

A Review: Ashwagandha (*Withania Somnifera*)

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ABSTRACT

Withania somnifera is a very reverb herb of the Indian Ayurveda System of Medicine as a Rasayana (tonic). *Withania somnifera* (Ashwagandha) is a medicinal plant that extends over a large area, from the Atlantic Ocean to Southeast Asia and from the Mediterranean region to South Africa. Medicinal plants are widely used by traditional medical practitioners for curing various diseases in their day-to-day practice. In the traditional system of medicine, different parts (leaves, stem, flower, root, seeds, bark, and even whole plant) of *Withania somnifera* a small herb seen throughout India. *Withania somnifera* is a commonly used herb in Ayurvedic medicine. Studies indicate Ashwagandha possesses anti-oxidant, anxiolytic, adaptogen, memory enhancing, antiparkinsonian, antivenom, anti-inflammatory, and anti-tumor properties. Various other effects like immunomodulation, hypolipidemic; antibacterial, cardiovascular protection, sexual behavior, tolerance, and dependence have also been studied. Ashwagandha is also used therapeutically as an adaptogen for patients with nervous exhaustion, insomnia, and debility due to stress and as an immune stimulant in patients with low white blood cell counts in the blood. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects.

Keywords: Ashwagandha, *Withania somnifera*, winter cherry, herbal medicine, plant extract, antimicrobial activity, anti-cancer activity, anti-inflammatory activity, Withanolides.

I. INTRODUCTION

Ashwagandha, also known as 'Winter Cherry'. Plants are one of the most important sources of medicine in the world. Today large numbers of drugs in use are derived from plants, like morphine from *Papaver Somnifera*, Eugenol from *Ocimum sanctum*, Ephedrine from *Ephedra vulgaris*, Atropine from *Atropa belladonna*, Reserpine from *Roulfia serpentina*, etc. The

medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance.

According to a survey (1993) of WHO, the practitioners of the traditional system of medicine treat about 80% of patients in India, 85% in Burma, and 90% in Bangladesh. ^[1]



Fig 1: Plant of *Withania Somnifera*

The medicinal use of plants is very old. The writing indicates that the therapeutic use of plants is as old as 4000-5000 B.C. and the Chinese used first natural herbal preparations as medicines. In India however, the earliest reference to the use of plants as medicine appears in Rigveda which is said to have been written between 3500-1600 B.C later it was studied by Ayurveda. ^[2]

In Ayurveda Ashwagandha is considered a rasayana herb. This herb is also considered an adaptogen which is an herb that works to normalize physiological function, working on the HPA axis and the neuroendocrine system. In Ayurveda, the fresh roots are sometimes boiled in milk, before drying, to leach out undesirable constituents. ^[3]

The berries are used as a substitute for rennet, to coagulate milk in cheese making. Some herbalists refer to ashwagandha as Indian ginseng, since it is used in Ayurvedic medicine in a way similar to that ginseng is used in traditional Chinese medicine.

In recent years, there has been a growing interest in the potential health benefits of Ashwagandha, particularly in the areas of stress

management, cognitive function, and physical performance. Several studies have suggested that Ashwagandha supplementation may exhibit neuroprotective activity, be helpful in obsessive-compulsive disorder, and exhibit anti-inflammatory, immunomodulatory, and antibacterial properties.^[4]



Fig 2: Benefits of Ashwagandha^[5]

II. MORPHOLOGY

TAXONOMICAL CLASSIFICATION:

- Kingdom: Plantae, Plants
- Subkingdom: Tracheobionta, Vascular plants
- Superdivision : Spermatophyte, Seed plants
- Division : Angiosperm
- Class: Dicotyledons
- Order: Tubiflora
- Family: Solanaceae
- Genus: Withania
- Species : Somnifera Dunal

III. BOTANICAL DESCRIPTION:

WS is a small, woody shrub in the Solanaceae family that grows about two feet in height. It can be found growing in Africa, the Mediterranean, and India. An erect, evergreen, tomentose shrub, 30-150cm high, found throughout the drier parts of India in waste places and on bunds. Roots are short fleshy, whitish brown; leaves simple ovate, glabrous, those in the floral region smaller and opposite; flowers inconspicuous, greenish, or lurid-yellow, in axillary, umbellate cymes; berries small, globose, orange-red when mature, enclosed in the persistent calyx; seeds yellow, reniform. The roots are the main portions of the plants used therapeutically. The bright red fruit is harvested in the late fall and seeds are dried for planting in the following spring.

