Review Article

Therapeutic benefits of Withania somnifera: An Exhaustive Review

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ABSTRACT

This review was conducted with the objective of enlisting the diverse therapeutic benefits of Withania somnifera (Ws). Specifically, the literature was reviewed for articles pertaining to the therapeutic benefits of Ws. Literature was searched using PubMed and Science Direct as the major targets. All the research publications reporting therapeutic effects of Witahnia somnifera were studied. The quality of the studies was not evaluated because of wide range of methods employed by each study. Literature review indicate Withania somnifera possesses thyroid stimulant, anti-stress, anti-tumor, radiosensitizing, immunomodulatory, hepatoprotective, anticonvulsant, radio-sensitizing, cardioprotective, hypoglycemic, diuretic, hypocholesterolemic, adaptogenic and anti-oxidant properties. Ashwagandha is having diverse pharmacological actions on different systems. It is having great potential to be used for many therapeutic benefits. But the drug is lacking clinical proof of the various activities, so it needs to be worked upon on the clinical side.

INTRODUCTION

Withania somnifera is an extensively used herb in the Indian system of Medicine - Ayurveda. This herb is being used traditionally since more than 4000 years in India.

Indian name: Ashwagandha, Botanical name: Withania somnifera Dunal (Solanaceae)

Vernacular names

Ayurvedic:Ashwagandhaa, Hayagandhaa, Ashwakanda,Gandharvagandhaa, Turaga, Turagagandhaa, Turangagandhaa, Vaajigandhaa, Gokarnaa, Vrishaa, Varaahakarni, Varadaa, Balyaa, Vaajikari. (A substitute for Kaakoli and Kshirakaakoli.) Cultivated var.: Asgandh Naagori. (Indian botanists consider the cultivated plants distinct from the wild ones.), Unani: Asgandh, Siddha: Amukkuramkizhangu, English: Winter Cherry. (Physalis alkekengi is also known as Winter Cherry.)

It is distributed in arid parts of India up to 5,500 m. The plant is widely distributed in North-Western India, Bombay, Gujarat, Rajasthan, Madhya Pradesh, Uttar Pradesh, Punjab plains and extends upto the mountain regions of Himachal Pradesh and Jammu. The plant is distributed throughout the dry and arid subtropical regions of India, and not common in Kerala. The plant is also recorded to occur in Mediterranean (Israel), Canary Islands and Cape of Go[11-15].

Therapeutic properties of Ashwagandha

Anti-oxidant activity

A study done by Bhattacharya et al, 1997 investigated the anti-oxidant activity of active principles of Withania somnifera, consisting of equimolar concentrations of sitoindosides VII-X and Withaferin A, for their effects on rat brain frontal cortical and striatal concentrations of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX). When active glycowithanolides of W. somnifera (WSG) (10 and 20 mg/Kg, i.p.), were administered once daily for 21 days, there was a dose-related increase in SOD, CAT and GPX activity in frontal cortex and striatum, which was statistically significant on days 14 and 21.[5]

Another study reported by Bhattacharya in 2000 investigated the antioxidant activity of Withania somnifera (WS) glycowithanolides in chronic footshock

stress induced changes in rat brain frontal cortex and striatum. The stress procedure, given once daily for 21 days, induced an increase in superoxide dismutase (SOD) and lipid peroxidation (LPO) activity, with concomitant decrease in catalase (CAT) and glutathione peroxidase (GPX) activities in both the brain regions. WS glycowithanolides (WSG) administered orally 1 h prior to the stress procedure for 21 days, in the doses of 10, 20 and 50 mg/Kg, induced a dose-related reversal of the stress effects. Thus, they concluded that WSG tended to normalise the augmented SOD and LPO activities and enhanced the activities of CAT and GPX. Their results indicate that, at least part of chronic stress-induced pathology may be due to oxidative stress, which is mitigated by WSG, lending support to the clinical use of the plant as an antistress adaptogen[6].

Anti-stress activity

Archna et al conducted a study in 1998 for evaluating the anti-stressor properties using adult Wistar strain albino rats and cold water swimming stress test. The results indicated that the drug treated animals show better stress tolerance[4].

Anti-tumor and radiosensitizing activity

A study by Devi, 1996 confirmed the anti-tumor and radiosensitizing properties of Withania somnifera (Ashwagandha). The alcoholic extract of the dried roots of the plant as well as the active component Withaferin A isolated from the extract showed significant antitumor and radio sensitizing effects in experimental tumors in vivo, without any noticeable systemic toxicity[9].

