

Review

## Therapeutic use of *Withania somnifera*

Md. Khorshed Alam, Md. Obydul Hoq\* and Md. Shahab Uddin

Hakim Said Eastern Medical College & Hospital, 37 Nobab Katara (Nimtoli), Dhaka-1000, Bangladesh

\*Corresponding author: Md. Obydul Hoq, Hakim Said Eastern Medical College & Hospital, 37 Nobab Katara (Nimtoli), Dhaka-1000, Bangladesh. E-mail: dr.obydulhoq@gmail.com

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**Abstract:** *Withania somnifera* (L) Dunal is commonly called as Ashwagandha/Asgand and it belongs to the family Solanaceae. It is a well known medicinal plant widely used in the treatment of many clinical conditions in Indian subcontinent. It is an important medicinal plant commonly known as Asgand which has been used either single or in combination with other drugs in Unani as well as Ayurvedic system of medicine for centuries. It has been described by Dioscorides (78 AD) in his book “Kitab-ul-Hashaish”. Asgand consists of the roots of *Withania somnifera* which has various therapeutic actions such as anti - inflammatory (Muhallil-e-Warm), sedative (Musakkin), aphrodisiac (Muqawwi-e-Bah), hepatoprotective, immune-modulator activity, anti-oxidant, anti-ageing, anti-tumour activity, adaptogenic activity and has anti-anticonvulsant activity. Keeping in view the medicinal properties of *Withania somnifera* Dunal (Asgand), an attempt has been made in this paper to explore various dimensions of the drug including phytochemical and pharmacological studies carried out on this herb.

**Keywords:** *Withania somnifera*, Asgand, Anti-inflammatory activity, Immunomodulatory activity, Unani medicine.

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### 1. Introduction

Ashwagandha 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 Indian subcontinent. As a result of this wide growing range, there are considerable morphological and chemo-typical variations in terms of local species. However, the primary alkaloids of both the wild and the cultivated species appear to be the same. The roots are the main portion 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. The berries have been shown to have an emetic effect. The roots are used as a nutrient and health restorative in pregnant women and old people. The decoction of the root boiled with milk and ghee is recommended for curing sterility in women. The roots are also used in constipation, senile debility, rheumatism, general debility, nervous exhaustion, loss of memory, loss of muscular energy and spermatorrhoea (Scartezzini and Speroni, 2000). In Unani system of medicine, roots of *Withania somnifera* commonly known as Asgand are used for the medicinal properties. However, leaves of the plant are also reported to be used medicinally (Anonymous, 1982). This plant grows widely in all dried parts and subtropical India (widely cultivated in Bikaner and Pilani areas of Rajasthan, Rajputana, Punjab, Gujarat, Uttar Pradesh and Manasa (M.P.), Congo, South Africa, Pakistan, Afghanistan, Egypt, Morocco, Jordan, Sri Lanka, Egypt, Morocco, Jordan, Iraq, Iran, Syria and Turkey (Anonymous, 2007a; Dey and Bahadur, 1973; Dymock and Warden, 1976; Kirtikar and Basu, 1980; Nadkarni, 1982).

**2. Vernacular names**

Bengali	: Ashvaganda, Asvagandha
Arabic	: Kaknaj-e-Hindi
Urdu	: Asgand, Asgand Nagori
English	: Winter cherry
Gujarati	: Asan, Asana, Asoda, Asundha, Ghodaasoda
Hindi	: Asgandh, Punir
Malayalam	: Amukkiram, Pevetti Marathi: Askandha, Kanchuki, Tilli
Odiya	: Asugandha
Persian	: Kaknaj-e-Hindi, Asgand Nagaori
Sanskrit	: Ashvagandha, Ashvakandika, Gandhapatri, Palashaparni
Tamil	: Amukkira, Asubam, Asuvagandi
Telugu	: Asvagandhi, Penneru, Pennerugadda, Dommadolu

(Anonymous, 2007b; Kirtikar *et al.*, 1980).

