Insight: Kurapati et al. (2013) reported that a methanolic chloroform extract of Ashwagandha enhanced cell viability and PPAR- γ levels in the SK-N-MC neuroblastoma cell line treated with β -amyloid, suggesting that Ashwagandha can help maintain cellular integrity and function.

7. Protection of Neuronal Cells Against A β -Induced Cytotoxicity

Aqueous extracts of Ashwagandha containing withanolide derivatives, including withaferin A, have shown promising results in protecting neuronal cells from β -amyloid-induced cytotoxicity.

Study Insight: Kumar et al. (2010) demonstrated that Ashwagandha extract protected differentiated pheochromocytoma PC12 cells from the cytotoxic effects of both hydrogen peroxide and β -amyloid. This indicates that Ashwagandha's neuroprotective action may extend to various types of neuronal cells and oxidative stressors.

8. Cognitive Improvement and Neurogenesis

Some studies have suggested that Ashwagandha may help improve cognitive functions and support neurogenesis, possibly due to its effects on brain-derived neurotrophic factor (BDNF) and other neuroprotective pathways.

Study Insight: Studies on rodents and in vitro models indicate that Ashwagandha not only protects against cognitive decline but may also promote the regeneration of neuronal networks that are crucial for learning and memory.

• Ashwagandha in Parkinson's Disease :

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily characterized by the loss of dopaminergic neurons in the substantia nigra. This condition is associated with oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation. Various studies have explored the potential of Ashwagandha in alleviating Parkinson's symptoms.

Research has shown that an ethanolic root extract of Ashwagandha can reverse Parkinson-like symptoms in MPTP-induced Parkinson's disease in Balb/c mice (Bhatnagar et al., 2017). In a study using the rotenone model of Parkinson's in *Drosophila melanogaster*, Ashwagandha was found to suppress oxidative stress and mitochondrial dysfunction, thereby improving impaired cholinergic function and restoring dopamine levels (Manjunath and Muralidhara, 2015).

In another study involving mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), treatment with 100 mg/kg of Ashwagandha normalized dopamine levels, as well as markers of antioxidants (glutathione and glutathione peroxidase), and lipid peroxidation (thiobarbituric acid reactive substances). This treatment also improved motor functions (RajaSankar et al., 2009a,b).

A 2007 study also reported improvements in behavior, antioxidant status, and reduced lipid peroxidation levels in the brains of Parkinson's-induced mice treated with Ashwagandha (RajaSankar et al., 2007).

In 2013, Prakash et al. demonstrated that Ashwagandha root extract administered to Maneb-Paraquat (MB-PQ) induced Parkinsonian mice improved motor movements and grip strength. The extract also helped to counterbalance oxidative stress by decreasing catalase levels and increasing nitrite and lipid peroxidation levels, which protected against the effects of pro-oxidants (Prakash et al., 2013).

Further research in 2014 revealed that Ashwagandha alleviated Parkinson's symptoms by inhibiting apoptotic pathways and reducing oxidative stress in dopaminergic neurons. The treatment led to a significant improvement in oxidative stress markers and apoptosis, with reduced expression of iNOS and Bax, and an increase in Bcl-2 protein expression in the MB-PQ-induced Parkinsonian mouse model (Prakash et al., 2014).

These findings suggest that Ashwagandha may have neuromodulatory effects that could be beneficial in managing Parkinson's disease. However, further studies are needed to clarify the exact mechanisms of action and support its use as an anti-Parkinsonian therapeutic.

• Recent patents of Ashwagandha in brain disorders :

Recent patents on Ashwagandha for brain disorders emphasize its neuroprotective effects, particularly in conditions like Alzheimer's, Parkinson's, and depression. Notably, compounds such as withanolides, withaferin A, and sitoindosides have been identified for their potential in reducing cognitive decline, enhancing memory, and countering neurodegenerative symptoms. These patents focus on Ashwagandha's antioxidant, anti-inflammatory, and neuro-modulatory properties, with applications aimed at improving brain function and combating stress and anxiety.

While these findings are promising, clinical studies to confirm the precise mechanisms and efficacy in humans remain limited, highlighting the need for further research to solidify Ashwagandha's role as a therapeutic agent for brain disorders.

• Conclusion :

Ashwagandha holds great promise as a natural remedy for brain disorders, owing to its neuroprotective, adaptogenic, and mood-stabilizing properties. While research supports its potential in managing conditions like Alzheimer's, Parkinson's, and depression, further clinical trials are needed to establish its efficacy, safety, and mechanisms of action in larger, more diverse human populations. As interest in natural supplements grows, Ashwagandha could become an important adjunct in the management of cognitive and mood disorders, particularly when integrated with conventional treatments under the guidance of healthcare professionals.

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