PARTS USED:

Whole plant, roots, leaves, stem, green, berries, fruits, seeds, and bark are used

SYNONYMS:

- 1) Sanskrit - Ashwagandha, Turangi-Gandhi
- 2) English - Winter cherry
- 3) Hindi - Punir , asgandh
- 4) Bengali - Ashvagandha
- 5) Gujrati - Ghodakun , Ghoda , Asoda , Asan
- 6) Telgu - Pulivendram , Panneru-gadde , Pannaeru
- 7) Tamil - Amukkura , Amkulang
- 8) Karnataka - Viremaddlinagadde, Pannaeru
- 9) Goa- Fatarfoda
- 10) Punjabi-Asgand, isgand

ASHWAGANDHA FARMING GUIDE TABLE^[6]

Botanical Name	Withania Somnifera
Family	Solanaceae
Varieties	Raj Vijay 100, Jawahar Asgand-134, Jawahar Asgand-20, Nagori
Common Names	Indian Ginsegn, Poison Gooseberry, Winter Cherry
Uses of Ashwagandha	The herb is used in medicines and herbs to treat mental stress and anxiety-related symptoms
Soil Condition	Mild red soil or sandy loam, black or heavy solids with pH between 7.5 to 8.
Propagation Methods	Broadcasting, Line Sowing, Nursery Raising
Weed Management	The cultural method is ideal for weeding at the proper interval of 20 to 25 days.
Fertilizer Schedule	10 to 12 tons FYM, 20-25 Kg Nitrogen, 15-20 Kg Phosphorus
Irrigation Requirement	1-2 irrigation schedules at the interval of 15 days should be planned
Pest & Diseases	No serious pests or diseases detected
Harvesting & Yield	3-6 Quintals Dry Root/hectare Seeds up to 60 to 75 kg

IV. ACTIVE COMPOUNDS:

Ashwagandha is characterized by a rich phytochemical composition. Depending on the location of the raw materials, it exhibits a diverse composition of chemical compounds. Its active substances that play a crucial role in pharmacological action are witanolides and alkaloids.

Witanolides are compounds whose essential structures are that of ergotoxine. The group of witanolides includes witanopherine A, witanolides A-Y, witanone, widadomniferin A and witasomniferols AC.

Alkolides include witanin somniferin, somnin, tropin, somniferinin, psudotropin, choline, kuskohigrin, isopeletrine and anaferin. Also present in a raw material are flavonoids which include 3-0 rutinoside, 6,8- dihydroxyemferol, quercetin, and glycoside derivation, and 3-0 rutinoside-7-0 glycoside.



Fig 3: Withania Somnifera root, fruit, and oil

Additionally, witanolid glycosides, which have a structure that contains a glucose moiety are also present in the raw material.

This group of compound includes sitoindosid IX and sitoindosid X. Ashwagandha also contains steroidal saponin that contains a acyl group-sitoindoside VII and sitoindoside VIII. Saponins, coumarins (scopoletin), sterols, chlorogenic acid, resins, lipids, carbohydrates, and fatty acids have also been identified in raw materials.

VII. BIOLOGICAL/PHARMACOLOGICAL ACTIVITIES:

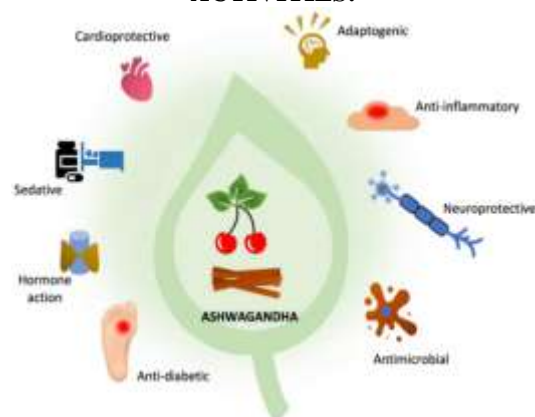


Fig 4: The Health Benefits of Ashwagandha

1. Ashwagandha Use in Alzheimer's Disease

The aging population issue has long been recognized, and it also suggests a notable rise in the proportion of the population experiencing dementia disorders. A brain disease that usually has a chronic and progressive course can cause a variety of symptoms that make up dementia, a syndrome with a complex etiology. Higher cerebral functions, such as memory, cognitive skills, orientation, understanding, learning capacities, and emotional regulation, are impacted by this disorder.