**3. Unani description**

Unani name	: Asgand
Botanical name	: <i>Withania somnifera</i> (Linn.) Dunal (Family: Solanaceae)
Synonyms	: <i>Withania ashwagandha</i> Kaul <i>Physalis. flexuosa</i> Linn. (Anonymous, 2007)
Properties	: Mizaj Hot 1°, Dry 1°
Maza	: Mucilaginous, bitter and acrid
Boo	: Pungent odor, smell of horse's urine
Muzir	: Mehrooreen (for persons with hot temperament)
Mukhrij	: Expels Balgham (Phlegm) and Sauda (Black Bile)
Nafa-e-Khas	: Muqawwi-e-Bah (Aphrodisiac)

**4. Classification of *Withania somnifera***

Kingdom	: Plantae
Division	: Angiosperms
Class	: Dicotyledoneae
Order	: Tubiflorae
Family	: Solanaceae
Genus	: <i>Withania</i>
Species	: <i>somnifera</i>

**5. Important formulations**

Important Unani formulations containing Asgand are as follows:

- Habbe Asgand
- Kushta Gaodanti
- Majoon Salab
- Majoon Zanjabeel
- Sarbat Jinsin
- Sarbat Niswan
- Sarbat Rehmin
- Sarbat Amla

(Anonymous, 2007b and BNUF, 2010)

**6. Biochemical properties**

The biochemical composition of *Withania somnifera* has been widely studied. Some 35 compounds had been analyzed in the laboratory.

- Alkaloids: About 13 alkaloids are known as Isopelletierine, Anaferine, Cuseohygrine, Anahygrine, Tropine etc.
- Somniferin: It is a bitter alkaloid with some hypnotic activity.
- Steroidal Lactones: Withanolides, Withanofेरins.
- Saponins: These are with an additional acyl group (Sitoindoside VII and VIII).
- Iron.

• Others: Resin, fat, coloring matters, a reducing sugar, phytosterol, Ipuranol and a mixture of saturated and unsaturated acids (Anonymous, 2007; Kirtikar *et al.*, 1980).

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 (Umadevi *et al.*, 2012). 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- $\alpha$ -gloyloxytropine, choline, cuscohygrine, isopelletierine, anaferine and anahydrine. 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. 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 and withanolide D. Further chemical analysis has shown the presence of the following:

Anaferine (Alkaloid), Anahygrine (Alkaloid), Beta-Sisterol, Chlorogenic acid (in leaf only), Cysteine (in fruit), Cuscohygrine (Alkaloid), Iron, Pseudotropine (Alkaloid), Scopoletin, Somniferinine (Alkaloid), Somniferiene (Alkaloid), Tropanol (Alkaloid), Withanine (Alkaloid), Withananine (Alkaloid) and Withanolides A-Y (Steroidal lactones) (Bone, 1996).

## 7. Pharmacological activity

Centuries of Unani and Ayurvedic medical experience using *Withania somnifera* have revealed it to have pharmacological value as anti-inflammatory (Muhallil-e-Warm), sedative (Munabbim), alterative (Muaddil), aphrodisiac (Muqawwi-e-Bah), hepatoprotective, immune-modulator activity, anti-oxidant, anti-ageing, anti-tumour activity, adaptogenic activity and has anti-convulsant activity.

### 7.1. Anti-oxidant activity

In Banaras Hindu University of India some researchers have discovered that some of the chemicals found in *Withania somnifera* are powerful antioxidants. Studies conducted on rats' brains showed the herb produced an increase in the levels of three natural antioxidants- superoxide dismutase, catalase and glutathione peroxidase. Through the study, these findings are consistent with the therapeutic use of *Withania somnifera* as an Ayurvedic rasayana. The antioxidant effect of active principles of *Withania somnifera* root may explain the reported anti-stress, cognition-facilitating, antiinflammatory and anti-ageing effects produced by them in experimental animals, and in clinical situations.

