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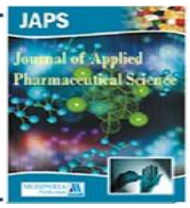

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Phytochemical and Pharmacological Profile of *Withania somnifera* Dunal: A Review

Qamar Uddin, L. Samiulla, V. K. Singh and S. S. Jamil

Qamar Uddin, L. Samiulla
Regional Research Institute of Unani Medicine (RRIUM), Motel Chhak, Mathasahi, Bhadrak-756100, Orissa, India.

V.K. Singh and S.S. Jamil
Central Council for Research in Unani Medicine (CCRUM), 61-65, Institutional Area, Janakpuri, New Delhi-110058, India.

For Correspondence
Qamar Uddin
Research Officer, Regional Research Institute of Unani Medicine (RRIUM), Motel Chhak, Mathasahi, Bhadrak-756 100, Orissa, India,
Mobile: 09861290095, 09776189515

ABSTRACT

Withania somnifera (L) Dunal is a well known Indian medicinal plant widely used in the treatment of many clinical conditions in India. It is an important drug 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*), alterative (*Muaddil*) and aphrodisiac (*Muqawwi-e-Bah*). Keeping in view the medicinal properties of *Withania somnifera* Dunal (Asgand), an attempt has been made in this review paper to explore various dimensions of the drug including phytochemical and pharmacological studies carried out on this drug.

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

INTRODUCTION

Withania somnifera Dunal belongs to the family solanaceae. It is a xerophytic plant, found in the drier parts of India, Sri Lanka, Afghanistan, Baluchistan and Sind and is distributed in the Mediterranean regions, the Canaries and Cape of Good Hope. It is found in high altitude ascending to 5,500 feet in the Himalayas. This shrub is common in Bombay and Western India, occasionally met within Bengal. It grows wildly throughout India particularly in hotter parts, on waste places and on road sides. It is also cultivated for medicinal purposes in fields and open grounds throughout India. It is widely cultivated in Bikaner and Pilani areas of Rajasthan, Rajputana, Punjab and Manasa (M.P.) (Anonymous, 2007, Chopra *et al*., 1980, Dey *et al*., 1973, Dymock *et al*., 1976, Kirtikar *et al*., 1980, Nadkarni, 1982). 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). The fresh roots are collected during January to March and dried under shade for several days. The drug retains its therapeutic efficacy for less than 2 years. It is prone to decomposition and loses its potentials within 2 years. So the fresh dried roots are preferred for medicinal uses. Two varieties of Asgand have been mentioned in classical Unani literatue: 1) *Asgand Nagori* and 2) *Asgand Dakani.* Asgand Nagori is preferred for its more potential medicinal properties (Anonymous, 1982, Behl *et al*., 1993, Ghani, 1920, Kirtikar *et al*., 1980, Sivarajan *et al*., 1994).

VERNACULAR NAMES

Arabic	:	Kaknaj-e-Hindi
Bengali	:	Ashvaganda, Asvagandha
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
Urdu	:	Asgand, Asgand Nagori (Anonymous, 2007, Chopra *et al.*,1980, Kirtikar *et al.*, 1980).

UNANI DESCRIPTION

Unani name	:	Asgand
Botanical name	:	*Withania somnifera* (Linn.) Dunal (Family: Solanaceae)
Synonyms	:	*Withania ashwagandha* Kaul (Khare, 2007) *Physalis flexuosa* Linn. (Anonymous, 2007, Chopra *et al*. 1980)
Properties	:	*Mizaj* Hot 1°, Dry 1° (Ali, 1997, Lubhaya, 1984, Nadkarni, 1982).
Maza	:	Mucilaginous, bitter and acrid **(**Anonymous, 2007)
Boo	:	Pungent odor, smell of horse's urine (Ali, 1997)
Muzir	:	Mehrooreen (for persons with hot temperament) (Haleem, 2009)
Mukhrij	:	Expels Balgham (Phlegm) and Sauda (Black Bile) (Nadkarni, 1982)
Nafa-e-Khas	:	Muqawwi-e-Bah (Aphrodisiac) (Kabiruddin, 1955)

