

Pharmacological Profile of *Withaniasomnifera* (Ashwagandha): A Review

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Abstract: *Withaniasomnifera* (Ashwagandha) is a plant used in medicine from the time of Ayurveda, the ancient system of Indian medicine. The dried roots of the plant are used in the treatment of nervous and sexual disorders. This review article is presented to compile all the updated information on its phytochemical and pharmacological activities, which were performed by widely different methods. Studies indicate ashwagandha possesses antioxidant, anxiolytic, adaptogen, memory enhancing, antiparkinsonian, antivenom, anti-inflammatory, antitumor properties. Various other effects like immunomodulation, hypolipidemic, antibacterial, cardiovascular protection, sexual behavior, tolerance, and dependence have also been studied. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveals other potential therapeutic effects. Clinical trials using ashwagandha for a variety of conditions should also be conducted..

Keywords: Ashwagandha, WithaniaSomnifera, Withanolide

I. INTRODUCTION

Withaniasomnifera (WS), also known as Ashwagandha, Indian ginseng, and Winter cherry, it has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. The roots of the plant are categorised as Ramayana's, which are reputed to promote health and longevity by augmenting defense against disease, arresting the ageing process, revitalizing the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing [1]. It is in use for a very long time for all age groups and both sexes and even during pregnancy without any side effects[2]. The pharmacological effects of the roots of WS are attributed to the presence of withanolides, a group of steroidal lactones[3]. Its leaves are used in Ayurvedic and Unani systems for treatment of tumors and tubercular glands[4]. A number of withanolides steroidal lactones have been isolated from the leaves of *Withaniasomnifera*[5] and exhibit antibacterial, anti-fungal and antitumor properties [6]. Ashwagandha is used to calm the mind, relieve weakness and nervous exhaustion, build sexual energy, and promote healthy sleep. The herb is termed a Ramayana in Ayurvedic practice, which means it acts as a tonic for vitality and longevity. It is also classified as an adaptogen[7]. Two varieties of *WithaniaSomnifera* have been mentioned in classical Unani literature:

1) *WithaniaSomnifera*Nagori and 2) *WithaniaSomnifera* Dakani. *WithaniaSomnifera*Nagori is preferred for its more potential medicinal properties[8].



Fig 1. Leaf of Ashwagandha



Fig 2. Root of Ashwagandha

Taxonomical Classification:

Kingdom: Plantae, Plants.
 Subkingdom: Tracheobionta, Vascular plants.
 Super division: Spermatophyta, Seeds plants.
 Division: Angiospermae
 Class: Dicotyledons
 Order: Tubiflorae
 Family: Solanaceae
 Genus: Withania
 Species: Somnifera
 Dunal Part Used: Roots, Leaves
 Habitat: Cultivated throughout drier parts of India. Product offered: Roots
 Product offered: Roots

Botanical Description

WithaniaSomnifera 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, 30-150 cm high, found throughout the drier parts of India in waste places and on bunds. Roots are stout fleshy, whitish brown; leaves simple ovate, glabrous, those in the floral region smaller and opposite; flowers inconspicuous, greenish, or lubrid-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 plant 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, bark are used.

II. CHEMICAL COMPOSITION

The biologically active chemical constituents are alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanoloides with a glucose at carbon 27 (sitonidoside XI and X). Withaniasomnifera is also rich in iron. The roots of Withaniasomnifera consist primarily of compounds known as withanolides, which are believed to account for its extraordinary medicinal properties.

Withanolides are steroidal and bear a resemblance, both in their action and appearance, to the active constituents of Asian ginseng (*Panax ginseng*) known as ginsenosides. Chemical analysis of Ashwagandha show its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine, anaferineandanahydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII have been isolated from root. The leaves contain steroidal lactones, which are commonly called withanolides. The withanolides have C28 steroidal nucleus with C9 side chain, with a six membered lactone ring[11].

