IJMPR 2022, 6(4), 51-57

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

COMPREHENSIVE REVIEW ON PHYTOPHARMACOLOGICAL POTENTIAL OF *WITHANIA SOMNIFERA*

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Received on: 15/03/2022
Revised on: 05/04/2022
Accepted on: 25/04/2022

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ABSTRACT

Withania somnifera also known as ashwagandha, Indian ginseng, and winter cherry, it has been an important herb in the Ayurvedic. The traditional systems of medicine have used the plant successfully to treat many disorders including anxiety, as an antioxidant, adaptogen, aphrodisiac, liver tonic, anti-inflammatory agent, astringent etc. The folklore medicine also advocates the use of this plant for diseases. The presence of potentially active Phytochemical and their multifunctional properties make *Withania somnifera* leaves, root, bark, and stem perfect candidates for the production of phyto-pharmaceutical products. So having this in mind this review article focuses on collecting the documentation of all the research work that is performed on *Withania somnifera* and is the segregation of the pharmacology, chemistry and traditional claims of the activities that are attributed to the plant.

KEYWORDS: *Withania somnifera*, Medicinal plant, Traditional, Ashwagandha, Anxiety.

INTRODUCTION

Medical herbalism is today a sophisticated system of natural medicine using plant extracts and herbs to treat physical and mental disorders. Herbalism is a traditional or folk medicinal practice based on the use of whole plant, plant extracts, plant parts such as seeds, berries, roots, leaves or flowers etc., for medicinal purposes. It is also known as herbal medicine or botanical medicine or phyto-medicine or medical herbalism or herbology and phytotherapy.[1] The scope of herbal medicine is extended to include fungal and bee products as well as minerals, shells and certain animal parts. Herbalism as a long tradition of use outside of conventional medicine, it is becoming more stream as improvements in analysis and quality control along with advances in clinical research show the value of herbal medicine is treating and preventing disease.[1,2]

Herbal Medicine

Herbal care or traditional system of medicine are used throughout the world and from century's herbs have been the original source for most of the drugs. Medicinal plants contain so many chemical compounds which are the major source of therapeutic agents to cure human diseases. Herbal drugs enjoy the advantages of comparatively less toxic than synthetic drugs, more harmony with the biological system and affordable to all classes of people. Recent discovery and advancement in medicinal and aromatic plants have lead to the enhancement of health care of mankind. Various medicinal plants like Neel, Neem, Arjuna, Aswagandha, Tulsi, etc. traditionally used for treating various disese.[1,3, 4]

Plant Profile[5-8]

Regional Name

Sanskrit- Ashwagandha, Bengali- Ashwagandha, Gujrati- Asandha, Hindi- Asgandha, Kannada- Ashwagandhi, Tamil- Amukara, Telugu- Penneru, English- Winter cherry

Taxonomical Classification

Kingdom: Plantae, Plants;
Division: Angiosperma
Class: Dicotyledons
Order: Tubiflorae
Family: Solanaceae
Genus: Withania
Species: Somnifera
Binomial name: *Withania somnifera* (L.) Dunal

Fig. 1: *Withania somnifera* Plant.

Fig. 2: *Withania somnifera* Root.

Withania somnifera (WS), also known as ashwagandha, Indian ginseng, and winter cherry, it has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years.[9]

Botanical description

WS 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 India. An erect, evergreen, tomentose shrub, 30-150 cm high, found throughout the drier parts of India in waste places and on bunds. Roots are stout fleshy, whitish brown; leaves simple ovate, glabrous, those in the floral region smaller and opposite; flowers inconspicuous, greenish or lubrid-yellow, in axillary, umbellate cymes; berries small, globose, orange-red when mature, enclosed in the persistent calyx; seeds yellow, reniform. The roots are the main portions 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.[8-10]

Parts used: Whole plant, roots, leaves, stem, green berries, fruits, seeds, bark are used.