### 7.2. Immunomodulatory activity

*Withania somnifera* is a general tonic to increase energy and prevent disease may be partially related to its effect on the immune system. Glycowithanolides and a mixture of sitoindosides IX and X isolated from *Withania somnifera* were evaluated for their immuno-modulatory and central nervous system effects (antistress, memory, and learning) in Swiss mice (15-25 g, 5-6 months old) and Wistar strain albino rats (120-150 g and 250-300 g) (Bone, 1996). Both materials produced statistically significant mobilization and activation of peritoneal macrophages, phagocytosis, and increased activity of the lysosomal enzymes. Both compounds (50-200 mg/kg orally) also produced significant antistress activity in albino mice and rats, and augmented learning acquisition and memory retention in both young and old rats. Root extract of *Withania somnifera* was tested for immunomodulatory effects in three myelosuppression models in mice: cyclophosphamide, azathioprine, or prednisolone (Ghosal *et al.*, 1989). Significant increases ( $p < 0.05$ ) in hemoglobin concentration, red blood cell count, white blood cell count, platelet count, and body weight were observed in *Withania somnifera* treated mice compared to untreated control mice. The authors also reported significant increases in hemolytic antibody responses toward human erythrocytes which indicated immunostimulatory activity. The effect of WS was also studied on the functions of macrophages obtained from mice treated with the carcinogen ochratoxin A (OTA) (Ziauddin *et al.*, 1996). OTA treatment of mice for 17 weeks significantly decreased the chemotactic activity of the macrophages. Interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF- $\alpha$ ) production was also markedly decreased.

### 7.3. Anti-aging activity

In a double-blind clinical trial *Withania somnifera* was tested for its anti-aging properties. 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 hemoglobin, 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 (Dhuley, 1997).

### 7.4. Anti-stress activity

Chronic stress can result in a number of adverse physiologic conditions including cognitive deficit, immune-suppression, 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 chronic stress induced ulcers, reverse chronic stress induced inhibition of male sexual behavior, and inhibit the adverse effects of chronic stress on retention of learned tasks. Both botanicals also reversed chronic stress induced immune-suppression, 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 (Bone, 1996).

### 7.5. Anxiety and Depression

In an animal study assessing the anxiolytic and antidepressive actions of *Withania somnifera* 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 (Bhattacharya and Muruganandam, 2003). Other similar studies confirm these results, lending support to the use of ashwagandha as an antistress adaptogen (Bhattacharya *et al.*, 2000; Bhattacharya *et al.*, 2001; Singh *et al.*, 2001).

### 7.6. Anti-inflammatory activity

Research has explored the capacity of *Withania somnifera* to ease the symptoms of arthritis and other inflammatory conditions. These studies have proven that the herb acts as an effective anti-inflammatory agent. Its naturally occurring steroidal content is much higher than that of hydrocortisone, a commonly-prescribed anti-inflammatory (Archana and Namasivayam, 1999). The effectiveness of *Withania somnifera* in a variety of rheumatologic conditions may be due in part to its anti-inflammatory properties. Rats given powdered root of *Withania somnifera* orally one hour before being given injections of an inflammatory agent over a three day period showed that *Withania somnifera* produced anti-inflammatory responses comparable to that of hydrocortisone sodium succinate (Anbalangan & Sadique, 1981).

### 7.7. Antitumor activity

In one study, *Withania somnifera* was evaluated for its anti-tumor effect in urethane-induced lung adenomas in adult male albino mice (Begum, 1988). Simultaneous administration of *Withania somnifera* (ethanol extract of whole plant, 200 mg/kg daily orally for seven months) and urethane (125 mg/kg without food biweekly for seven months) reduced tumor incidence significantly (tumor incidence: untreated control, 0/25; urethane treated, 19/19; *Withania somnifera* treated, 0/26, and *Withania somnifera* plus urethane treated, 6/24,  $p < 0.05$ ). The histological appearance of the lungs of animals protected by *Withania somnifera* was similar to those observed in the lungs of control animals. No pathological evidence of any neoplastic change was observed in the brain, stomach, kidneys, heart, spleen, or testes of any treated or control animals. In addition to providing protection from carcinogenic effects, *Withania somnifera* treatment also reversed the adverse effects of urethane on total leukocyte count, lymphocyte count, body weight, and mortality. The growth inhibitory effect of *Withania somnifera* was also observed in Sarcoma 180 (S-180), a transplantable mouse tumor (Singh *et al.*, 1986). Ethanol extract of *Withania somnifera* root (400 mg/kg and up, daily for 15 days) after intra-dermal inoculation of  $5 \times 10^5$  cells of S-180 in BALB/c mice produced complete regression of tumor after the initial growth. A 55-percent complete regression was obtained at 1000 mg/kg; however, it was a lethal dose in some cases. *Withania*