Important Formulations

Important Unani formulations containing Asgand are as follows:

- Habbe Asgand
- Kushta Gaodanti
- Majoon Salab
- Majoon Zanjabeel (Anonymous, 2007)

Therapeutic Actions

Asgand (*Withania somnifera*) possesses a number of therapeutic actions which include anti-inflammatory (*Mohallil-e-Warm*), sedative (*Musakkin*), hypnotic (*Munawim*), narcotic (*Munashshi*), general tonic (*Muqawwi-e-Aam*), diuretic (*Mudir-e-Baul*) (Fruits & Seeds), aphrodisiac (*Muqawwi-e-Bah*), alterative (*Muaddil*), deobstruent (*Mufatteh Sudad*), (Ali, 1997, Anonymous, 2007, Chopra *et al*. 1980, Ghani, 1920, Kabiruddin, 1955, Khare, 2007, Kirtikar *et al.*, 1980, Nadkarni, 1982), uterine tonic (*Muqawwi-e-Rahem*) and increases production of semen (*Muwallid-e-Mani*) (Anonymous, 2007, Ghani, 1920, Kabiruddin, 1955).

Therapeutic Uses

Asgand (*Withania somnifera*) has been recommended for the treatment of various ailments which include polyarthritis (*Waja-ul-Mafasil*), rheumatoid arthritis (*Hudar*), lumbago (*Waja-ul-Qutn*), painful swellings (*Tawwarum-e-Alami*), spermatorrhoea (*Jaryan-e-Mani*), asthma (*Zeeq-un-Nafas*), leucoderma (*Bars*), general debility (*Zof-e-Aam*), sexual debility (*Zof-e-Bah*), (Ali, 1997, Anonymous, 2007, Ghani, 1920, Kabiruddin, 1955, Khare, 2007, Kirtikar *et al*., 1980, Nadkarni, 1982), amnesia (*Nisyan*) (Ali, 1997, Ghani, 1920), anxiety neurosis (*Qalaq-e-Usabi*), (Ali, 1997, Khare, 2007), scabies (*Jarb*), ulcers (*Qurooh*), marasmus (*Saghal*) and leucorrhoea (*Sailan-ur-Rahem*) (Anonymous, 2007).

MORPHOLOGY

Withania somnifera is an evergreen, erect, branching, tomentose shrub, 30-150 cm in height. Leaves are simple, ovate, glabrous, and up to 10 cm long. Flowers are greenish or lurid yellow, small about 1 cm long; few flowers (usually about 5) born together in axillary, umbellate cymes (short axillary clusters). Fruits are globose berries, 6 mm in diameter, orange red when mature, enclosed in the inflated and membranous persistent calyx. Seeds are yellow, reniform and 2.5 mm in diameter (Anonymous, 2007). The drug Asgand consists of the dried mature roots of the plant which has the following morphological properties:

Macroscopic

The stout fleshy roots when dry are cylindrical, gradually tapering down, straight, unbranched, 10-17.5 cm long and 6-12 mm in diameter. The main roots bear fiber-like secondary roots. The outer surface of the roots is brownish white and interior is creamy white when broken. They have a short and uneven fracture, a strong odour and mucilaginous biter and acrid taste (Anonymous, 1982).

Microscopic

The young root has a single layered epidermis followed by a parenchymatous cortex of 4-5 layers of cells, the endodermis being conspicuous by the presence of casparian stripes. The cork cambium arises in the outermost layer of the cortex. The endodermis persists even after the secondary growth has taken place (Shah *et al*., 1993). Measurement of cells is given in (Table 1).

Table. 1: Measurement of cells (in microns).