Damage that cannot be repaired occurs when the central nervous system is destroyed by neurodegenerative diseases. β -amyloid protein is found abnormally deposited in the brain during Alzheimer's disease. It has a neurotoxic effect in its fibrillar form because it causes free radicals to be formed and disrupts the transport of glucose in neurons, resulting in cell damage and death. In Alzheimer's disease, clusters of β -amyloid surround the core of the senile plaque, which is made of hyperphosphorylated τ proteins. In a physiological sense, τ proteins and other proteins work together to stabilize microtubules. Microglia, which are inflammatory response cells, accompany senile plaque accumulation and try to degrade and eliminate both the plaque and any damaged or dead neurons. Toxins produced by microglia cells kill both healthy and diseased cells and increase the inflammatory response in the brain.^[7]

Ashwagandha has been demonstrated to counteract the harmful effects of β -amyloid in experiments on human nerve cells, which may have implications for neurocognitive impairment during HIV infection.^[8] Rats were used in the study, and vitamin—an ingredient isolated from *Withania somnifera* root—was given to them orally. The suppression of amyloid β -42 was shown to significantly improve cognitive function; pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and MCP-1, as well as nitric oxide and lipid peroxidation, were also shown to decrease... The activity of the enzymes β and γ -secretase, which form the insoluble neurotoxic aggregates of β -amyloid, was also reduced.^[9] Furthermore, ashwagandha's withaferin A extract seems to be a promising component in the treatment of Alzheimer's disease. It functions by blocking the accumulation of τ protein and decreasing β -amyloid aggregation. Furthermore, withaferin A controls the expression of heat shock proteins (HSPs), which are activated in response to cellular stressors, and inhibits oxidative and pro-inflammatory chemicals. To evaluate withaferin A's safety and validate its neuroprotective benefits in the management of Alzheimer's disease, additional research is necessary.^[10] Furthermore, it has been reported that the ashwagandha extract's withaferin A strongly suppresses the expression of genes linked to NF- κ B-related neuroinflammatory molecules as well as the synthesis of amyloid β .^[11] Another study involved transgenic mice that received a half-purified *Withania somnifera* root extract, primarily consisting of withanolides, for 30 days. Following this, it was discovered that ashwagandha increased

the liver's levels of the LDL receptor-related protein LRP1 (low-density lipoprotein-related protein 1), which helped to counteract the detrimental effects of Alzheimer's disease.^[12] Raising LRP1 levels reversed the behavioral deficits associated with Alzheimer's disease and decreased amyloid β .^[13] According to studies, LRP1 functionally regulates the processes necessary for the formation of the β -amyloid precursor protein APP, which is essential for the synthesis of amyloid β and the processing of APP.^[14] LRP1 is a crucial regulator of protein proliferation τ , as the study also demonstrates.^[15] It investigated how *Withania somnifera* derivatives affected the development of β -amyloid 42 deposits in Alzheimer's patients. Withanolide A, B, witanoside IV, and witanoside V have been shown to interact in the form of an oligomer with the hydrophobic core of β -amyloid 1–42, which inhibits additional interaction with monomers and decreases aggregation.^[16, 17]

2. Ashwagandha Use in Parkinson's Disease

The nigrostriatal system's dopaminergic neurons are seen to be degenerating in Parkinson's disease. This results in an imbalance between the excitatory effects of glutamic acid and acetylcholine and the inhibitory action of dopamine. The following are some of the factors that cause nigrostriatal cells to degenerate:

- Genetic conditions;
- Endo- and exogenous toxic factors;
- Neuroinfections;
- Oxidative stress;
- Reduced growth factors;
- The sum of the action of several of the above factors.