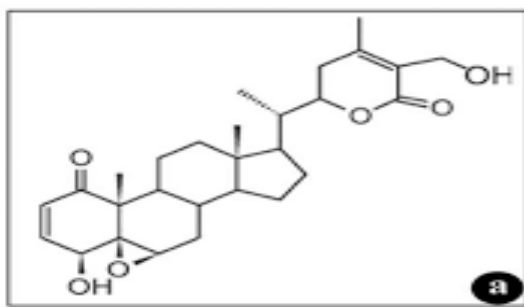


Fig 3. WITHANIOLIDE A

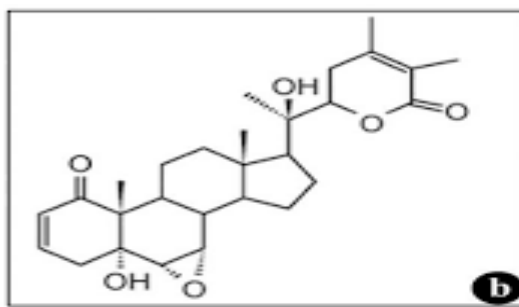


Fig 4. WITHANIOLIDE B

III. PHARMACOLOGICAL ACTIVITY

Centuries of Ayurvedic medical experience using *Withaniasomnifera* have revealed it to have pharmacological value as an adaptogen, antibiotic, abortifacients, aphrodisiac, astringent, anti-inflammatory, deobstruent, diuretic, narcotic, sedative, and tonic. Ashwagandha has been found to: Provide potent antioxidant protection[14,15]. Stimulate the activation of immune system cells, such as lymphocytes and phagocytes [16,17]. Counteract the effects of stress and generally promote wellness[18].

1) Anti-inflammatory Activity

Withaferin A exhibits potent anti-arthritis and anti-inflammatory activities. Anti-inflammatory activity has been attributed to biologically active steroids, of which Withaferin A is a major component. It is as effective as hydrocortisone sodium succinate dose for dose[19]. It was found to suppress effectively arthritic syndrome without any toxic effect. Unlike hydrocortisone-treated animals which lost weight, the animals treated with Withaferin A showed gain in weight in arthritic syndrome. It is interesting that Withaferin A seems to be more potent than hydrocortisone in adjuvant-induced arthritis in rats, a close experimental approximation to human rheumatoid arthritis. In its oedema inhibiting activity, the compound gave a good dose response in the dose range of 12-25 mg/kg body weight of Albino rats intraperitoneally and a single dose had a good duration of action, as it could effectively suppress the inflammation after 4 hours of its administration [20]. *Withaniasomnifera* has been shown to possess anti-inflammatory property in many animal models of inflammations like carrageenan-induced inflammation, cotton pellet granuloma and adjuvant-induced arthritis. Detailed studies were carried out to investigate the release of serum β -1 globulin during inflammation by two models of inflammations viz. primary phase of adjuvant induced arthritis and formaldehyde-induced arthritis. The experiments showed interesting results as most of the APR were influenced in a very short duration and suppressed the degree of inflammation[21].

2) Anti-stress: -

A study conducted by the Institute of Basic Medical Sciences at Calcutta University examined the effects of Ashwagandha on chronic stress in rodents. For a period of 21 days, the animals received a mild electric shock to their feet. The resulting stress on the animals produced hyperglycemia, glucose intolerance, increase in plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression, and mental depression [22]. Researchers using *Withaniasomnifera* discovered the animals given the herb an hour before the foot shock experienced a significantly reduced level of stress. This research confirms the theory that Ashwagandha has a significant anti-stress apoptogenic effect [23]. Research conducted at the Department of Pharmacology, University of Texas Health Science Centre indicated that extracts of Ashwagandha produce GABA-like activity, which may account for the herb's anti-anxiety effects[24]. GABA (Gamma Amino-butyric acid) is an inhibitory neurotransmitter in the brain. Its function is to decrease neuron activity and inhibit nerve cells from over firing. This action produces a calming effect. Excessive neuronal activity can lead to restlessness and insomnia, but GABA inhibits the number of nerve cells that fire in the brain, and helps to induce sleep, uplift mood, and reduce anxiety. Ashwagandha has traditionally been used to stabilize mood in patients with behavioral disturbances. Research has revealed that the herb produces an anti-depressant and anti-anxiety effect in rodents comparable to the anti-depressant drug imipramine and the anti-anxiety drug lorazepam (Ativan) [25]. In fact, Ashwagandha is one of the most widespread tranquilizers used in India, where it holds a position of importance like ginseng in China. It acts mainly on the reproductive and nervous systems, having a rejuvenative effect on the body, and is used to improve vitality and aid recovery after chronic illness [26]. Chronic stress can cause conditions such as cognitive deficit, immunosuppression, sexual dysfunction, gastric ulceration, irregularities in glucose homeostasis, and changes in plasma corticosterone levels. In a rat model of chronic stress syndrome, *Withaniasomnifera* and *Panax ginseng* extracts were compared for their abilities to relieve some of the adverse effects of chronic stress [27]. Research results showed that both Ashwagandha and *Panax ginseng* decreased the frequency and severity of stress-induced ulcers, reversed stress-induced inhibition of male sexual behavior, and inhibited the effects of chronic stress on retention of learned tasks. Both botanicals also reversed stress-induced immunosuppression, but only the *Withania* extract increased peritoneal macrophage activity. The activity of the *Withania* extract was about the same as the activity of the ginseng extract. *Withaniasomnifera*, however, has an advantage over *Panax ginseng* in that it does

