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An overview of ashwagandha (*Withania somnifera*): A review

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Abstract
Due to its medicinal properties, *Withania somnifera* has great significance. *Withania somnifera* is a plant that has anti-tumorigenic properties and has been used in Ayurveda. The discovery of bioactive molecules that can kill cancer cells continues to draw interest in science. It has been noted that *Withania Somnifera* possesses anti-tumor properties, according to evidence from cell culture and animal studies.
Not only has it been shown that *Withania Somnifera* has therapeutic potential against cancer, it also has cancer preventive properties. The cancer-fighting properties are not only root extracts, but also leaf extracts that are an underused portion of the Ashwagandha plant. Withaferin A has hepatoprotective properties in addition to defense against carcinogenesis.

Keywords: *Withania somnifera*, withanolides, anti-cancer, anti-tumor

Introduction
Withania Somnifera is part of the Solanaceae family or the nightshade family, commonly known as Ashwagandha. For over 3000 years, Ashwagandha has been an essential herb in Ayurveda. In the northwestern Indian states of Gujarat, Madhya Pradesh, Maharashtra, Rajasthan, Uttar Pradesh, and the Punjab plains extending to the Himachal Pradesh and Jammu mountain regions, Withania species are generally distributed. It is cultivated in parts of Rajasthan and Madhya Pradesh. Triterpene lactines-withanolides, withaferin a, alkaloids, steroidal lactones, tropines and cuscohygrine-are the major chemical constituents of withanolides. Withanolides are structurally similar to Panax Ginseng ginsenosides, hence it is often referred to as Indian Ginseng. Withanolides have a range of biological functions, including anti-cancer, anti-inflammatory, immunomodulatory, anti-aging, anti-biotic, cardiovascular, anti-Parkinsonian, etc.

Botanical Description
In Latin, the species name somnifera means "inducing sleep." The name ashwagandha is a combination of ashva in Sanskrit, meaning horse and gandha meaning scent, reflecting that the root has an odor like a strong horse. It belongs to the Solanaceae family, while the subfamily is Asteridae and the order is Solanales. The plant is an upright, evergreen, 0.5 to 2m tall tonentose shrub [1].

Plant Description
A 60-90 cm tall suffruticose shrub. Ascending Branches. Stellate-tomentose Shoots. 4-13 x 2-9 cm leaves, elliptical-ovate to narrowly ovate, acute, cuneate or oblique, whole to replicate. The 10-20 mm-long Petiole. Easy, ovate and glabrous leaves. Flowers in the axillary, umbellate cymes are inconspicuous, greenish-yellow in color. Fruits: When mature, the berries are globose, orange-red, enclosed in the calyx. The seeds are yellow and resin-shaped [2].

Family Description
The Solanaceae are a flowering plant family that ranges from annual and perennial herbs to vines, lianas, epiphytes, shrubs and trees, and includes a variety of crops, medicinal plants, spices, grasses, and ornamentals. There are several family members that contain potent alkaloids, and some are extremely toxic. The family belongs to the Solanales order, in the Magnoliopsida asteride group and class. There are some 98 genera and some 2,700 species in the Solanaceae, with a great diversity of habitats, morphology and ecology [3].

Local Names
Indian ginseng, winter cherry, poison gooseberry

Chemical Constituents
Alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins), and saponins are major chemical constituents. Sitoindoside and acylsterylglucoside are anti-stress agents in Ashwagandha. Ashwagandha's active concepts, Sitoindosides VII-X and Withaferin-A, have anti-stress activity. Alkaloids and steroidal lactones are the primary constituents of Ashwagandha. Withanine and other substituents such as somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine and anaferine are composed of alkaloids. Steroidal lactones include steroidal lactones of the ergostane type, withaferin a, withanolide A-Y, withasomniferin-A, withasomidienone, withasomniferol A-C, withanone, etc. Withanolides have a C28 steroidal nucleus with a six-membered lactone ring with a C9 side chain. Also mentioned are the presence of saponins containing an additional acyl group (sitoindoside VII and VIII) and withanolides containing carbon 27 glucose (sitoindoside IX and X) 7. The plant exhibits variation with regional distribution in phytochemical composition. Withanine is the key constituent of the

numerous alkaloids. Thirteen positive Dragendroff alkaloids were isolated from the Indian variety. One of the main withanolidal active principles isolated from the plant is Withaferin A, chemically characterized as 4b, 27-dihydroxy- 5b-6b-epoxy-1-oxowitha-2, 24-dienolide. Chemogenetic variation was shown by *Withania Somnifera* and three chemotypes I, II and III have been identified so far. These are chemically similar but differ especially in the content of withanolide in their chemical constituents [4].