Phytochemistry

Chemical constituents of WS are always of an interest for the researchers. The biologically active chemical constituents are **alkaloids** (ashwagandhine, cuscohygrine, anahygrine, tropine etc), **steroidal compounds**, including ergostane type steroidallactones, withaferin A, withanolides A-y, withasomniferin-A, withasomidienone, withasomniferols A-C, withanone etc. Other constituents include saponins containing an additional acyl group (sitoindoside VII and VIII), and **withanolides** with a glucose at carbon 27 (sitoindoside IX and X). Apart from these contents plant also contain chemical constituents like withaniol, acylsteryl glucosides, starch, reducing sugar, hantreacotane, ducitol, a variety of amino acids including aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, cystine, tryptophan, and high amount of iron. Withaferin A, chemically characterized as 4b,27-dihydroxy- 5b-6b-epoxy-1-oxowitha-2, 24-dienolide, is one of the main withanolidal active principles isolated from the plant. WS showed chemogenetic variation and so far three chemotype I, II and III had been reported. These are chemically similar but differ in their chemical constituents especially in withanolide content. In Indian variety thirteen Dragendroff positive alkaloids have been obtained. [11, 12] The reported alkaloids are anaferine (bis (2-piperidylmethyl) ketone); isopelletierine; tropine; pseudotropine; 3α-tigloyloxtropine; 3- tropyltigloate; cuscohygrine; dl-isopelletierine; anahygrine; hygrine; mesoanaferine; choline; somniferine; withanine; withananine; hentriacontane; visamine; withasomnine, a pyrazole derivative from West Germany; pseudowithanine and ashwagandhine. Withaniol (mixture of withanolides) and number of withanolides including withaferine-A; withanolide N and O; withanolide D; withanolide p and 8; withanolide Q and R; withanolide y, 14α-hydroxy steroids and withanolides G, H, I, J, K and U. Seven new withanolide glycosides called withanosides I, II, III, IV, V,VI and VII had been isolated and identified. Much of WS pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D. [13-15]

Traditional Uses

It is in use for a very long time for all age groups and both sexes and even during pregnancy without any side effects. Historically, the plant has been used as an antioxidant, adaptogen, aphrodisiac, liver tonic, anti-inflammatory agent, astringent and more recently to treat ulcers, bacterial infection, venom toxins and senile dementia. Clinical trials and animal research support the use of WS for anxiety, cognitive and neurological disorders, inflammation, hyperlipidemia and Parkinson's disease. WS chemo-preventive properties make it a potentially useful adjunct for patients undergoing radiation and chemotherapy. Recently WS is also used to inhibit the development of tolerance and dependence on chronic use of various psychotropic drugs.[16,17]

The roots of the plant are categorized as rasayanas, which are reputed to promote health and longevity by augmenting defense against disease, arresting the ageing process, revitalizing the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing.[18,19]

The root smells like horse ("ashwa"), that is why it is called Ashwagandha (on consuming it gives the power of a horse). It is commonly used in emaciation of children (when given with milk, it is the best tonic for children), debility from old age, rheumatism, vitiated conditions of vata, leucoderma, constipation, insomnia, nervous breakdown, goiter etc. [20] The paste formed when roots are crushed with water is applied to reduce the inflammation at the joints. [21] It is also locally applied in carbuncles, ulcers and painful swellings. [22] The root in combination with other drugs is prescribed for snake venom as well as in scorpion-sting. It also helps in leucorrhoea, boils, pimples, flatulent colic, worms and piles. [23] The Nagori Ashwagandha is the supreme among all Ashwagandha varieties. Maximum benefit appears when fresh Ashwagandha powder is used.[24]

The leaves are bitter and are recommended in fever, painful swellings. The flowers are astringent, depurative, diuretic and aphrodisiac. The seeds are anthelmintic and combined with astringent and rock salt remove white spots from the cornea. Ashwagandharishta prepared from it is used in hysteria, anxiety, memory loss, syncope, etc. It also acts as a stimulant and increases the sperm count.[25]

Pharmacological Properties

Anxiety and depression

Active compond glycol-withanolides (WSG), isolated from WS roots investigated for anxiolytic and antidepressant actions in rats. WSG (20 and 50 mg/kg) was administered orally once daily for 5 days and the results were compared by those elicited by the benzodiazepine lorazepam (0.5 mg/kg, i.p.) for anxiolytic studies, and by the tricyclic anti-depressant, imipramine (10 mg/kg, i.p.), for the antidepressant investigations. Both these standard drugs were administered once, 30 min prior to the tests. WSG induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus-maze, social interaction and feeding latency in an unfamiliar environment, tests. Further, both WSG and lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioural despair' and 'learned helplessness' tests.[26,27]

Other study indicates that WS may alleviate these conditions predominantly through modulation of the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, as well as through GABAergic and serotonergic pathways.[28]

Antioxidant potential

In this study Several assays were performed to determine the antioxidant properties of this herb including 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) scavenging activity, ferric reducing antioxidant power (FRAP), ferrous chelation and inhibition of β-carotene bleaching.