not appear to result in ginseng-abuse syndrome., a condition characterized by high blood pressure, water retention, muscle tension, and insomnia [28].

3) Antibiotic Activity: -

The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10 μ g/ml inhibited the growth of various Gram-positive bacteria, acid-fast and aerobic bacilli, and pathogenic fungi. It was active against *Micrococcus pyogenes* var aureus and partially inhibited the activity of *Bacillus subtilis* glucose-6- phosphate dehydrogenase. Withaferin A inhibited Ranikhet virus. The shrub's extract is active against Vaccinia virus and *Entamoeba histolytica* [29]. *WithaniaSomnifera* showed the protective action against systemic *Aspergillus* infection. This protective activity was probably related to the activation of the macrophage function revealed by the observed increases in phagocytosis and intracellular killing of peritoneal macrophages induced by Ashwagandha treatment in mice [30]. Antibiotic activity of Withaferin A is due to the presence of the unsaturated lactone-ring. The lactone showed strong therapeutic activity in experimentally induced abscesses in rabbits, the being somewhat stronger than that of Penicillin. It substantiates the reputation of the leaves as a cure for ulcers and carbuncles in the indigenous system of medicine [31].

4) Antioxidant effect: -

The brain and nervous system are relatively more susceptible to free radical damage than other tissues because they are rich in lipids and iron, both known to be important in generating reactive oxygen species. Free radical damage of nervous tissue may be involved in normal aging and neurodegenerative diseases, e.g., epilepsy, schizophrenia, Parkinson's, Alzheimer's, and other diseases. The active principles of WS, sitoindosides VII-X and withaferin A (glycowithanolides), have been tested for antioxidant activity using the major free-radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) levels in the rat brain frontal cortex and striatum. Decreased activity of these enzymes leads to accumulation of toxic oxidative free radicals and resulting degenerative effects. An increase in these enzymes would represent increased antioxidant activity and a protective effect on neuronal tissue. Active Glycowithanolides of WS were given once daily for 21 days, dose-related increased in all enzymes were observed: the increases comparable to those seen with diphenyl (a known antioxidant) administration. This implies that WS does have an antioxidant effect in the brain, which may be responsible for its diverse pharmacological properties [32]. In another study, an aqueous suspension of WS root extract was evaluated for its effect on stress-induced lipid peroxidation (LPO) in mice and rabbits. LPO blood levels were increased by lipopolysaccharides (LPS) from *Klebsiella pneumoniae* and peptidoglycans (PGN) from *Staphylococcus aureus*. Simultaneous oral administration of WS extract prevented an increase in LPO [33]. Apart from hepatic lipid peroxidation (LPO), the serum enzymes, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase, were assessed as indices of hepatotoxicity. Silymarin (20 mg/kg, p.o.) was used for comparison. Iron overload induced marked increase in hepatic LPO and serum levels of the enzymes, which was attenuated by glycowithanolides (WSG) in a dose-related manner, and by silymarin [34].