Synonyms

Physalis somnifera L.

Withania kansuensis Kuang

Withania microphysalis Suess

Ecology

It grows on rocky, shallow soil. In arid conditions and low quality, alkaline soils, the plant thrives. While most plants in this area may suffer from extreme stress, Ashwagandha thrives [5].

Anti-Cancer Activity

It has been noted that *Withania Somnifera* possesses anti-tumor properties, according to evidence from cell culture and animal studies. Not only has it been shown that *Withania Somnifera* has therapeutic potential against cancer, it also has cancer preventive properties. The cancer-fighting properties are not only root extracts, but also leaf extracts that are an underused portion of the Ashwagandha plant. Withaferin A has hepatoprotective properties in addition to defense against carcinogenesis. According to Ayurveda, Ashwagandha has many significant effects for the treatment and prevention of cancer. The dosage of Ashwagandha given as cancer therapy, however is possibly very different from what is given as a general supplement that promotes good health [5].

***In-Vivo* Studies**

The tumor incidence of urethane (125 mg/kg biweekly for seven months) induced lung adenomas in adult male albino mice was substantially decreased by the alcoholic extract of whole plant *W.Somnifera* (200 mg/kg orally daily for seven months). The histological appearance of the lungs of animals covered by *W.Somnifera* was close to that of control animals found in the lungs. The reactive molecules contributing to antimutagenesis and anticarcinogenesis have been found to be scavenged by this drug. The *W.Somnifera* root alcoholic extract was injected intraperitonially (ip) at daily doses of 200 to 1000 mg/kg for 15 days, beginning 24 hours after intradermal inoculation in Balb/c mice of 5 to 10(5) cells of Sarcoma 180 (S 180). In this tumor, cumulative doses of 7.5 to 10 g, ip, at daily doses of 500 to 750 mg/kg tend to produce a good response. The antitumor effect of the *W.Somnifera* root extract and its heat modification on the S 180 tumor grown on the dorsum of the adult Balb/c mouse was studied *In vivo*. The alcoholic root extract of the plant generated an *in vivo* growth inhibitory effect on the mouse tumor, the alcoholic root extract of the plant produced an *in vivo* growth inhibitory effect on the mouse tumor, and the alcoholic root extract of the dried root of the plant, as well as its active component withaferin A, showed important antitumor effect in *in vivo* experimental tumors [6].

Feasible Anti-Cancer Mechanism of *W. Somnifera*

W. Somnifera's anticancer activity is related to its multiple functions. The overall efficacy of the treatment of cancer can be improved by *W. Somnifera*. It is probable that its anticancer activity is due to the action of its main constituents, *viz*. Withaferin A which inhibits the production of RNA and proteins, and withanolide D, which inhibits production of RNA. Inhibition of RNA and proteins can lead to increased death of cancer cells. Both antioxidant and pro-oxidant activities are found in *W. Somnifera*. Via mass spectrometry, *W. Somnifera* was identified as the most potent tumor-inhibiting constituent of *W. Somnifera*. There is also a beneficial effect of *W. Somnifera* on the immune system, which may explain some of its antitumor activity. NK cell activity has been reported to be significantly enhanced by *W. Somnifera* during tumorigenesis [6].

Pharmacological Activities

Anti-Inflammatory Activity

Withaferin A has relatively strong anti-arthritic and anti-inflammatory function. Biologically active steroids, of which Withaferin A is a major component, have been linked to anti-inflammatory activity. Without any toxic effects, it has been found to effectively suppress arthritic syndrome. The animals treated with Withaferin a demonstrated weight gain in arthritic syndrome, unlike hydrocortisone-treated animals that lost weight. In several animal models of inflammation, such as carrageenan-induced inflammation, cotton pellet granuloma and adjuvant-induced arthritis, Ashwagandha (*Withania somnifera*) has been shown to have anti-inflammatory properties [7].

Immunomodulatory Activity

In animal models, Ashwagandha showed considerable variance in immune reactivity. Ashwagandha administration was found in mice treated with three immunosuppressive drugs, *viz*., to prevent myelo-suppression. Azathioprin, cyclophosphamide, and prednisolone. Ashwagandha treatment was found to significantly increase the concentration of hemoglobin, RBC count, and platelet count and body weight in mice. Ashwagandha extract administration was found to substantially reduce cyclophosphamide (CTX)-induced leucopenia. Ashwagandha extract administration increased the amount of β-esterase-positive cells in the bone marrow of animals treated with CTX. Ashwagandha extract administration substantially decreased leukopenia caused by the sub-lethal dose of gamma radiation. Withaferin A and Withanolide E had an immunosuppressive effect on lymphocytes B and T in humans. Withanolide E had a particular impact on T lymphocytes, while both B and T lymphocytes were affected by Withaferin A [7].