Cork	35-72 × 20-42
Phelloderm	32-52-165 × 25-35-70
Xylem vessels	240-295-390 × 40-50-70
Tracheids	160-280-470 × 26-40-50
Fibre tracheids	190-325-525 × 15-22-29
Fibres	220-400-650 × 13-20-25
Starch grains	11-24-40 × 9-20-30

(Anonymous, 2007)

PHYTOCHEMICAL STUDIES

A review of literature reveals the presence of various chemical constituents in the different parts of the plant which are as follows:

Root

The roots are reported to contain alkaloids, amino acids, steroids, volatile oil, starch, reducing sugars, glycosides, hentriacontane, dulcitol, withaniol, an acid (m.p. 280-283° decomp.), and a neutral compound (m.p. 294-296°). The total alkaloidal content of the Indian roots has been reported to vary between 0.13 and 0.31 percent, though much higher yields (up to 4.3%) have been recorded elsewhere (Anonymous, 1982, Anonymous, 2007). Identity, purity, strength and assay of the dried roots of the plant are given in (**Table 2**).

Table. 2: Identity, purity, strength and assay.

Foreign organic matter	Not more than 2%
Physicochemical constants	
Ash values (%)	
Total ash	6.0
Acid insoluble ash	1.5
Water soluble ash	3.0
pH values	
1% solution	5.5
10% solution	5.5
Loss on drying at 105℃	8.7%
Solid contents	91.3%
Successive extractive values (%)	
Pet. Ether	0.348
Chloroform	0.304
Acetone	0.305
Alcohol	0.184

(Anonymous, 2007)

Many biochemically heterogeneous alkaloids have been reported in the roots. Basic alkaloids include cuscohygrine, anahygrine, tropine, pseudotropine, anaferine, isopelletierine, withananine, withananinine, pseudo-withanine, somnine, somniferine, somniferinine. Neutral alkaloids include 3-tropyltigloate and an unidentified alkaloid. Other alkaloids include withanine, withasomnine, and visamine. Withanine is sedative and hypnotic (Khare, 2007). Withasomnine has been separated from the roots of the plant grown in West Germany. Visamine is a new alkaloid which has been separated from the roots of the plant grown in Soviet Union. It prolonged hexanal-induced sleeping time and showed hypothermic and nicotinolytic effects in mice (Rastogi *et al*., 1998).The free amino acids identified in the root includeaspartic acid, glycine, tyrosine, alanine, proline, tryptophan, glutamic acid, and cystine (Khare, 2007).

Leaf

The leaves of the plant (Indian chemotype) are reported to contain 12 withanolides, 5 unidentified alkaloids (yield, 0.09%), many free amino acids, chlorogenic acid, glycosides, glucose, condensed tannins, and flavonoids (Khare, 2007).

The leaves of the plant from different habitats contain different withanolides–a group of C28 steroids characterized by a 6-membered lactone ring in the 9-carbon atom side chain.

Withaferin A, a steroidal lactone is the most important withanolide isolated from the extract of the leaves and dried roots of *Withania somnifera*. It is thermostable and slowly inactivated at pH 7.2. It is insoluble in water and is administered in the form of suspension. For its separation, the leaves are extracted with cold alcohol; the extract is purified and dried, and finally crystallized from aqueous alcohol (yield, 0.18% air dry basis). The yield of this compound from the South-African plants is reported to be as high as 0.86 percent. The curative properties of the leaves and roots are attributed to Withaferin A (Anonymous, 1982).

Fruit

The green berries contain amino acids, a proteolytic enzyme, condensed tannins, and flavonoids. They contain a high proportion of free amino acids which include proline, valine, tyrosine, alanine, glycine, hydroxyproline, aspartic acid, glutamic acid, cystine and cysteine. The presence of a proteolytic enzyme, *chamase*, in the berries may be responsible for the high content of the amino acid.

Shoots

The tender shoots are rich in crude protein, calcium and phosphorous, and are not fibrous. They are reported to contain *scopoletin*.

Stem

The stem of the plant contains condensed tannins and flavonoids.

Bark

The bark contains a number of free amino acids (Anonymous, 1982).

PHARMACOLOGICAL STUDIES

The drug consists of the dried roots of *Withania somnifera* which is official as a sedative in the pharmacopoeia of India. The pharmacological activity of the roots is attributed to the presence of several alkaloids. The total extract (70% alcoholic) of the roots possesses the same properties as the total alkaloids, but is nearly half as potent (Anonymous, 1982).