*somnifera* was also found to act as a radio- and heat sensitizer in mouse S-180 and in Ehrlich ascites carcinoma (Devi *et al.*, 1992). Anti-tumor and radiosensitizing effects of withaferin (a steroidal lactone of *Withania somnifera*) were also seen in mouse Ehrlich ascites carcinoma in vivo. Withaferin A from *Withania somnifera* gave radiosensitizer ratio of 1:5 for in vitro cell killing of V79 Chinese hamster cell at a non-toxic concentration of about 2 mM/L. These studies are suggestive of antitumor activity as well as enhancement of the effects of radiation by *Withania somnifera*.

### 7.8. Effects on the endocrine system

Based on the observations that *Withania somnifera* provides protection from free radical damage in the mouse liver, studies were conducted to determine the efficacy of *Withania somnifera* in regulating thyroid function (Devi *et al.*, 1995; Panda, 1997). Mice were given WS root extract (1.4 g/kg by gavage, daily for 20 days). The treatment significantly increased the serum levels of 3,3',5-triiodothyronine (T3) and tetraiodothyronine (T4), while the hepatic concentrations of glucose 6-phosphatase activity and hepatic iodothyronine 5'-monodeiodinase activity did not change significantly. *Withania somnifera* significantly reduced hepatic lipid peroxidation and increased the activity of superoxide dismutase and catalase. The results suggest *Withania somnifera* stimulates thyroidal activity and also promotes hepatic antioxidant activity. A combination formula of *Withania somnifera*, *Tinospora cordifolia*, *Eclipta alba*, *Ocimum sanctum*, *Picorrhiza kurroa*, and shilajit was found to cause a dose-related decrease in streptozotocin-induced hyperglycemia (Panda and Kar, 1998). None of the herbs given individually, however, produced any effect on the hyperglycemia, indicative perhaps of why Ayurvedic medicine generally prefers combinations of herbs rather than single herbs.

### 7.9. Anticonvulsant activity

Administration of *Withania somnifera* 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 pentylene tetrazole (PTZ)-induced convulsions was evident from EEG wave pattern. Asgand root extract showed reduction in severity of mot or seizures induced by electrical stimulation in right basilateral amygdaloid nuclear complex through bipolar electrodes. The protective effect of Asgand extract in convulsions has been reported to involve GABAergic mediation.

### 7.10. Hemopoetic effect

In a study, administration of *Withania somnifera* extract was found to significantly reduce leukopenia induced by cyclophosphamide (CTX) treatment in Swiss albino mice (Ghosal *et al.*, 1989). Total white blood cell count on the 12<sup>th</sup> day of the CTX-treated group was 3720/mm<sup>3</sup>; that of the CTX-plus- *Withania somnifera* group was 6120/mm<sup>3</sup>. In the CTX-plus- *Withania somnifera* mice, the cellularity of the bone marrow was significantly increased ( $13.1 \times 10^6/\text{femur}$ ) ( $p < 0.001$ ) compared to the CTX-alone treated group ( $8 \times 10^6/\text{femur}$ ). Similarly, the number of alpha-esterase positive cells (1130/4000 cells) in the bone marrow of the CTX-plus *Withania somnifera* mice increased compared to the CTX-alone mice (687/4000 cells). The major activity of *Withania somnifera* may be the stimulation of stem cell proliferation. These studies indicated *Withania somnifera* reduced CTX-induced toxicity and may prove useful in cancer chemotherapy. Further studies need to be conducted to confirm the hemopoetic effect with other cytotoxic agents and to determine its usefulness as an adjuvant in cancer chemotherapy.