Antibiotic Activity

Recently, the antibiotic function of both roots and leaves has been demonstrated experimentally. Withaferin A inhibited the growth of many Gram-positive bacteria, acid-rapid and aerobic bacilli, and pathogenic fungi at a concentration of 10μg/ml. It was active against the inhibited Ranikhet virus of Micrococcus pyogenes var aureus and Withaferin A. The extract of the shrub is active against the viruses Vaccinia and Entamoeba histolytica. Ashwagandha showed defensive action against infection with systemic Aspergillus. The shrub extract is active against the Vaccinia and Entamoeba

histolytica viruses. Defensive action against systemic Aspergillus infection was shown by Ashwagandha [7].

Anti-Aging Activity

In a clinical trial, Ashwagandha was tested for its anti-aging properties. The herb was given to a group of 101 healthy males, aged 50-59 years, at a dosage of 3 grams daily for one year. In hemoglobin, red blood cell count, hair melanin, and sitting stature, the subjects experienced substantial improvement. Serum cholesterol was reduced and calcium was retained in the nails. Seventy percent of the study subjects reported sexual performance enhancement [7].

Antiparkinsonian Properties

Haloperidol or reserpine-induced catalepsy was substantially inhibited by *Withania Somnifera* and offered hope for treatment of Parkinson's disease. Due to the potent antioxidant, antiperoxidative and free radical quenching properties, antiparkinsonian effects of *Withania Somnifera* extract have been recorded [7].

Cardiovascular Protection

As stated in the following reports, *Withania Somnifera* may be useful as a general tonic, in part because of its beneficial effects on the cardiopulmonary system. The effect of *Withania Somnifera* has been studied in dogs and frogs on the cardiovascular and respiratory systems. There was a sustained hypotensive, bradycardiac, and respiratory stimulant action of the alkaloids in dogs. In the experimental model of isoprenaline-induced myonecrosis in rats, *Withania Somnifera* showed a strong cardioprotective effect. It can contribute to its cardioprotective effect by increasing endogenous antioxidants, retaining myocardial antioxidant status and significantly restoring most of the altered haemodynamic parameters [8].

Effect on Central Nervous System Cognition Promoting Effect

Ashwagandha belongs to a sub-group of Rasayanas known as Medhyarasayanas and is a well-known Ayurvedic Rasayana. Usually, Medhya relates to the mind and mental/intellectual capacity. Thus, Medhya Rasayana, like Ashwagandha, is used to encourage memory and intellect. Medhya Rasayanas' cognition-promoting influence is best seen in children with memory deficiencies, or when memory is impaired after head injury or prolonged illness and in old age [9].

Anxiolytic Effect

In all three standard anxiety measures, Ashwagandha produced a relaxing anxiolytic effect that was equivalent to the medication Lorazepam: elevated plus-maze, social contact and feeding delay in an unfamiliar environment. In addition, both Ashwagandha and Lorazepam decreased the levels of tribulin in the rat brain, an endocoid marker of clinical anxiety, when levels were increased following administration of pentylenetetrazole, the anxiogenic agent [9].

Anti-Arthritic Effect

Ashwagandha is an analgesic that soothes the pain response of the nervous system. Ashwagandha's strong anti-arthritic properties are now generally recognized and documented; it is also found to be effective as both antipyretic and analgesic as well.

For a rat experiencing heat analgesia induced by the hot plate process, Ashwagandha (1000 mg/kg/oral) developed significant analgesic activity. Ashwagandha's peak analgesic effect at the 2nd hour of administration was reported as 78.03 percent. Pre-treatment with paracetamol (100 mg/kg, ip) and cyproheptadine (10 mg/kg, ip) was tested for the involvement of pain mediators; prostaglandin and 5-hydroxytryptamine in Ashwagandha analgesic operation. Cyproheptadine greatly potentiated the analgesic function of Ashwagandha, but paracetamol did not display any substantial improvement in its activity, indicating the role of serotonin, but not prostaglandins, in Ashwagandha's analgesic activity [9].

Anti-Hyperglyceamic Effect

Ashwagandha has been reported to minimize streptozocin (STZ)-induced hyperglycaemia in rats, along with other composite formulation ingredients. This anti-hyperglycaemic effect may be attributable to the involvement of pancreatic islet free radical scavenging because the hyperglycaemic activity of STZ is a product of a decrease in the activity of pancreatic islet cell superoxide dismutase (SOD) leading to the accumulation of islet-beta cells of degenerative oxidative free radicals [9].