Although the exact cause of the disease is unknown, it is believed that the protective function of estrogen may be the reason why men are slightly more likely than women to get it.^[18]

Rats with Parkinson's disease induced by 6-hydroxydopamine were used in a study. Before the rats received an injection of 6-hydroxydopamine into the striatum, they were given an oral dose of 100, 200, and 300 mg/kg body weight of *Withania somnifera* extract for three weeks. Administration of ashwagandha was found to significantly reduce lipoperoxidation, increase glutathione concentration, increase the activities of superoxide dismutase and catalase, glutathione reductase, glutathione peroxidase, catecholamines, and dopamine D2 receptor

binding, as well as enhance the expression of tyrosine hydroxylase.^[19]

The effects of *Withania somnifera* vary depending on the dosage given, even though it dramatically improves biochemical parameters in Parkinson's disease.^[19, 20, 21] Furthermore, it has been demonstrated in a fruit fly study that administering a standardized methanol extract of ashwagandha root mitigates deficiencies linked to Parkinson's disease.^[22] When compared to the control group, ashwagandha extract treatment improved biochemical parameters and decreased motor impairment in Parkinson's disease-ridden mice.^[21, 23]

Oral administration of *Withania somnifera* extract (100 mg/kg, i.p.) to mice has been observed to normalize the levels of lipoperoxidation markers in the striatum of the mice and increase the levels of dopamine (DA), homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DOPAC).^[21]

3. Use of Ashwagandha in the Treatment of Huntington's Disease

The illness known as Huntington's disease is terminal. The drugs that are currently on the market only treat the symptoms, not the illness itself. Because the condition is inherited in an autosomal dominant manner, half of the progeny are expected to carry the disease-causing allele. Huntingtin (htt) undergoes a conformational shift into its insoluble form due to a mutation in the IT15 gene on chromosome 4. Neuronal apoptosis is accelerated when the expanded polyglutamine repeats found in the N-terminal region of the mutant huntingtin protein accumulate. Acetylcholine, serotonin, GABA, and dopamine become unbalanced as a result.^[24]

One strong neurotoxin is 3-nitropropionic acid (3-NP). It causes complex II of the mitochondrial electron transport chain to become inhibited, which results in a proton energy deficit. It also causes oxidative and nitrosative stress and causes biochemical and neurobehavioral alterations that are strikingly similar to those seen in Huntington's disease. Intraperitoneal injection of 3-NP was used to artificially induce Huntington's disease symptoms in an animal model. Because of the plant's antioxidant qualities, it was found that long-term administration of ashwagandha extract improved biochemical markers and motor function. Lipoperoxidation was reduced, lactate and nitrate dehydrogenase levels dropped, superoxide dismutase and catalase levels increased, and the mitochondrial complex was unblocked, allowing

ATP synthesis to resume. There were dose-dependent effects at 100 and 200 mg/kg.^[25] The advantageous effects of withaferin A, which is isolated from ashwagandha, were shown in another study conducted on mice. An indication of aging and a characteristic of many neurodegenerative illnesses, such as Huntington's disease, is a cell's incapacity to maintain proteostasis. Withaferin A delays the onset of the disease and activates the heat shock response in this mouse model to improve the compromised proteostasis. Withaferin A treatment for Huntington's disease resulted in noticeably longer lifespans for the mice, as well as the restoration of behavioral and motor deficits, including a decrease in body weight. The enhancement of striatal function in the mouse brain, the activation of heat shock, and the decrease in mutant huntingtin aggregates were all verified by biochemical investigations. Additionally, as evidenced by a decrease in microglia activity, withaferin A dramatically lowered inflammatory processes.^[26, 27]

4. Treatment of Obsessive-Compulsive Disorder, Alcohol Withdrawal Syndrome

Patients with obsessive-compulsive disorder (OCD) experience intrusive thoughts and imagery as symptoms of this long-term mental illness. They are viewed by patients as unwelcome, unwanted, obsessive, and unreasonable. OCD makes life much more difficult, even though the severity of the cognitive disturbance varies greatly from patient to patient—especially in its severe form, where it can significantly impair psychosocial functioning.^[28, 29, 30] Although structural and functional abnormalities within the central nervous system are equally important, genetic and psychological factors also play a significant role in the etiology of OCD.^[29, 30] It is believed that serotonergic dysregulation is linked to obsessive-compulsive disorder.^[31] When treating patients with obsessive-compulsive disorder, ashwagandha root extract may be a useful addition to SSRIs.^[31] Mice that displayed behavioral symptoms akin to those seen in OCD were used in a study. Mice in this animal model were given an aqueous extract and a methanolic extract of *Withania somnifera* (doses: 10, 25, 50, and 100 mg/kg). Without influencing motor activity, it was found that giving the mice aqueous and methanolic extract of ashwagandha greatly improved their behavioral deficiencies. The outcomes matched those of the usual therapies, which included parachlorophenylalanine, ritanserin, and fluoxetine.^[32]