### 7.11. Rejuvenating effect

The growth-promoting effect of *Withania somnifera* was studied for 60 days in a double-blind study of 60 healthy children, age 8-12 years, who were divided into five groups of 12 (Davis and Kuttan, 1998). Group 1 was given purified and powdered WS 2 g/day fortified in 100 cc of milk (no details about purification and powdering methods were disclosed). Similarly, Group 2 received 2 g daily of a mixture of equal parts WS and punarnava (*Boerhaavia diffusa*), Groups 3 and 4 were given ferrous fumarate 5 mg/day and 30 mg/day, respectively, and Group 5 received placebo. Group 1 experienced a slight increase in hemoglobin, packed cell volume, mean corpuscular volume, serum iron, body weight, and hand grip, and significant increases in mean corpuscular hemoglobin and total proteins ( $p < 0.01$ ) at the end of 60 days when compared to the initial level and the placebo group. There was an increase in body weight in all groups over the control group. Group 2, treated with WS and punarnava, showed a significant increase in the level of hemoglobin at the end of 30 days compared to the initial value. Marked increases in the levels of hemoglobin, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin, serum iron, and hand grip were also observed at the end of 60 days when compared to initial levels. However, when compared with the placebo group, only hemoglobin

and handgrip showed significant increase ( $p < 0.05$ ). No change was seen in other parameters. It was noted that 13 of 15 children had an increase in body weight, 10 children had an increase in hemoglobin and packed cell volume, and 11 children had an increase in serum iron. Group 3 (5 mg ferrous fumarate) had no significant change in any parameters, while Group 4 (30 mg ferrous fumarate) showed a significant increase in hemoglobin ( $p < 0.01$ ), mean corpuscular hemoglobin ( $p < 0.05$ ), mean corpuscular hemoglobin concentration ( $p < 0.01$ ), serum iron, ( $p < 0.05$ ), and hand grip ( $p < 0.05$ ), and a marked increase in packed cell volume. Group 5 (placebo) had no significant change in any parameter. The study demonstrated that WS may be useful as a growth promoter and hematinic in growing children. In another clinical trial, *Withania somnifera* purified powder was given 3 g/day for one year to 101 normal healthy male volunteers, age 50-59 years (Venkataraghavan *et al.*, 1980). All subjects showed significantly increased hemoglobin and RBC count, and improvement in hair melanin and seated stature. They also showed decreased SED rate, and 71.4 percent of the subjects reported improvement in sexual performance. In summary, these studies indicate *Withania somnifera* may prove useful in younger as well as older populations as a general health tonic.

### 7.12. Free radicle scavenging activities

The effect of the aqueous solution of root extract of *Withania somnifera* on lipid peroxidation was investigated on stress induced rabbits and mice. The oral administration of the extract prevented the elevation in lipid peroxidation by the free radical scavenging activity. The free radical scavenging activity of *W. coagulans* was detected by Hemalatha *et al.*, 2004. It was concluded that administration of aqueous extract of *W. coagulans* to diabetic rats significantly lowered the liver and serum lipid peroxidation. The presence of free radical scavenging activity and lipid peroxidation lowering activity in aqueous extract of *W. coagulans* might have helped in providing protection to some degree against oxidative damage to beta cells of pancreas.

### 8. Drug-botanical interactions

There are anecdotal reports that *Withania somnifera* may potentiate the effects of barbiturates; therefore, caution should be used if taking this combination.

### 9. Side effects and toxicity

*Withania somnifera* is generally safe when taken in the prescribed dosage range (Kuppurajan *et al.*, 1980). Large doses have been shown to cause gastrointestinal upset, diarrhoea, and vomiting.

### 10. Dosage

A typical dose of *Withania somnifera* is 3-6 grams daily of the dried root, 300-500 mg of an extract standardized to contain 1.5 percent withanolides, or 6-12 ml of a 1:2 fluid extract per day.

### 11. Warnings and contraindications

Large doses of *Withania somnifera* may possess abortifacient properties; therefore, it should not be taken during pregnancy. Since ashwaganda acts as a mild central nervous system depressant, patients should avoid alcohol, sedatives, and other anxiolytics while taking ashwagandha.

### 12. Conclusions

Although the results from this review are quite promising for the use of *Withania somnifera* as a multi-purpose medicinal agent, several limitations currently exist in the current literature. While ashwagandha has been used successfully in Unani and Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use. It is also important to recognize that *Withania somnifera* may be effective not only in isolation, but may actually have a potentiating effect when given in combination with other herbs or drugs.

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### Conflict of interest

None to declare.

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