

THERAPEUTIC USES OF WITHANIA SOMNIFERA (ASHWAGANDHA) WITH A NOTE ON WITHANOLIDES AND ITS PHARMACOLOGICAL ACTIONS

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ABSTRACT

Withania somnifera is a medicinal plant extends over a large area, from the Atlantic ocean to South East Asia and from the Mediterranean region to South Africa. The medicinal plants are widely used by the traditional medical practitioners for curing various diseases in their day to day practice. In traditional systems of medicine, different parts (leaves, stem, flower, root, seeds, bark and even whole plant) of *Withania somnifera* (known as Ashwagandha in Hindi), a small herb seen throughout India, have been recommended for the treatment of aphrodisiac, liver tonic, anti-inflammatory agent, astringent, and more recently to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia etc. Clinical trials and animal research support the therapeutic use of ashwaganda for anxiety, cognitive and neurological disorders, inflammation, and Parkinson's disease. Ashwaganda's chemopreventive properties make it a potentially useful adjunct for the patients undergoing radiation and chemotherapy. Ashwaganda 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 blood. The major biochemical constituents of ashwaganda root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides.

Keywords: *Withania somnifera*, Withanolides, Medicinal plants, Ashwagandha

INTRODUCTION

Plants are one of the most important sources of medicines in world. Today the large numbers of drugs in use are derived from plants, like morphine from *Papaver somniferum*, Eugenol from *Ocimum sanctum*, Ephedrine from *Ephedra vulgaris*, Atropine from *Atropa belladonna*, Reserpine from *Rouphia serpentina* etc. The medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance.

The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability [1, 2]. Because of these advantages the medicinal plants have been widely used by the traditional medical practitioners in their day to day practice. According to a survey (1993) of World Health Organization (WHO), the practitioners of traditional system of medicine treat about 80% of patients in India, 85% in Burma and 90% in Bangladesh [2, 3].

In traditional systems of medicine the Indian medicinal plants have been used in successful management of various disease conditions like bronchial asthma, chronic fever, cold, cough, malaria, dysentery, convulsions, diabetes, diarrhea, arthritis, emetic syndrome, skin diseases, insect bite etc. and in treatment of gastric, hepatic, cardiovascular & immunological disorders [2, 4-8].



Fig. 1: Plant of *Withania somnifera*

The medicinal use of plants is very old. The writings indicate that therapeutic use of plants is as old as 4000–5000 B.C. and Chinese used first the natural herbal preparations as medicines. In India, however, earliest references of use of plants as medicine appear in

Rigveda which is said to be written between 3500–1600 B.C. Later the properties and therapeutic uses of medicinal plants were studied in detail and recorded empirically by the ancient physicians in Ayurveda (an indigenous system of medicine) which is a basic foundation of ancient medical science in India [9].



Fig. 2: Photographs of dried root of *Withania somnifera*

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, prior to drying, in order to leach out undesirable constituents.

The berries are used as a substitute for rennet, to coagulate milk in cheese making. Ashwagandha in Sanskrit means "horse's smell," probably originating from the odor of its root which resembles that of sweaty horse. In Tamil, it is called Amukkrang Kilangu and is used in several medicines. The species name *somnifera* means "sleep-inducing" in Latin, indicating that to it are attributed sedating properties, but it has been also used for sexual vitality and as an adaptogen. 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.

Withania somnifera

A plant from genus *Withania*

Among the plants known for medicinal value, the plants of genus *Withania* belonging to family Solanaceae are very important for their therapeutic potentials. *Withania coagulans*, *Withania simonii*, *Withania adunensis*, *Withania riebeckii* are examples of known

important species of genus *Withania* which grow in different parts of the world and are known to have medicinal properties [1, 3-9]. *Withania somnifera* Dunal and *Withania somnifera* Kaul are the two sub-species of the plant.

Therapeutic uses of *Withania somnifera*

Withania somnifera is one of the major herbal components of geriatric tonics mentioned in Indian systems of medicine. In the traditional system of medicine Ayurveda, this plant is claimed to have potent aphrodisiac rejuvenative and life prolonging properties. It has general animating and regenerative qualities and is used among others for the treatment of nervous exhaustion, memory related conditions, insomnia, tiredness potency issues, skin problems and coughing. It improves learning ability and memory capacity.

The traditional use of 'Ashwagandha' was to increase energy, youthful vigour, endurance, strength, health, nurture the time elements of the body, increase vital fluids, muscle fat, blood, lymph, semen and cell production. It helps counteract chronic fatigue, weakness, dehydration, bone weakness, loose teeth, thirst, impotency, premature aging emaciation, debility, convalescence and muscle tension. It helps invigorate the body by rejuvenating the reproductive organs, just as a tree is invigorated by feeding the roots [10-14].