Researchers looked at ashwagandha's impact on rats experiencing alcohol withdrawal syndrome (AWS). It was found that giving ashwagandha orally reduced the anxiety associated with chronic alcohol consumption, suggesting that the study plant has a protective role in the treatment of ethanol-withdrawal reactions.^[33] Ashwagandha has been shown by Haque et al. to be effective in reducing anxiety, seizures, and behavioral changes in rats experiencing alcohol withdrawal symptoms. It also enhances locomotor activity.^[34]

5. Anti-Inflammatory/Immunomodulatory Effects

Withania somnifera is being researched for the treatment of numerous inflammatory diseases, including diabetes, cancer, neurodegenerative diseases, and pulmonary, cardiovascular, and autoimmune disorders. Preclinical research has shown that this plant inhibits inflammatory markers like cytokines (like TNF- α and IL-6), nitric oxide, and reactive oxygen species, which in turn reduces inflammation and regulates mitochondrial function and apoptosis. Meanwhile, ashwagandha root powder's possible inhibitory effect in lupus-ridden mice was shown in cases of proteinuria and nephritis.^[35] Research is also being done on the effectiveness of ashwagandha in treating rheumatoid arthritis. Rats in a study using an animal model were given *Withania somnifera* root powder orally for three days, one hour before the injection of CFA (complete Freund's adjuvant), which caused inflammation. Rats in the positive control group (control group) received phenylbutazone. Significant reduction in inflammation was observed, accompanied by changes in the concentrations of several serum proteins, including albumin, acute phase protein α_1 , and α_2 glycoprotein.^[36] An aqueous solution from Ashwagandha root was found to inhibit the NF- κ B and MAPK (mitogen-activated protein kinase) pathways by increasing the expression of anti-inflammatory cytokines and decreasing the expression of pro-inflammatory cytokines, such as interleukin (IL)-8, IL-6, tumor necrosis factor (TNF- α), IL-1 β , and IL-12, in a study using the HaCaT human keratinocyte cell line. Based on these findings, it is possible to employ ashwagandha's anti-inflammatory properties to prevent skin inflammation.^[37] Ashwagandha water extract (ASH-WEX) was found to have anti-neuroinflammatory effects against lipopolysaccharide-induced systemic

neuroinflammation. In a preclinical study, animals treated with ASH-WEX showed reduced expression of nitro-oxidative stress enzymes, inflammatory cytokines like TNF- α , IL-1 β , and IL-6, and inhibition of reactive gliosis. The underlying molecular processes for ASH-WEX's anti-inflammatory properties seem to entail blocking the NF κ B, P38, and JNK/SAPK MAPK pathways that are activated by lipopolysaccharide (LPS).

The study's findings point to the possible application of *Withania somnifera* in reducing inflammation of the nervous system, which is linked to several neurological conditions.^[38] Evidence from a study by Kanjilal et al.^[39] Suggested that patients with arthritis may benefit from applying ashwagandha extract for eight to twelve weeks. A study on the impact of *Withania somnifera* root powder on the stimulation of immune activity in immunodeficient mice confirmed the immunomodulatory effect. The administration of *Withania somnifera* was observed to increase the titer of circulating antibodies and antibody-producing cells, as well as the total number of white blood cells and bone marrow cells. It was also found to stimulate the production of immune cells and the phagocytosis of macrophages.^[40] An open-label extension was carried out in a randomized, double-blind, placebo-controlled trial to assess the impact of ashwagandha extract on the immune system in healthy individuals. The study's findings demonstrated that, in comparison to a placebo, ashwagandha extract dramatically raised cytokine levels and natural killer cell activity.^[41]