The values for DPPH, FRAP, ferrous chelation and inhibition of β carotene bleaching for the three types of extracts ranged from 101.73-801.93 µg/ml, 2.26-3.29 mM Fe/kg, 0.22-0.65 mg/ml and 69.87-79.67%, respectively, indicating that W. somnifera, particularly the leaves, possesses significant antioxidant properties. The mean ascorbic acid content was 20.60-62.60 mg/100 g, and the mean anthocyanin content was 2.86-12.50 mg/100 g.[28, 29]

In other study active principles of Withania somnifera was investigated for their effects on rat brain frontal cortical and striatal concentrations of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX). Active glycowithanolides of W. somnifera (WSG) (10 and 20 mg/kg, i.p.), administered once daily for 21 days, induced a dose-related increase in SOD, CAT and GPX activity in frontal cortex and striatum, which was statistically significant on days 14 and 21, except with the lower dose of WSG on GPX activity, where the effect was evident only on day 21. The data were comparable to those induced by deprenyl (2 mg/kg/day, i.p.) with respect to SOD, CAT and GPX activities, which were evident by day 14. [30]

Antibacterial activities

Antibacterial activities were measured using the agar well diffusion method and five pathogenic Gram-negative bacteria: Escherichia coli, Salmonella typhi, Citrobacter freundii, Pseudomonas aeruginosa and Klebsiella pneumoniae. The leaf extracts displayed the highest activity against S. typhi (32.00 ± 0.75 mm zone of inhibition), whereas the lowest activity was against K. pneumoniae (19.00 ± 1.48 mm zone of inhibition). The lowest minimum inhibitory concentration value was 6.25 mg/ml, which was against S. typhi, followed by 12.5 mg/ml against E. coli.[30,31]

Immuno-modulatory Potential

WS root extract enhanced 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.[32]

In another study, Glycowithanolides and a mixture of sitoindosides IX and X isolated from WS, both produced statistically significant mobilization and activation of peritoneal macrophages, phagocytosis, and increased

activity of the lysosomal enzymes. Root extract of WS was tested for immunomodulatory effects in three myelosuppression models in mice: cyclophosphamide, azathioprin, or prednisolone.[33]

In one more study, WS also stimulated immunological activity in Balb/c mice. Treatment with five doses of WS was found to enhance the total WBC count on 10th day. Bone marrow cellularity as well as alpha-esterase positive cell number also increased significantly. Treatment with WS along with the antigen (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen. Maximum number of PFC (985 PFC/10(6) spleen cells) was obtained on the fourth day. WS inhibited delayed type hypersensitivity reaction in mice (Mantoux test). Administration of WS also showed an enhancement in phagocytic activity of peritoneal macrophages when compared to control in mice. These results confirm the immunomodulatory activity of WS extract in indigenous medicine. [34]

Nootropic Potential

Ashwagandha (Withania somnifera L.) root extract (50, 100 and 200 mg/kg; orally) improved retention of a passive avoidance task in a step-down paradigm in mice. Ashwagandha (50, 100 and 200 mg/kg; orally) also reversed the scopolamine (0.3 mg/kg)-induced disruption of acquisition and retention and attenuated the amnesia produced by acute treatment with electroconvulsive shock (ECS), immediately after training. Chronic treatment with ECS, for 6 successive days at 24 h intervals, disrupted memory consolidation on day 7. Daily administration of ashwagandha for 6 days significantly improved memory consolidation in mice receiving chronic ECS treatment. Ashwagandha, administered on day 7, also attenuated the disruption of memory consolidation produced by chronic treatment with ECS. On the elevated plus-maze, ashwagandha reversed the scopolamine (0.3 mg/kg)-induced delay in transfer latency on day 1.[35,36]

Cardiovascular protection

The effect of WS was studied on the cardiovascular and respiratory systems in dogs and frogs (55). The alkaloids had a prolonged hypotensive, bradycardiac, and respiratory-stimulant action in dogs. The study found that the hypotensive effect was mainly due to autonomic ganglion blocking action and that a depressant action on the higher cerebral centers also contributed to the hypotension. The alkaloids stimulated the vasomotor and respiratory centers in the brain stem of dogs. The cardio-inhibitory action in dogs appeared to be due to ganglion blocking and direct cardiodepressant actions. The alkaloids produced immediate predominant but short-lived cardio-depressant effects and a weak but prolonged cardiotonic effect in isolated normal and hypodynamic frog hearts.[37,38]

Hypo- glycemic and Hypo-lipidemic effect

For analysis of hypoglycemic potential six mild NIDDM subjects and six mild hypercholesterolemic subjects were treated with the powder of roots of WS for 30 days. Suitable parameters were studied 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.