Immunomodulation and Hematopoiesis

A series of animal studies show ashwagandha to have profound effects on the hematopoietic system, acting as an immunoregulator and a chemoprotective agent [15, 16]. In a mouse study, administration of a powdered root extract from ashwagandha was found to enhance total white blood cell count. In addition, this extract inhibited delayed-type hypersensitivity reactions and enhanced phagocytic activity of macrophages when compared to a control group [17].

Recent research suggests a possible mechanism behind the increased cytotoxic effect of macrophages exposed to *W. somnifera* extracts [18]. Nitric oxide has been determined to have a significant effect on macrophage cytotoxicity against microorganisms and tumor cells. Luvone et al demonstrated *Withania somnifera* increased. No production in mouse macrophages in a concentration-dependent manner. This effect was attributed to increased production of inducible nitric oxide synthase, an enzyme generated in response to inflammatory mediators and known to inhibit the growth of many pathogens [19].

Ashwagandha exhibited stimulatory effects, both in vitro and in vivo, on the generation of cytotoxic T lymphocytes, and demonstrated the potential to reduce tumor growth [20]. The chemopreventive effect was demonstrated in a study of ashwagandha root extract on induced skin cancer in Swiss albino mice given ashwagandha before and during exposure to the skin cancercausing agent 7,12-dimethylbenz[a]anthracene.

A significant decrease in incidence and average number of skin lesions was demonstrated compared to the control group. Additionally, levels of reduced glutathione, superoxide dismutase, catalase, and glutathione peroxidase in the exposed tissue returned to near normal values following administration of the extract. The chemopreventive activity is thought to be due in part to the antioxidant/ free radical scavenging activity of the extract [21].

An in vitro study showed withanolides from *Withania somnifera* inhibited growth in human breast, central nervous system, lung, and colon cancer cell lines comparable to doxorubicin. Withaferin A more effectively inhibited growth of breast and colon cancer cell lines than did doxorubicin. These results suggest *Withania somnifera* extracts may prevent or inhibit tumor growth in cancer patients, and suggest a potential for development of new chemotherapeutic agents [22].

Anti-Aging

In a double-blind clinical trial, ashwagandha was tested in a group of 101 healthy males, 50-59 years old, at a dosage of 3 grams daily for one year. A significant improvement in hemoglobin, red blood

cell count, hair melanin, and seated stature was observed. Serum cholesterol decreased and nail calcium was preserved. Erythrocyte sedimentation rate decreased significantly and 71.4 percent reported improvement in sexual performance [23].

Chronic Stress

Chronic stress (CS) can result in a number of adverse physiologic conditions including cognitive deficit, immunosuppression, sexual dysfunction, gastric ulceration, irregularities in glucose homeostasis, and changes in plasma corticosterone levels. In a rat model of chronic stress *Withania somnifera* and Panax ginseng extracts were compared for their ability to attenuate some effects of chronic stress. Both botanicals were able to decrease the number and severity of CS-induced ulcers, reverse CS-induced inhibition of male sexual behavior, and inhibit the adverse effects of CS on retention of learned tasks.

Both botanicals also reversed CS-induced immunosuppression, but only the *Withania* extract increased peritoneal macrophage activity in the rats. The activity of the *Withania* extract was approximately equal to the activity of the Panax ginseng extract. *Withania somnifera*, 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 [24].

Cardiovascular Protection

Hypoglycemic, diuretic, and hypocholesterolemic effects of ashwagandha root were assessed in human subjects, in which six type 2 diabetes mellitus subjects and six mildly hypercholesterolemic subjects were treated with a powder extract for 30 days. A decrease in blood glucose comparable to that of an oral hypoglycemic drug was observed. Significant increases in urine sodium, urine volume, and decreases in serum cholesterol, triglycerides, and low-density lipoproteins were also seen [25].

Hypothyroidism

Animal studies reveal ashwagandha has a thyrotropic effect.[26, 27] An aqueous extract of dried *Withania* root was given to mice via gastric intubation at a dose of 1.4 g/kg body weight daily for 20 days. Serum was collected at the end of the 20- day period and analyzed for T3 and T4 concentrations and lipid peroxidation was measured in liver homogenate via antioxidant enzyme activity. Significant increases in serum T4 were observed, indicating the plant has a stimulatory effect at the glandular level.

No changes in T3 levels were observed. *Withania* may also stimulate thyroid activity indirectly, via its effect on cellular antioxidant systems. *Withania* extract significantly decreased lipid peroxidation in the liver homogenate and significantly increased catalase activity, promoting scavenging of free radicals that can cause cellular damage. These results indicate ashwagandha may be a useful botanical in treating hypothyroidism [26].