6. Antibacterial Properties

Despite being widely acknowledged now, drug resistance in microorganisms is a significant and expanding threat. A serious issue in recent years has been the marked rise in infections brought on by drug-resistant strains. It is well known that the careless and frequently unnecessary use of antibiotics has led to the emergence of drug-resistant strains and, in certain cases, the total ineffectiveness of these medications. For this reason, ashwagandha seems to be a useful supplement to medication when treating bacterial infections. Despite their effectiveness, many of the medications currently used to treat bacterial infections have several harmful side effects because of their toxicity. Plant ashwagandha is safe, non-toxic, and has very few adverse effects. It has been demonstrated in studies to successfully stop the growth of methicillin-resistant *Staphylococcus*

aureus and Enterococcus species.^[42] Additionally, it has been demonstrated that the root extract of *Withania somnifera* efficiently inhibits the growth of *Salmonella typhi*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, and *Klebsiella pneumoniae*, which are Gram-negative bacteria.^[43, 44, 45] Many of its characteristics are thought to be responsible for its antimicrobial action; among these are cytotoxic effects, gene silencing, and immunomodulatory effects due to its enhancement of immune reactivity (immunopotentiality).^[46]

Additionally, research using animal models demonstrates that *Withania somnifera* effectively reduces the course of infection after contracting salmonellosis.^[47] Depending on the dosage, *Withania somnifera* may also be a useful anti-caries agent. Bacteria in the mouth cavity, including *Streptococcus sobrinus* and *Streptococcus mutant*, are considerably slowed down in growth by it. Moreover, it prevents the formation of biofilms, acid tolerance, and bacterial acid production.^[48] It works especially well against *Salmonella typhi*.^[35] By triggering apoptosis, which results in the release of reactive oxygen species from mitochondria, and interfering with the potential of the mitochondrial membrane, the withanolides extracted from ashwagandha cause cell death (act on promastigotes) in *Leishmania donovani*.^[49] Research has demonstrated that ashwagandha possesses significant antifungal characteristics against specific fungal species, specifically inhibiting *Candida albicans*. It is noteworthy that the compounds it contains appear to be resistant to *Aspergillus flavus* and *Aspergillus niger*.^[44] On the other hand, the glycoprotein of *Withania somnifera* that was extracted from its root tubers exhibits antibacterial and antifungal characteristics against *Clavibacter michiganensis* subsp. *Michiganensis* and *Aspergillus flavus*, *Fusarium oxysporum*, and *Fusarium verticilloides*.^[50] *W. somnifera* extract demonstrated enhanced antibacterial activity against *P. aeruginosa*, according to Murugan et al.^[51] The mechanism of action of Ashwagandha extract's antibacterial activity was investigated through morphological analysis and membrane stabilization assays. The results indicated that the extract works by causing damage to *P. aeruginosa*'s cell membrane.

Additionally, studies conducted on mice demonstrate that *Withania somnifera* extracts, particularly those at higher concentrations,

effectively treat malaria by dramatically lowering parasitemia.^[52]

7 .Support for Infertility Treatment

The World Health Organization (WHO) defines infertility as the inability to become pregnant after a year of regular sexual activity (three to four times per week) and not using contraception. About 1.5 million Polish couples are estimated to be affected by this issue, and the number of people seeking assistance has increased recently. A significant social, psychological, and demographic issue is infertility.^[53] Increases in sperm count, semen volume, and sperm motility were noted in men with oligospermia who received 90 days of *Withania somnifera* treatment. While levels of FSH (folliculotropic hormone) and PRL (prolactin) decreased, levels of testosterone and luteinizing hormone also rose. Research on men with normozoospermia revealed that giving ashwagandha in the form of powdered root also markedly improved the parameters of semen. The likelihood of pregnancy in women was also raised by an increase in sperm count, an improvement in sperm morphology, an increase in sperm volume, and an increase in sperm motility. Semen plasma also showed an improvement in the hormonal profile as well as an increase in antioxidant enzymes and antioxidant vitamins A, C, and E.^[54, 55, 56] There were no negative effects noted. Lipid peroxidation was inhibited, protein carbonyl groups (CO) were decreased, and semen quality and reproductive hormone levels improved in men taking the drug orally in the form of ashwagandha root.^[54, 57] One good marker of protein peroxidation is the presence of CO in blood and tissues. Numerous diseases have been linked to elevated CO levels. The precise connection between oxidative stress, disease, and CO groups is still unknown. Nonetheless, because CO groups are relatively stable and emerge early, using them as a biomarker is advantageous.^[58] It has no negative effects and enhances sperm parameters in men with idiopathic infertility. Furthermore, ashwagandha may be taken into consideration as a pentoxifylline substitute.^[55] Although the results are extremely promising, there is not enough information available to fully investigate this topic. Regarding the treatment of male infertility, the precise molecular mechanisms of action of *Withania somnifera* and its active ingredients are yet unknown.^[59] One study found that giving healthy women an oral supplement containing high-concentration Ashwagandha root extract (HCARE)

