Review

THERAPEUTIC USE OF *WITHANIA SOMNIFERA* : A REVIEW

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ABSTRACT

In India it is estimated that around 70,000 plant species, approximately 7500 species have been recorded to have medicinal value. There are estimated to be more than 717,319 registered practitioners of ayurveda, siddha, unani and homeopathy in India and in recent years, the growing demand for herbal products has led to the extinction of many important herbs. *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. *Withania somnifera* possess good immunomodulatory anti-inflammatory, anti-tumor, antioxidant, anticancer properties and medicinally important chemicals, they protect the cells from oxidative damage and diseases. Keeping in view the medicinal properties of *Withania somnifera* Dunal (Asgand), an attempt has been made in this review paper we have tried to explore the various dimensions of the drug including phytochemical and therapeutic knowledge about Ashwagandha, which is used to exploit novel medicines.

KEYWORDS: *Withania somnifera*; immunomodulatory; anti-inflammatory; antioxidant and Unani medicine

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INTRODUCTION

According to the World health organization, traditional medicines are widely used in India. Approximately 80% of the population of developing countries depend on traditional medicines for their primary health care needs [1-3]. Plants are one of the most important sources of medicines in world. The medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance. The medicinal plants contain several phytochemicals such as Vitamins (A, C, E, and K), Carotenoids, Terpenoids, Flavonoids, Polyphenols, Alkaloids, Tannins, Saponins, Saponins, Enzymes, and Minerals etc. etc. These phytochemical possess antioxidant activities, which can be used in the treatment of multiple ailments. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability [4, 5]. Because of these advantages the medicinal plants have been widely used by the traditional medical practitioners in their day to day practice. 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, 6-10]. *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 medical system for over 3000 years. Numerous studies indicated that ashwagandha possesses antioxidant, antitumor, antistress, anti-inflammatory, immunomodulatory, hematopoetic, anti-ageing, anxiolytic, antdepressive rejuvenating properties and also influences various neurotransmitter receptors in the central nervous system [11].

The researchers revealed that a specific extract from the plant, Withaferin A, was more effective in the inhibition than the common cancer chemotherapy drug, doxorubicin, they used to compare it with [12].

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, and a neutral compound. 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 [13,14].

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.[15]

Leaves

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 (15). 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 roperties of the leaves and roots are attributed to Withaferin A [13].

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 [13].

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 [16-20].

Anti-inflammatory Activity

Withaferin A exhibits fairly potent anti-arthritic and antiinflammatory 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[15]. 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 [13, 21]. 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 .The studies were carried out to investigate the release of serum -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 [22].

Antibiotic Activity

The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10 g/ml inhibited the growth of various Gram-positive bacteria, a. The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10g/ml inhibited the growth of various Gram-positive bacteria, acid-fast and aerobic bacilli, and pathogenic fungi. It was active against Micrococcus pyogenes varaureus and partially inhibited the activity of Bacillus subtilis glucose-6-phosphatedehydrogenase.

Withaferin A inhibited Ranikhet virus. The shrub's extract is active against Vaccinia virus and Entamoeba histolytica[13,15,21]. 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 [23]. 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 [13].

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 peroxidise (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, antiaging and cognition-facilitating effects produced by them in experimental animals, and in clinical situations [24].

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 [25].

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 [26].A withanolide-free aqueous fraction isolated from the roots of Withania somnifera exhibited anti-stress activity in a dose dependent manner in mice [15]. 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 [24,27].