Root powder of WS decreased total lipids, cholesterol and triglycerides in hypercholesteremic animals. Also elevate plasma HDL-cholesterol levels, HMG-CoA reductase activity and bile acid content of liver. A similar trend also reported in bile acid, cholesterol and neutral sterol excretion in the hypercholesteremic animals with WS administration.[39]

In another study aqueous extract of *Withania somnifera* (WS) investigated for insulin sensitivity in non-insulin-dependent diabetes mellitus (NIDDM) rats.Treatment with WS reduced the elevated levels of blood glucose, HbA_1c and insulin in the NIDDM rats. An oral glucose tolerance test was also performed in the same groups, in which author found a significant improvement in glucose tolerance in the rats treated with WS. The insulin sensitivity was assessed for both peripheral insulin resistance and hepatic insulin resistance. WS treatment significantly improved insulin sensitivity index (K_{ITT}) that was significantly decreased in NIDDM control rats.[40]

Anticancer Potential

The Anticancer effect was stated in a work of WS root extract on induced skin tumor in mice given WS before and during exposure to the skin cancer causing agent 7,12-dimethylbenz anthracene. A significant decrease in incidence and average number of skin lesions was demonstrated compared to the control group. Additionally, levels of reduced glutathione, SOD, CAT, and GPX in the exposed tissue returned to near normal values following administration of the extract.[41]

An in vitro study showed withanolides from WS 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 WS extracts may prevent or inhibit tumor growth in cancer patients and suggest a potential for development of new chemotherapeutic agents.[42]

In another study WS was evaluated for its antitumor effect in urethane-induced lung adenomas in adult male albino mice. Simultaneous administration of WS (200 mg/kg daily orally for seven months) and urethane (125 mg/kg biweekly for seven months) reduced tumor incidence significantly. The histological appearance of the lungs of animals protected by WS was similar to

those observed in the lungs of control animals. WS treatment also reversed the adverse effects of urethane on total leukocyte count, lymphocyte count, body weight, and mortality.[43]

Neuro-protective Potential

In the evaluation of anti-parkinsonian effects of WS extract, rats were pretreated with 100, 200 and 300 mg/kg b.w. of the W. somnifera extract orally for 3 weeks. On day 21, 2 microL of 6-OHDA (10 microg in 0.1% in ascorbic acid-saline) was infused into the right striatum while sham operated group received 2 microL of the vehicle. Three weeks after 6-OHDA injections, rats were tested for neurobehavioral activity and were killed 5 weeks after lesioning for the estimation of lipidperoxidation, reduced glutathione content, activities of glutathione-S-transferase, glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase, catecholamine content, dopaminergic D2 receptor binding and tyrosine hydroxylase expression. W. somnifera extract was found to reverse all the parameters significantly in a dose-dependent manner.[44,45]

Aphrodisiac Potential

WS was found to improve reproductive system function by many ways. WS extract decreased infertility among male subjects, due to the enhancement in semen quality which is proposed due to the enhanced enzymatic activity in seminal plasma and decreasing oxidative stress. Also, WS extract improved luteinizing hormone and follicular stimulating hormone balance leading to folliculogenesis and increased gonadal weight, although some animal studies had concluded that WS had reversible spermicidal and infertilizing effects in male subjects.[46,47]

CONCLUSION

The extensive survey of literature revealed that WS is an important source of many pharmacologically and medicinally important chemicals. In view of the activities that are established and proven scientifically for antidiabetic, immune mudulatory, epileptic, anxiolytic, antiparkinsonian, anti-cancer, anti-oxidant etc. the plant had been used traditionally for treatment of many diseases in the folklore. Although WS has been used successfully in Ayurvedic medicine for centuries, still more clinical trials should be conducted to support its therapeutic use. The present review would further help for the renaissance of other pharmacological activities on the plant and can also give a lead to take clinical studies based on present reported activities.

Conflicts of interest

There are no conflicts of interest.

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