Anti-inflammatory Activity

Withaferin A exhibits fairly potent anti-arthritic 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 (Khare, 2007). 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 (Anonymous, 1982, Rastogi *et al*., 1998). Asgand (*Withania somnifera*) 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 (Sharma *et al*., 191, Sahni *et al*., 1994). Detailed studies were carried out to investigate the release of serum α-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 also suppressed the degree of inflammation (Anabalagan *et al*., 1985).

Antibiotic Activity

The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10μg/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* (Anonymous, 1982, Rastogi *et al*., 1998, Khare, 2007). Asgand 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 (Dhuley, 1998). 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 (Anonymous, 1982).

Antitumour Activity

Withaferin A, withanolide D & E exhibited significant antitumour activity in vitro against cells derived from human epidermoid carcinoma of nasopharynx (KB) and in vivo against Ehrlich ascites carcinoma, Sarcoma 180, Sarcoma Black (SBL), and E 0771 mammary adenocarcinoma in mice in doses of 10, 12, 15 mg/kg body-weight. Growth of Ehrlich ascites carcinoma was completely inhibited in more than half the mice which survived for 100 days without the evidence of growth of the tumour. They also acted as a mitotic poison arresting the division of cultured human-larynx carcinoma cells at metaphase and in HeLa cultures similar to star metaphase. Withaferin A caused mitotic arrest in embryonic chicken fibroblast cells. Methylthiodeacetyl colchicine potentiated the effect of Withaferin A. The presence of an unsaturated lactone in the side-chain to which an allelic primary alcohol group is attached at C25 and the highly oxygenated rings at the other end of the molecule may well suggest specific chemical systems possessing carcinostatic properties (Anonymous, 1982, Rastogi *et al*., 1998, Khare, 2007). Withaferin A has been shown to possess growth inhibitory and radio-sensitizing effects on experimental mouse tumours (Ganasoundary *et al*., 1997). Administration of Withaferin A in mice inoculated with Ehrlich ascites carcinoma cells was found to inhibit tumour growth and increase tumour-free animal survival in a dose dependent manner (Devi *et al*., 1995, Sharada *et al*., 1996). The alcoholic extract of the dried roots of the plant as well as the active component Withaferin A isolated from the extract showed significant antitumour and radio-sensitizing effects in experimental tumours in vivo, without any noticeable systemic toxicity. One-hour treatment with Withaferin A in a non-toxic dose of 2.1 μM before irradiation significantly enhanced cell killing. Withaferin A gave a sensitizer enhancement ratio (SER) of 1.5 for in vitro cell killing of V79 Chinese hamster cells at a non-toxic concentration of approximately 2 μM. SER increased with drug dose (Devi *et al*., 1996).

Immunomodulatory Activity

Asgand showed a significant modulation of immune reactivity in animal models. Administration of Asgand was found to prevent myelo-suppression in mice treated with three immunosuppressive drugs viz. cyclophosphamide, azathioprin, and prednisolone. Treatment with Asgand was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice (Ziauddin *et al*., 1996). Administration of Asgand extract was found to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Administration of Asgand extract increased the number of α-esterase positive cells in the bone marrow of CTX treated animals, compared to the CTX alone treated group (Davis *et al*., 1998). Administration of Asgand extract was found to significantly reduce leucopenia induced by sub-lethal dose of gamma radiation (Kuttan, 1996). Withaferin A and Withanolide E exhibited specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes. Withanolide E had specific effect on T lymphocytes whereas Withaferin A affected both B and T lymphocytes (Aggarwal *et al*., 1999, Davis *et al*., 2000, Gautam *et al*., 2004, Rasool *et al*., 2006, Rastogi *et al*., 1998).

Anti-stress/Adaptogenic Activity

Anti-stressor effect of Asgand was investigated in rats using cold water swimming stress test. The drug treated animals showed better stress tolerance (Archana *et al*., 1999). A withanolide-free aqueous fraction isolated from the roots of *Withania somnifera* exhibited anti-stress activity in a dose-dependent manner in mice (Khare, 2007). Asgand has been evaluated for its adaptogenic activity. Administration of Asgand with other drugs in experimental animals exposed to a variety of biological, physical and chemical stressors was found to offer protection against these stressors (Bhattacharya, 1992, Rege *et al*., 1999).