Nootropic Effect

The effects on brain cholinergic, glutamatergic and GABAergic receptors in rats of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of the roots of cultivated varieties of WS were studied. In the lateral septum and globus pallidus, the compounds significantly enhanced acetylcholinesterase (AChE) activity and decreased AChE activity in the vertical diagonal band. These changes were followed by increased binding of the M1-muscarinic-cholinergic receptor in the lateral and medial septum as well as in the frontal cortices, whereas in a variety of cortical regions, including the cingulate, frontal, parietal, and retrospinal cortex, M2-muscarinic receptor binding sites were increased. The results indicate that the compounds preferentially influence events in the cholinergic-signal transduction cascade of the cortical and basal forebrain. The drug-induced increase in the ability of the cortical muscarinic acetylcholine receptor could partially explain the cognition-enhancing and memory-improving effects of animal and human WS extracts. Neurite outgrowth in cultured rat cortical neurons was induced in a study by Zhao *et al* Withanoside IV (a constituent of WS; the origin of WS). In Abeta-injected mice, oral administration of withanoside IV significantly enhanced memory deficits and prevented loss of axons, dendrites, and synapses. After oral administration of withanoside IV, Sominone, an aglycone of withanoside IV, was reported as the principal metabolite. In cultured rat cortical neurons harmed by Abeta, Sominone induced axonal and dendritic regeneration and synaptic reconstruction significantly. Withanoside IV in Alzheimer's disease can boost neuronal dysfunction and that sominone is the active principle after metabolism. Reserpine-treated animals have displayed low memory retention in the elevated plus maze task model in another study. The administration of Chronic WS dramatically reversed reserpine-induced retention deficits. In a step-down paradigm in mice, retention of a passive avoidance task was improved in different experiments with WS root extract. WS also reversed the scopolamine-induced

acquisition and retention disruption and, immediately after training, attenuated the amnesia caused by acute electroconvulsive shock (ECS) treatment. Chronic ECS therapy, for 6 consecutive days at 24 h intervals, disturbed the consolidation of memory on day 7. In mice undergoing chronic ECS therapy, regular administration of WS for 6 days significantly enhanced memory consolidation. The disturbance of memory consolidation triggered by chronic ECS care was also attenuated by WS, administered on day 7. WS overturned the scopolamine-induced delay in transfer latency on day 1. On the elevated plus-maze. It is proposed on the basis of these results that WS exhibits a nootropic-like effect in naive and amnesiac mice [10].

Uses

Hypothyroidism

Ashwaganda has a thyrotropic influence, animal studies show. There were no shifts in T3 levels observed. Using its effect on cellular antioxidant systems, Withania can also indirectly stimulate thyroid activity. Withania extract substantially reduced lipid peroxidation and significantly increased catalase activity in the liver homogenate, facilitating free radical scavenging that can cause cellular harm. These findings suggest that Ashwaganda can be a useful botanical agent in the treatment of hypothyroidism. Significant increases were observed in serum T4, suggesting that the plant has a glandular stimulatory impact [11].

Anxiety and Depression

In an animal study investigating the anxiolytic and antidepressant actions of Ashwagandha, a root extract was administered orally to rats once daily for five days compared with widely prescribed pharmaceuticals. Results were compared for anxiolytic activity with benzodiazepine lorazepam and for antidepressant investigation with tricyclic antidepressant imipramine. Reduced brain levels of a predictor of psychiatric anxiety were seen by both the Ashwagandha group and the lorazepam group. In the forced swim-induced "behavioral despair" and "learned helplessness" studies, Ashwagandha also demonstrated an antidepressant effect comparable to that caused by imipramine [11].

Type 2 Diabetes

Ashwagandha can help normalize high blood sugar and boost insulin, according to some studies carried out [3].

Osteoarthritis

The effects of Ashwagandha on human cartilage have been tested and it was found that the herb can help protect against osteoarthritis-related inflammation and cartilage damage [8].

Anti-Malarial

Withania somnifera leaves and root extracts showed a dose-dependent parasite suppressing effect and a defensive effect on the volume of packed cells [11].

Conclusion

Studies indicate that *Withania Somnifera* is useful in treating cancer and has shown many anti-cancer activities over a number of studies carried out. Though more research is to be carried out in order for this to be implemented in human as all these earlier studies were conducted on animals and human trials could differ. Barring from anti-cancer activities, *W.Somnifera* has many other biological activities which it can also be further used for.

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