Immunomodulatory activity

Agarwal et al, 1999 conducted a study confirming the immunomodulatory activities of extracts from Ashwagandha, Withania somnifera (L.) Dunal (Solanaceae), namely WST and WS2, in mice for immune inflammation: active paw anaphylaxis and delayed type hypersensitivity (DTH). He assessed the immunomodulatory effect in IgE-mediated anaphylaxis as reduction of ovalbumin-induced paw edema, in animals treated with WS2 at doses of 150 and 300 mg/Kg, and compared the results with the standard drug disodium chromoglycate.[1] Davis, 2001 found that the administration of an extract from the powdered root of the plant Withania somnifera could stimulate immunological activity in Balb/C mice. Treatment with five doses of Withania root extract (20 mg/dose/animal; i.p.) was found to enhance the total WBC count (17 125 cells/mm^3) on 10th day. Bone marrow cellularity (27×10^6 cells/femur) as well as α-esterase positive cell number (1800/4000 cells) also increased significantly after the administration of Withania extract. Treatment with Withania extract along with the antigen (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen[8].

Hepatoprotective activity

Harikrishnan et al, 2008 investigated the influence of W.somnifera root powder on the levels of circulatory ammonia, urea, lipid peroxidation products such as TBARS (thiobarbituric acid and reactive substances), HP (hydroperoxides) and liver marker enzymes such as AST (aspartate transaminase), ALT (alanine transaminase) and ALP (alkaline phosphatase), for its hepatoprotective effect in ammonium chloride induced hyperammonemia. Ammonium chloride treated rats showed a significant increase in the levels of circulatory ammonia, urea, AST, ALT, ALP, TBARS and HP. These changes were significantly decreased in rats treated with W.somnifera root powder and ammonium chloride[12].

Anticonvulsant activity

In 2008 a study by Kulkarni et al elucidated the effect of Withania somnifera root extract (Ws) on pentylenetetrazole (PTZ) seizure threshold in mice. They recorded the minimal dose of PTZ needed to induce different phases of convulsions as an index of seizure threshold. Ws (100 or 200

mg/Kg, p.o.) increased the PTZ seizure threshold for the onset of tonic extension phase whereas a lower dose (50 mg/Kg, p.o.) did not show any effect on the seizure threshold. Co-administration of a sub-effective dose of Ws alongwith a subprotective dose of either GABA (25mg/Kg, i.p.) or diazepam (0.5 mg/Kg, i.p.) increased the seizure threshold[16].

Antiproliferative activity

Jayaprakasam et al, 2003 isolated twelve withanolides such as withaferin A (1), sitoindoside IX (2), 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2,3-dihydrowithaferin A (3), 2, 3-dihydrowithaferin A (4), 24, 25-dihydro-27-desoxywithaferin A (5), physagulin D (1→6)-β-D-glucopyranosyl- (1→4)-β-D-glucopyranoside (6), 27-O-β-D-glucopyranosylphysagulin D (7), physagulin D (8), withanoside IV (9), and 27-O-β-D-glucopyranosylviscosalactone B (10), 4, 16-dihydroxy-5β, 6β-epoxyphysagulin D (11), viscosalactone B (12) from the leaves of this species. Compounds 1–12 and diacetylwithaferin A (13) were tested for their antiproliferative activity on NCI-H460 (Lung), HCT-116 (Colon), SF-268 (Central Nervous System; CNS and MCF-7 (Breast) human tumor cell lines. The inhibitory concentration to afford 50% cell viability (IC_{50}) for these compounds was determined by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. Withaferin A and its derivatives exhibited inhibitory concentrations (50%) ranging from 0.24±0.01 to 11.6±1.9 µg/mL. Viscosalactone B (12) showed the 50% inhibition at concentrations ranging from 0.32±0.05 to 0.47±0.15 µg/mL whereas its 27-O-glucoside derivative (10) exhibited IC_{50} between 7.9±2.9 and 17.3±3.9 µg/ml. However, Physagulin D type withanolides showed either weak or no activity at 30 µg/mL. Therefore, they concluded that the incorporation of withanolides in the diet may prevent or decrease the growth of tumors in human.[13]

Radio-Sensitizing activity

Devi, 1996 isolated Withaferin A, a steroidal lactone from the roots of the Indian medicinal plant Withania somnifera, and found that it reduced survival of V79 cells in a dose-dependent manner. LD 50 for survival was 16 muM. They gave one-hour treatment with a nontoxic dose of 2.1 muM before irradiation and found that it significantly enhanced cell killing, giving a sensitizer enhancement ratio (SER) of 1.5 for 37% survival and 1 .4 for 10% survival. SER increased with drug dose, but at higher doses the increased lethality appeared to be due to two effects-drug toxicity and radiosensitization. The drug induced a G 2/M block, with a maximum accumulation of cells in G 2-M phase at 4 h after treatment with 10.5 muM withaferin A for 1 h[10].