Anxiety and Depression

In an animal study assessing the anxiolytic and antidepressive actions of ashwagandha compared to commonly prescribed pharmaceuticals, an extract of the root was administered orally to rats once daily for five days. The results were compared to a group administered the benzodiazepine lorazepam for anxiolytic activity, and the tricyclic antidepressant imipramine for antidepressant investigation.

Both the ashwagandha group and the lorazepam group demonstrated reduced brain levels of a marker of clinical anxiety. Ashwagandha also exhibited an antidepressant effect comparable to that induced by imipramine in the forced swim-induced "behavioral despair" and "learned helplessness" tests. Other similar studies confirm these results, lending support to the use of ashwagandha as an antistress adaptogen [28, 29].

Studies show ashwagandha to be effective in the treatment of osteoarthritis [30], inflammation,[31, 32] stroke,[33] and tardive dyskinesia [34]. Studies also reveal ashwagandha to be a potential

antimicrobial agent, with antifungal activity [35, 36] and moderate antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [37].

Pharmacological actions of withanolides

The roots of *Withania somnifera* 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. Ashwagandha's withanolides have been researched in a variety of animal studies examining their effect on numerous conditions, including immune function and even cancer [38].

The withanolides have C28 steroidal nucleus with C9 side chain, with a six membered lactone ring. Twelve alkaloids, 35 withanolides, and several sitoindosides from *Withania somnifera* have been isolated and studied. A sitoindoside is a withanolide containing a glucose molecule at carbon 27. Much of Ashwagandha's pharmacological activity has been attributed to two main withanolides, withaferin A, D and withanolide G.

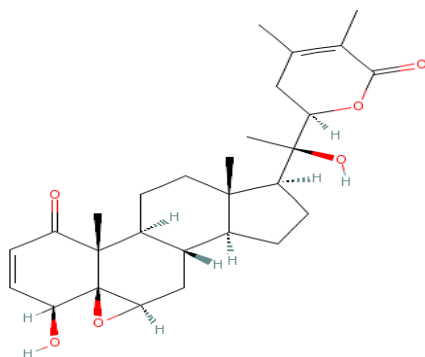


Fig. 3: Withanolide A

The withanolides serve as important hormone precursors that can convert into human physiologic hormones as needed. Ashwagandha is thought to be amphoteric; i.e., it can help regulate important physiologic processes.

The theory is that when there is an excess of a certain hormone, the plant-based hormone precursor occupies cell membrane receptor sites so the actual hormone cannot attach and exert its effect. If the hormone level is low, the plant-based hormone exerts a small effect. Ashwagandha is also considered to be an adaptogen, facilitating the ability to withstand stressors, and has antioxidant properties as well. Other studies have shown ashwagandha to have an immunostimulatory effect.

CONCLUSION

As modern medicine continues to expand, so do the uses of botanical medicines. *Withania somnifera* shows great potential as a safe and effective in Immunomodulation and Hematopoiesis. More research is needed to determine if *Withania somnifera* can duplicate this action in humans, and to determine an optimal dosage range for achieving these effects.

The potential beneficial effects of *Withania* in anxiety, cognitive and neurological disorders, inflammation, and Parkinson's disease. Experienced natural medicine practitioners, working hand-in-hand with oncologists, could increase effectiveness and decrease side effects of conventional treatments with the use of *Withania somnifera*.