improved their sexual function. Significant improvements in sexual arousal, lubrication, orgasm, and the number of successful sexual encounters were noted when compared to placebo.^[60] According to Chauhan et al., supplementing with ashwagandha root extract was linked to a statistically significant increase in the overall DISF-M (Derogatis interview for sexual functioning male) scores when compared to a placebo.^[61]

8. Anticancer Effects

A class of diseases known as cancer is characterized by unchecked cell division. This is caused by mutations in proteins that encode genes and are involved in the cell cycle, such as anti- and proto-oncogenes. Cancer is a significant and rapidly expanding health and social issue, according to statistics. Even with international research efforts, cancer is still a leading cause of death.

Research has indicated that several chemicals that have been extracted from the root, stem, and leaves of ashwagandha have anti-cancer qualities. As a result, they can be used either by themselves or in conjunction with other chemotherapeutic agents to treat cancer.^[62] The plant contains alkaloids called witanolides, which have strong anti-cancer properties. Given their significant role in apoptosis induction, they are also the most promising compounds exhibiting this action. Ashwagandha is beneficial against blood cancers as well as cancers of the breast, colon, lung, and prostate.^[63] It functions as a chemotherapeutic agent against a wide variety of breast cancer subtypes, particularly triple-negative and ER/PR-positive breast cancer.^[64] It exhibits characteristics that not only treat it but also shield against it. Additionally, studies indicate that ashwagandha may help breast cancer patients live better.^[64] Research indicates that ashwagandha-derived withaferin A is also useful in the management of melanoma. This substance inhibits the migration of melanoma cells, lowers cell proliferation, and causes apoptosis.^[65] Investigated were withaferin A's antitumor mechanisms in glioblastoma multiforme (GBM). The signaling pathways impacted by withaferin A were identified using RNA-seq analysis, Western blot, immunofluorescence staining, qRT-PCR, and siRNA gene silencing. In vitro and in vivo, it markedly suppressed GBM growth and induced intrinsic apoptosis in GBM cells. It did this by dephosphorylating Thr161 CDK1, which stopped

GBM cells in the G2/M phase of the cell cycle. This discovery holds significance for enhancing withaferin A-based regimens intended for glioblastoma multiforme prevention and/or treatment.^[66] Intermittent fasting combined with ashwagandha extract has been shown by Jawarneh et al.^[67] to be a promising adjunct to cisplatin for the treatment of breast cancer. The combination was found to reduce cisplatin-induced toxicity in the liver and kidney, as well as to decrease the proliferation of cancer cells by inducing apoptosis. According to Azab et al.^[68], the extract reduced oxidative stress and inflammation in the tissues of the liver and spleen, protecting against the negative effects of radiation exposure. According to these results, *Withania somnifera* root extract may have therapeutic uses in preventing radiotherapy-induced harm to critical organs like the liver and spleen.

9. Antidiabetic Activity

The anti-diabetic effects of ashwagandha are also taken into consideration when using it. There aren't many reports on this problem, though. In an intriguing review paper, Durg et al. described the raw material's antidiabetic properties.^[59] The preclinical studies yielded encouraging results. Its capacity to lower blood glucose levels has been demonstrated in studies on animals.^[69, 70, 71, 72, 73] Furthermore, Tekula et al.^[74] verified that Withaferin A has substantial therapeutic potential since it can effectively regulate type 1 diabetes in rats that have been induced by modulating Nrf2/NFκB signaling. Molecular docking has also been used in silico studies to validate the potential of withaferin A.^[75] Only one clinical study, conducted in 2000, demonstrated a direct reduction in blood glucose levels.^[76]