5) Anti-aging activity

Ashwagandha was tested for its anti-aging properties in a double-blind clinical trial. A group of 101 healthy males, 50-59 years old were given the herb at a dosage of 3 grams daily for one year. The subjects experienced significant improvement in haemoglobin, red blood cell count, hair melanin, and seated stature. Serum cholesterol decreased and nail calcium was preserved. Seventy percent of the research subjects reported improvement in sexual performance [35].

6) Anticonvulsant Activity: -

Administration of *WithaniaSomnifera* root extract was found to reduce jerks and clonus in 70% and 10% animals respectively with dose of 100mg/kg and reduction in the severity of pentylenetetrazole (PTZ)-induced convulsions was evident from EEG wave pattern [36]. *WithaniaSomnifera* root extract showed reduction in severity of motor seizures induced by electrical stimulation in right basilateral amygdaloid nuclear complex through bipolar electrodes. The protective effect of *WithaniaSomnifera* extract in convulsions has been reported to involve GABAergic mediation [37].

7) Antiparkinsonian properties: -

Parkinson's disease is a neurodegenerative disease characterized by the selective loss of dopamine (DA) neurons of the substantia nigra pars compacta. The events, which trigger and/or mediate the loss of nigral DA neurons, however, remain unclear. Neuroleptic induced catalepsy has long been used as an animal model for screening drugs for Parkinsonism. Administration of haloperidol or reserpine significantly induced catalepsy in mice. WS significantly inhibited haloperidol or reserpine-induced catalepsy and provide hope for treatment of Parkinson's disease [42]. In another study, 6-Hydroxydopamine (6-OHDA) is one of the most widely used rat models for Parkinson's disease. There is ample evidence in the literature that 6-OHDA elicits its toxic manifestations through oxidant stress. Antiparkinsonian effects of WS extract has been reported due to potent antioxidant, antiperoxidative and free radical quenching properties in various diseased conditions. Rats were pretreated with the WS extract orally for 3 weeks. On day 21, 6-OHDA was infused into the right striatum while sham operated group received the vehicle. Three weeks after 6-OHDA injections, rats were tested for neurobehavioral activity and were killed 5 weeks after lesioning for the estimation of lipidperoxidation, reduced glutathione content, activities of glutathione-S- transferase, glutathione reductase, GPX, SOD and CAT, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression. WS extract Reversed all the parameters significantly in a dose-dependent manner [43]. The pathophysiology of this disabling and commonly irreversible movement disorder is still obscure. Vacuous chewing movements in rats are widely accepted as an animal model of tardive dyskinesia. Oxidative stress and products of lipid peroxidation are implicated in the pathophysiology of tardive dyskinesia.

8) Cardiovascular protection: -

WS may be useful as a general tonic, due in part to its beneficial effects on the cardiopulmonary system, as reported in the following studies. The effect of WS was studied on the cardiovascular and respiratory systems in dogs and frogs [46]. The alkaloids had a prolonged hypotensive, bradycardia, and respiratory stimulant action in dogs. The study found that the hypotensive effect was mainly due to autonomic ganglion blocking action and that a depressant action on the higher cerebral centers also contributed to the hypotension. The alkaloids stimulated the vasomotor and respiratory centers in the brain stem of dogs. The cardio-inhibitory action in dogs appeared to be due to ganglion blocking and direct cardio depressant actions. The alkaloids produced immediate predominant but short-lived cardio-depressant effects and a weak but prolonged cardiotoxic effect in isolated normal and hypodynamic frog hearts. In another study, left ventricular dysfunction was a decrease in heart rate, left ventricular rate of peak positive and negative pressure change and elevated left ventricular end-diastolic pressure in the control group was recorded. WS showed strong cardioprotective effect in the experimental model of isoprenaline-induced myonecrosis in rats. Augmentation of endogenous antioxidants, maintenance of the myocardial antioxidant status and significant restoration of most of the altered hemodynamic parameters may contribute to its cardioprotective effect [47].