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REFERENCES

- Atal CK, Kapoor BM. Cultivation and utilization of medicinal plants (Eds. PID CSIR), 1989.
- Siddiqui HH. Safety of herbal drugs-an overview. *Drugs News & Views* 1993; 1(2): 7-10.
- WHO survey. In medicinal plants (Eds. Haq. I.) Hamdard Foundation Press, Karachi, 13, 1993.
- Sanyal, PK. Homeopathic Pharmacy in India. In: Cultivation and utilization of medicinal plants. Editor: Atal CK and Kapoor BM (Published by PID CSIR) 1989.
- Chopra RN, Chopra IC, Handa KL, Kapoor LD. Indigenous drugs of India (Published by UN Dhar, Pvt. Ltd., Calcutta) 1993.
- Chopra RN, Nayar SI, Chopra IC. Glossary of Indian Medicinal Plants (Published by CSIR, New Delhi) 1956.
- Satyavati GV, Raina MK, Sharma M. Medicinal Plants of India (Published by ICMR, New Delhi), 1976.
- Nadkarni AK, Nadkarni KM. Indian Materia Medica (Published by Popular Prakashan Pvt. Ltd., Bombay) 1976.
- Sirkar NN. Pharmacological basis of Ayurvedic therapeutics. In: Cultivation and utilization of medicinal plants. Editors: Atal CK and Kapoor BM (Published by PID CSIR) 1989.
- Charaka Samhita, Chikitsa Sthana, Second Chapter, 1997, Chowkambha Publishers, 38(English Edition)
- Sharma PV, Dravyaguna Vigyan, Chowkambha Sanskrit Sansthan, 1997
- Vaidyaratnam P.S Varier's, "Indian Medicinal Plants, a compendium of 500 species", (Warrier.P.K. Nambiar V.P.K, Ramankutty Eds.), PartII, 1994; 52-55, by Orient Longman Publications, Hyderabad.
- Nadakarni, Indian Materia Medica, 1993, 1; 1292.
- Shastri V.D, Bhavaprakasha Nighantu, Motilal Banarasidas Publications, Chowkambha
- Publications, p.218
- Kuttan G. Use of *Withania somnifera* Dunal as an adjuvant during radiation therapy. *Indian J Exp Biol* 1996;34:854-856.
- Ziauddin M, Phansalkar N, Patki P, et al. Studies on the immunomodulatory effects of Ashwagandha. *J Ethnopharmacol* 1996;50:69-76.
- Davis L, Kuttan G. Immunomodulatory activity of *Withania somnifera*. *J Ethnopharmacol* 2000;71:193-200.
- Iuvone T, Esposito G, Capasso F, Izzo A. Induction of nitric oxide synthase expression by *Withania somnifera* in macrophages. *Life Sci* 2003;72:1617- 1625.
- Bogdan C. Nitric oxide and the immune response. *Nature Immunol* 2001;2:907-916.
- Davis L, Kuttan G. Effect of *Withania somnifera* on CTL activity. *J Exp Clin Cancer Res* 2002;21:115-118.
- Prakash J, Gupta SK, Dinda AK. *Withania somnifera* root extract prevents DMBA-induced squamous cell carcinoma of skin in Swiss albino mice. *Nutr Cancer* 2002;42:91-97.
- Jayaprakasam B, Zhang Y, Seeram N, Nair M. Growth inhibition of tumor cell lines by withanolides from *Withania somnifera* leaves. *Life Sci* 2003;74:125-132.
- Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Monographs for the Western Herbal Practitioner. Australia: Phytotherapy Press; 1996:137-141.
- Bhattarcharya SK, Muruganandam AV. Adaptogenic activity of *Withania somnifera*: an experimental study using a rat model of chronic stress. *Pharmacol Biochem Behav* 2003;75:547- 555.
- Andallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (*Withania somnifera*) root. *Indian J Exp Biol* 2000;38:607-609.
- Panda S, Kar A. *Withania somnifera* and *Bauhinia pupurea* in the regulation of circulating thyroid hormone concentrations in female mice. *J Ethnopharmacol* 1999;67:233-239.
- Panda S, Kar A. Changes in thyroid hormone concentrations after administration of ashwagandha root extract to adult male mice. *J Pharm Pharmacol* 1998;50:1065-1068.
- Bhattacharya A, Ghosal S, Bhattacharya SK. Antioxidant effect of *Withania somnifera* glycowithanolides in chronic footshock stress-induced perturbations of oxidative free radical

- scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. *J Ethnopharmacol* 2001;74:1-6.
30. Dhuley JN. Adaptogenic and cardioprotective action of ashwagandha in rats and frogs. *J Ethnopharmacol* 2000;70:57-63.
 31. Kulkarni RR, Patki PS, Jog VP, et al. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *J Ethnopharmacol* 1991;33:91-95.
 32. Angalagan K, Sadique J. Influence of an Indian medicine (ashwagandha) on acute-phase reactants in inflammation. *Indian J Exp Biol* 1981;19:245-249.
 33. Begum VH, Sadique J. Long-term effect of herbal drug *Withania somnifera* on adjuvant-induced arthritis in rats. *Indian J Exp Biol* 1988;26:877-882.
 34. Chaudhary G, Sharma U, Jagannathan N, Gupta Y. Evaluation of *Withania somnifera* in a middle cerebral artery occlusion model of stroke in rats. *Clin Exp Pharmacol Physiol* 2003;30:399-404.
 35. Bhattacharya SK, Bhattacharya D, Sairam K, Ghosal S. Effect of *Withania somnifera* glycowithanolides on a rat model of tardive dyskinesia. *Phytomedicine* 2002;9:167-170.
 36. Abou-Douh AM. New withanolides and other constituents from the fruit of *Withania somnifera*. *Arch Pharm* 2002;335:267-276.
 37. Choudhary MI, Dur-e-Shahwar, Parveen Z, et al. Antifungal steroidal lactones from *Withania* coagulance. *Phytochemistry* 1995;40:1243-1246.
 38. Ali NA, Julicch WD, Kusnick C, Lindequist U. Screening of Yemeni medicinal plants for antibacterial and cytotoxic activities. *J Ethnopharmacol* 2001;74:173-179.
 39. Grandhi, A. Comparative pharmacological investigation of ashwagandha and ginseng. *Journal of Ethnopharmacology (Ireland)*, 1994: vol. 3, pp 131-135.