However, several studies have indicated a positive impact on the lipidemic profile. Both the cholesterol levels and the antioxidant effects of *Withania somnifera* were found to decrease in a study involving white albino rats that had hypercholesterolemia.^[72,73,77] Although there was no discernible impact on blood sugar levels in the context of clinical trials on diabetes,

Agnihotri et al.'s study^[78] produced some intriguing improvements in body weight, blood pressure, and lipidemic profile. Using the DDS17 scale to gauge patients' distress, Nayak et al.^[79] demonstrated improvements in the lipidemic profile and patient assessment. According to Usharani et al.^[80], administering a standardized ashwagandha extract under the brand name SENSORIL enhanced the lipidemic profile and

antioxidant parameters while also proving the raw material's safety and tolerability. Despite its safety and tolerability, Usharani et al. showed that it had an impact on the lipidemic profile and altered the reflection index (RI).

10. Cardioprotective Properties

In a group of albino rats treated with isoprenaline to induce myocardial necrosis, the effects of ashwagandha were investigated. The group of rats treated with *Withania somnifera* showed a decrease in glutathione levels as well as a decrease in the activity of catalase, creatinine phosphokinase, lactate dehydrogenase, and superoxide dismutase. Levels of lipid peroxidation also sharply dropped. These findings suggest that in an experimental model of isoprenaline-induced necrosis in rats, *Withania somnifera* has a cardioprotective effect.^[81] Additionally, studies using induced cardiac ischemia on rats were carried out. Significant myocardial necrosis, an imbalance between oxidation and antioxidation, and an increase in lipoperoxidation were the results of this. According to histopathological investigations, taking *Withania somnifera* by mouth considerably lessens the damage that ischemia causes to the heart. Because it restores the oxidative balance and has anti-apoptotic qualities, ashwagandha has a cardioprotective effect.^[82] A component of ashwagandha known for its anticancer properties, withaferin A, was also studied for its cardioprotective effects. Low doses of withaferin A were found to have a cardioprotective effect in this study in rats by upregulating the mitochondrial anti-apoptotic pathway as a result of increased Bcl-2/Bax ratio (AMPK) and AMP-activated protein kinase (AMPK) phosphorylation.^[83] This enzyme is involved in several processes that keep the body's energy balance stable at the cellular and overall levels. In addition to controlling the amounts of glucose, protein, and fat in peripheral tissues and the nervous system, AMPK also modulates food intake and energy expenditure in response to hormonal signals.^[84]

Furthermore, it is well known that AMPK is triggered by calorie restriction and plays a role in several age-related and disease-related processes that are common in the elderly. Because AMPK restores energy balance, life quality, and longevity are believed to be enhanced.^[84, 85, 86] Interestingly, though, withaferin A only had a cardioprotective effect at low doses (1 mg/kg). Higher doses (5 mg/kg) were not effective when administered.^[83]

V. CONCLUSION

For many years, traditional medical systems have utilized ashwagandha, a plant material, especially in Ayurvedic medicine. Research on the many benefits of ashwagandha on various body systems has been done over the years, and the results have demonstrated the plant's many positive effects. It's crucial to remember that ashwagandha research is still in its early stages and that additional studies will be required to confirm any potential therapeutic benefits as well as to establish the best dosages and usage times. Furthermore, it's critical to think about Ashwagandha's safety, especially when taking it with other drugs or supplements. Thus, more study is required to shed light on the possible advantages and disadvantages of utilizing ashwagandha as a therapeutic agent, especially in clinical trials. It is evident from the research done thus far that ashwagandha root is a plant raw material with multifaceted benefits. However, because so many new reports are being published, the knowledge about this raw material must be updated regularly, both in terms of its potential for use in the treatment of diseases and, most importantly, in terms of its safe use. Furthermore, more research is needed to determine the effects of ashwagandha, primarily in the clinical domain to verify the effectiveness of the herb. According to the research, ashwagandha may be useful as a medication, particularly for a variety of neurological conditions. The potential therapeutic applications of ashwagandha are supported by evidence, but the exact mechanisms through which it works are still unclear. To create more specialized and successful treatment plans, it is critical to identify the exact mechanisms of action of ashwagandha.

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