9) Immunomodulatory Activity: -

WithaniaSomnifera showed a significant modulation of immune reactivity in animal models. Administration of WithaniaSomnifera was found to prevent myeloid suppression in mice treated with three immunosuppressive drugs viz. cyclophosphamide, azathioprine, and prednisolone. Treatment with WithaniaSomnifera was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice [48]. Administration of WithaniaSomnifera extract was found to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Administration of WithaniaSomnifera extract increased the number of β -esterase positive cells in the bone marrow of CTX treated animals, compared to the CTX alone treated group [44]. Administration of WithaniaSomnifera extract was found to significantly reduce leucopenia induced by sub-lethal dose of gamma radiation [49]. Withaferin A and Withanolides E exhibited specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes. Withanolides E had specific effect on T lymphocytes whereas Withaferin A affected both B and T lymphocytes [50].

10) Anti-hyperglycemic Effect: -

WithaniaSomnifera along with other ingredients of a composite formulation (Transina) have been reported to decrease streptozocin (STZ)-induced hyperglycemia in rats. This anti-hyperglycemic effect may be due to pancreatic islet free radical scavenging activity because the hyperglycemic activity of STZ is a consequence of decrease in pancreatic islet cell superoxide dismutase (SOD) activity leading to the accumulation of degenerative oxidative free radicals in islet-beta cells [51].

11) Hypolipidemic effect :-

WS root powder decreased total lipids, cholesterol, and triglycerides in hypercholesteremic animals. On the other hand, significantly increased plasma HDL-cholesterol levels, HMG-CoA reductase activity and bile acid content of liver. A similar trend also reported in bile acid, cholesterol, and neutral sterol excretion in the hypercholesteremic animals with WS administration. Further, a significant decrease in lipid-peroxidation occurred in WS administered hypercholesteremic animals when compared to their normal counterparts. However, WS root powder was also effective in normal subjects for decreasing lipid profiles [52]. In another study with aqueous extract of fruits of Withania coagulants to high fat diet induced hyperlipidemic rats for 7 weeks, significantly reduced elevated serum cholesterol, triglycerides, and lipoprotein levels. This drug also showed hypolipidemic activity in triton-induced hypercholesterolemia. The histopathological examination of liver tissues of treated hyperlipidemic rats showed comparatively lesser degenerative changes compared with hyperlipidemic controls. The hypolipidemic effect of Withania coagulants fruits reported to be comparable to that of an Ayurvedic product containing Commiphoramukkul [53]. In another study, hypoglycemic, diuretic and hypocholesterolemia effects of roots of WS were assessed on human subjects. Six mild NIDDM subjects and six mild hypercholesterolemia subjects were treated with the powder of roots of WS for 30 days. Suitable parameters were studied in the blood and urine samples of the subjects along with dietary pattern before and at the end of treatment period. Decrease in blood glucose was comparable to that of an oral hypoglycemic drug. Significant increase in urine sodium, urine volume, significant decrease in serum cholesterol, triglycerides, LDL (low density lipoproteins) and VLDL (very low-density lipoproteins) cholesterol were observed indicating that root of WithaniaSomnifera is a potential source of hypoglycemic, diuretic and hypocholesterolemia agents [54].

12) Anti-carcinogenic activity: -

Ashwagandha is reported to have anti-carcinogenic effects. Research on animal cell cultures has shown that the herb decreases the levels of the nuclear factor kappa, suppresses the intercellular tumor necrosis factor, and potentiates apoptotic signaling in cancerous cell lines [56]. One of the most exciting of the possible uses of Ashwagandha is its capacity to fight cancers by reducing tumor size [57,58]. To investigate its use in treating various forms of cancer, the antitumor effects of Withaniasomnifera have been studied by researchers. In one study, the herb was evaluated for its anti-tumor effect in urethane-induced lung tumors in adult male mice [59]. Following administration of Ashwagandha over a period of seven months, the histological appearance of the lungs of animals which received the herb was similar to those observed in the lungs of control animals.

IV. CONCLUSION

Withaniasomnifera (Ashwagandha) is a plant used in medicine from the time of Ayurveda, the ancient system of Indian medicine. The plant has also been widely studied for their various pharmacological activities like antioxidant, anxiolytic, adaptogen, memory enhancing, antiparkinsonian, anti-inflammatory, antitumor properties. Various other effects like immunomodulation, hypolipidemic, antibacterial, cardiovascular protection, sexual behavior, have also been studied. Although the results from this review are quite promising for the use of WS as a multi-purpose medicinal agent, several limitations currently exist in the current literature. While WS has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use.

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