Anticonvulsant Activity

Administration of Asgand 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 (Kulkarni *et al*., 1996). Asgand 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 Asgand extract in convulsions has been reported to involve GABAergic mediation (Kulkarni *et al*., 1993).

Neuropharmacological Activity

Total alkaloidal fraction of root extract showed prolonged hypotensive, bradycardiac and respiratory stimulant activities in dogs. Hypotensive effect was mainly due to autonomic ganglion-blocking action and was augmented by the depressant action on higher cerebral centres. The total alkaloids produced a taming and a mild depressant effect (tranquillizer-sedative type) on the CNS in several experimental animals (Rastogi *et al*., 1998). Systemic administration of Asgand root extract led to differential effects on acetylcholinesterase (ACHE) activity in basal forebrain nuclei. Slightly enhanced ACHE activity was found in the lateral septum and globus pallidus. Asgand root extract affects preferentially events in the cortical and basal forebrain cholinergic signal transduction cascade. The drug induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognition-enhancing and memory-improving effects of extract from *Withania somnifera* observed in animals and humans (Schliebs *et al*., 1997).

Musculotropic Activity

The total alkaloids of Asgand showed relaxant and antispasmodic effects against several spasmogens on intestinal, uterine, bronchial, tracheal and blood vascular muscles. The pattern of smooth muscle activity of the alkaloids was similar to that of papaverine which suggested a direct musculotropic action (Anonymous, 1982).

Anti-oxidant Activity

Administration of active principles of *Withania somnifera*, consisting of equimolar concentrations of sitoindosides VII-X and Withaferin A, was found to increase superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) activity in rat brain frontal cortex and striatum.

Antioxidant effect of active glycowithanolides of *Withania somnifera* (WSG) may explain, at least in part, the reported anti-inflammatory, immunomodulatory, anti-stress, anti-aging and cognition-facilitating effects produced by them in experimental animals, and in clinical situations (Bhattacharaya *et al*., 1997).

Anti-ageing Effect

Double-blind clinical trial carried out to study the effect of plant on prevention of ageing in 101 normal healthy males in 50-59 years age group. Root powder (0.5 g) was given orally three times a day for 1 year. Results showed statistically significant increase in Hb, RBC, hair melanin, and seated stature in treated group in comparison to placebo group. Decrease in serum cholesterol was more in treated group than in placebo group (Rastogi *et al*., 1998).

Anti-hyperglycaemic Effect

Asgand along with other ingredients of a composite formulation (Transina) have been reported to decrease streptozocin (STZ)-induced hyperglycaemia in rats. This anti-hyperglycaemic effect may be due to pancreatic islet free radical scavenging activity because the hyperglycaemic 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 (Bhattacharaya *et al*., 1997).

Macrophage-Activating Effect

The chemotactic activity of macrophages and production of interleukin-1 (IL-1) and tumour necrosis factor (TNF) were significantly reduced in mice treated with the carcinogen ochratoxin A (OTA). Administration of Asgand with other drugs was found to significantly inhibit OTA-induced suppression of macrophage chemotaxis and production of IL-1 and TNF-α by macrophages (Dhuley, 1997).

Morphine Tolerance and Dependence-Inhibiting Effect

Repeated administration of Asgand in mice attenuated the development of tolerance to the analgesic effect of morphine. Asgand also suppressed morphine-withdrawal jumps, a sign of the development of morphine dependence (Kulkarni *et al*., 1997). Administration of glycowithanolides of *Withania somnifera* was found to suppress morphine- induced inhibition of intestinal motility and to attenuate the development of tolerance to the analgesic effect of morphine in mice (Rao *et al*., 1995).

Hepatoprotective Activity

Withaferin A at 10mg/kg dose showed significantly protective effect against CCl4-induced hepatotoxicity in rats. It was as effective as hydrocortisone dose for dose (Khare, 2007, Rastogi *et al*., 1998).

Other Effects

The combination of Asgand (*Withania somnifera*) and Ginseng (Panax ginseng) was orally administered in rats for 90 days using three doses. There was significant increase in body weight, food consumption and liver weight, and improved haematopoiesis was observed (Aphale *et al*., 1998).

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