Cardioprotective activity

Mohanty et al, 2004 designed a study to evaluate the cardioprotective potential of hydro-alcoholic extract of Withania somnifera on the basis of haemodynamic, histopathological and biochemical parameters in the isoprenaline-(isoproterenol) induced myocardial necrosis in rats and to compare with Vitamin E, a known cardioprotective antioxidant. They divided Wistar albino male rats (150–200 g) into six main groups: sham, isoprenaline control, Withania somnifera/Vitamin E control and Withania somnifera/Vitamin E treatment groups and administered Withania somnifera at doses 25, 50 and 100 mg/Kg and Vitamin E at a dose of 100 mg/Kg, orally for 4 weeks. On days 29 and 30, they gave isoprenaline (85 mg/Kg), subcutaneously at an interval of 24 hr to the rats in the isoprenaline control and Withania somnifera, Vitamin E treatment groups. On day 31, recorded the haemodynamic parameters and removed the hearts subsequently and processed for histopathological and biochemical studies. A significant decrease in glutathione ($P<0.05$), activities of superoxide dismutase, catalase, creatinine phosphokinase and lactate dehydrogenase ($P<0.01$) as well as increase in lipid peroxidation marker

malonyldialdehyde level (P<0.01) was observed in the hearts of isoproterenol control group rats as compared to sham control. Their data showed that Withania somnifera (25, 50 and 100 mg/Kg) exerts a strong cardioprotective effect in the experimental model of isoprenaline-induced myonecrosis in rat concluding that augmentation of endogenous antioxidants, maintenance of the myocardial antioxidant status and significant restoration of most of the altered haemodynamic parameters may contribute to its cardioprotective effect.[17]

Hypoglycemic, diuretic and hypocholesterolemic activity

Andallu et al, 2000 assessed the Hypoglycemic, diuretic and hypocholesterolemic effects of roots of W. somnifera (Ashwagandha) on human subjects. They treated six mild NIDDM subjects and six mild hypercholesterolemic subjects with the powder of roots of W. somnifera for 30 days and studied suitable parameters 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. They observed significant increase in urine sodium, urine volume, significant decrease in serum cholesterol, triglycerides, LDL (low density lipoproteins) and VLDL (very low density lipoproteins) cholesterol indicating that root of W. somnifera is a potential source of hypoglycemic, diuretic and hypocholesterolemic agents. Their clinical observations revealed no adverse effects.[3]

Adaptogenic activity

Singh et al, 1982 tested Withania somnifera for its adaptogenic properties. Pretreatment with this drug increased the swimming endurance in mice. It prevented gastric ulcers induced chemically or by stress in rats. Milk-induced leucocytosis was also prevented in mice. The drug prevented increase in adrenal weight and decrease in ascorbic acid and Cortisol content of adrenals during stress. They concluded that it appears to induce a state of non-specifically increased resistance (SNIR) during stress.[19]

Thyroid stimulant activity

Panda et al, 1999 investigated the effects of daily administration of Withania somnifera root extract (1.4 g/Kg body wt.) and Bauhinia purpurea bark extract (2.5 mg/Kg body wt.) for 20 days on thyroid function in female mice. While serum triiodothyronine (T_3) and thyroxine (T_4) concentrations were increased significantly by Bauhinia, Withania could enhance only serum T_4 concentration. Both the plant extracts showed an increase in hepatic glucose-6-phosphatase (G-6-Pase) activity and antiperoxidative effects as indicated either by a decrease in hepatic lipid peroxidation (LPO) and/or by an increase in the activity of antioxidant enzyme(s). It appears that these plant extracts are capable of stimulating thyroid function in female mice.[18]

Kuttan, 1996 found that the administration of a 75% methanolic extract of Withania somnifera significantly increases the total WBC count in normal Balb/C mice and reduces the leucopenia induced by sublethal dose of gamma radiation. Treatment with W. somnifera was found to increase the bone marrow cellularity significantly, the percentage increase being 146.3. Treatment with W. somnifera had normalised the ratio of normochromatic erythrocytes and polychromatic erythrocytes in mice after the radiation exposure. Major activity of W. somnifera seemed to be in the stimulation of stem cell proliferation.[14]

Davis et al, 1998 found the administration of Withania somnifera extract (Solanaceae) to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Treatment of Withania along with CTX was found to significantly (P<0.001) increase the bone marrow cellularity (13.1×10^6 cells/femur) compared to CTX alone treated group (8×10^6 cells/femur).[7]

CONCLUSION

The literature shows that Withania is a very promising plant. Although it is used widely in ayurvedic medicines, but the plant should be worked more on the clinical side. There is enough pre clinical data to prove the effects of Withania on almost every system. What it lacks is the clinical support data. The anti tumor effect of Withania should be researched more.

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