Antitumor Properties

To investigate its use in treating various forms of cancer, the antitumor and radiosensitizing effects of WS have been studied. In one study, WS was evaluated for its anti-tumor effect in urethane-induced lung adenomas in adult male albino mice [28].Simultaneous administration of WS (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; WS treated, 0/26, and WS plus urethane treated, 6/24, $p<0.05$). The histological appearance of the lungs of animals protected by WS 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, WS treatment also reversed the adverse effects of urethane on total leukocyte count, lymphocyte count, body weight, and mortality. The growth inhibitory effect of WS was also observed in Sarcoma 180 (S-180), a transplantable mouse tumor [29].Ethanol extract of WS root (400 mg/kg and up, daily for 15 days) after intra-dermal inoculation of 5x105 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. WS was also found to act as a radio- and heat sensitizer in mouse S- 180 and in Ehrlich ascites carcinoma [29-31].Antitumor and radiosensitizing effects of withaferin (a steroidal lactone of WS) were also seen in mouse Ehrlich ascites carcinoma *in vivo*[32]. Withaferin A from WS gave a 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.(29-31). These studies are suggestive of antitumor activity as well as enhancement of the effects of radiation by WS.

Hemopoetic Effect

Administration of WS extract was found to significantly reduce leukopenia induced by cyclophosphamide (CTX) treatment in Swiss albino mice.(33)Total white blood cell count on the 12th day of the CTX-treated group was 3720/mm^3; that of the CTX-plus-WS group was 6120/mm^3. In the CTX-plus-WS mice, the cellularity of the bone marrow was significantly increased (13.1 x 106 /femur) ($p<0.001$) compared to the CTX-alone treated group (8 x 106/femur). Similarly, the number of alpha-esterase positive cells (1130/4000 cells) in the bone marrow of the CTX-plus-WS mice increased compared to the CTX alone mice (687/4000 cells).The major activity of WS may be the stimulation of stem cell proliferation. These studies indicated WS 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.

Effects on the Endocrine System

Based on the observations that WS provides protection from free radical damage in the mouse liver, studies were conducted to determine the efficacy of WS in regulating thyroid function.(34-35) 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. WS significantly reduced hepatic lipid peroxidation and increased the activity of superoxide dismutase and catalase. The results suggest WS stimulates thyroidal activity and also promotes hepatic antioxidant activity.

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 [36]. 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 [37].

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 [21].

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 ganglionblocking 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 [21]. 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 [38].

General Toxicity Studies

An important consideration when investigating the medicinal properties of an unknown compound is diligent evaluation of its potential for harmful effects, usually evaluated through toxicity studies. For WS, no systematic study was found which included acute, sub-acute, sub-chronic or chronic toxicity of WS root powder, whole plant powder, or different extracts of the plant (e.g., water, alcohol, petroleum ether, purified alkaloids, and glycosides). The acute toxicity data found as a part of pharmacological studies are summarized here. Although one preliminary toxicity study of WS was conducted, it was of insufficient quality to support its findings as too few animals were used, body weight data was not collected, and survival data was not reported [39] In one central nervous system study, a two-percent suspension of ashwagandholine (total alkaloids from the roots of WS) prepared in ten-percent propylene glycol using two percent gum acacia as suspending agent was used to determine acute toxicity[40]. The acute LD50 was 465 mg/kg (332-651 mg/kg) in rats and 432 mg/kg (299-626 mg/kg) in mice.

In an antistress-effect study, an alcohol extract from defatted seeds of WS dissolved in normal saline was used to study LD50 in albino mice.(41) The acute LD50 was 1750 +/- 41 mg (p.o). In another antistress-effect study, aqueous-methanol extracts of the root from one-year-old cultivated WS (SG-1) and equimolar combinations of sitoindosides VII and VIII and withaferin-A (SG-2) were studied for acute toxicity.(42) The acute LD50 of SG- 1 and SG-2 by intraperitoneal administration in mice was 1076 +/- 78 mg/kg and 1564 +/-92 mg/kg, respectively.

CONCLUSION

Medicinal plants maintain the health & vitality of individuals & also cure disease, without causing toxicity. In the present study, we have discussed the chemical composition, therapeutic uses of *Withania somnifera*. In the past few years, many promising bioactivities such asanticancer, immunostimulant, Anticonvulsant and anti-oxidant activity of *Withania somnifera* have been reported. The pharmacological and medicinal significance of *Withania somnifera* is gradually increasing. In conclusion, this article provides the therapeutic knowledge about *Withania somnifera*, which is used by the people all over the world. Also, it is of significance to exploit novel medicines from *Withania somnifera*.

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