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Biomedical Applications of Withania Somnifera

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Abstract

Withania Somnifera (solanaceae), also known as Ashwagandha or winter cherry, is one of the most valuable plants in the traditional Indian system of medicine. It is a small evergreen shrub that grows to roughly four to five feet tall. In India, it is cultivated, on a commercial scale, in the states of Madhya pradesh, Uttar pradesh, Punjab, Gujarat and Rajasthan. This plant is used in more than 100 formulations in ayurveda, unani and siddha. Ashwagandha is one of the prime drugs of ayurveda material medica. It is attributed with balya, vrishya and rasayana properties and suggested as substitute of kakoli and kshirakakoli.Withania somnifera has been an important herb in the ayurvedic and indigenous medical systems for over 3000 years. Due to its pharmacological value and an inexhaustible source of novel biologically active compounds, it has been a great interest for researchers. Various withanolides, steroidal lactones, have been isolated from W.somnifera and were known to have high therapeutic value. Historically, the plant has been used as an antioxidant, adaptogen, aphrodisiac, liver tonic, antiinflammatory 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 diseases. Recently this plant is also used to inhibit the development of tolerance and dependence on chronic use of various psychotropic drugs.Withania species show a particularly wide distribution throughout drier climates of the world. In this article detailed study was made to address various applications of Withania somnifera

Keywords: Somnifera

Introduction

Ashwagandha in Sanskrit means "horse's smell" probably originated from the odour of its root, which resembles that of sweaty horse. The species name somnifera means "sleep-making" in latin, attributed to sedating properties, but it has been used for sexual vitality and as adaptogenic properties also. As a rasayana herb, the decoction and extracts of the herb shows excellent immunomodulatory activity by non-specific activation of macrophages, granulocytes, complement systems, natural killer cells and lymphocytes [2]. The plant is known to possess anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory and hemopoetic properties [1, 2].but did not specify what stimulated contraction. He based these opinions on a series of over 100 patients.

Uses of withania somniferous (root):

The root of ashwagandha is regarded as tonic, aphrodisiac, narcotic, diuretic, anthelmintic, astringent, thermogenic and stimulant. The root smells like horse ("ashwa"), that is why it is called Ashwagandha. It is commonly used in emaciation of children debility from old age, rheumatism, constipation, insomnia, nervous breakdown, goiter etc. The paste formed when roots are crushed with water and it is applied to reduce the inflammation at the joints. It is also locally applied in carbuncles, ulcers and painful swellings. 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 [4]. The Nagori Ashwagandha is the supreme among all ashwagandha varieties. Maximum benefit appears when fresh ashwagandha root powder is used [3, 4].

Uses of withania somnifera(leaves):

The leaves are bitter and are recommended in fever, painful swellings. The flowers are astringent, depurative, diuretic and aphrodisiac [5]. The seeds are anthelmintic and combined with astringent and rock salt remove white spots from the cornea. Ashwagandharishta prepared is used in hysteria, anxiety, memory loss, syncope, etc. It also acts as a stimulant and increases the sperm count.

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

Discription Of Withania Somnifera:

It is an evergreen, erect, branching small shrub. It grows as a short shrub (35–75 cm)

Leaves: Simple, glabrous and ovate, up to 10 cm in length.

Stem: Stellate central stem with radial secondary branching and densely covered with wooly hair.

Flowers: Small and green or yellow, about 1 cm in length [6].

Fruits: Globose berries, orange-red when ripe, 6 mm in diameter, enclosed in membranous persistent calyx with milk-coagulating properties.

Seeds: yellow, reniform (2.5 mm diameter).

Roots: Tuberous and long, brown in color with medicinal purposes.In southern Africa the flowering time is mostly from October to June, while the fruiting time is mostly from October to July [7].

1.2Withania Somnifera Medical Uses [5]:

1. Reducing side effects associated with medications called antipsychotics: Antipsychotics are used to treat schizophrenia but they can cause levels of fat and sugar in the blood to increase. Taking a specific ashwagandha extract, 400 mg three times daily for one month might reduce levels of fat and sugar in the blood in people using these medications [8].
2. Anxiety: Some clinical research shows that taking ashwagandha can reduce some symptoms of anxiety or anxious mood.
3. Bipolar disorder: Taking a specific ashwagandha extract (Sensoril, Natreon, Inc.) for 8 weeks might improve brain function in people being treated for bipolar disorder.
4. A brain condition called cerebellar ataxia: Preliminary research shows that ashwagandha in combination with an alternative form of medicine known as Ayurvedic therapy might improve balance in people with cerebellar ataxia [9].
5. Fatigue in people treated for cancer (chemotherapy): Early research suggests taking a specific ashwagandha extract 2,000 mg during chemotherapy treatment might reduce feelings of tiredness.
6. Diabetes: There is some evidence that ashwagandha might reduce blood sugar levels in people with diabetes.
7. High cholesterol: There is some evidence that ashwagandha might reduce cholesterol levels in patients with high cholesterol.
8. Underactive thyroid (hypothyroidism): People with underactive thyroid have high blood levels of a hormone called thyroid stimulating hormone (TSH) [10].
9. Male infertility: Some preliminary clinical evidence suggests that ashwagandha might improve sperm quality, but not sperm count, in infertile men.
10. Osteoarthritis: Early research shows that ashwagandha taken along with a zinc complex, guggul, and turmeric might improve arthritis symptoms. The impact of ashwagandha alone is unclear.
11. Parkinson's disease: Preliminary research suggests that a combination of herbs including ashwagandha improves Parkinson's symptoms. The effect of ashwagandha alone in Parkinson's is unknown.

1.3Pharmacological Properties of Ashwagandha[6]:

Anti-oxidant Effects of Ashwagandha:

Free radical scavenging activity of root powder of ashwagandha in mice is observed that root powder possesses free radical scavenging activity, which may be responsible for its pharmacological effects[(11)].The active principles of Ashwagandha, sitoindosides VII-X and withaferine A (glycowithanolides) have been tested for antioxidant activity using the major free-radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidise (GPX) levels in the rat brain frontal cortex and striatum. It was noted that the administration of active glycowithanolides of ashwagandha (10 or 20 mg/kg, i.p for 21 days) increases levels of all the enzymes [12]. This implies that ashwagandha does have an antioxidant effect in the rat brain which may be responsible for its diverse pharmacological properties. In another study, an aqueous suspension of ashwagandha roots extract was evaluated for its effect on stress-induced lipid peroxidation (LPO) in mice and rabbits. It was noted that the blood levels of LPO increased by administration of 0.2 mg/kg of lipopolysaccharides (LPS) from Klebsiella pneumoniae and 100 mg/kg of peptidoglycans (PGN) from Staphylococcus aureus. Simultaneous oral administration of Ashwagandha extract (100 mg/kg) prevented the increase in LPO.

Anti-inflammatory effect of Ashwagandha [7]:

The effectiveness of ashwagandha in a variety of rheumatologic conditions may be due to its anti-inflammatory properties, which have been studied by several authors. Powdered root of WS (1 g/kg suspended in 2% gum acacia, 50 mg/mL) was given orally one hour before the induction of inflammation by injection of Freund's complete adjuvant in rats and continued daily for three days; it was found that WS caused dose-dependent suppression of α2-macroglobulin (an indicator for anti-inflammatory drugs) in the serum of rats inflammed by sub-plantar injection of carrageenan suspension. The doses of WS root powder were 500, 1000, 1500, or 1200 mg/kg given as suspension orally 3-4 hours prior to induction of inflammation. Maximum effect (about 75%) was seen at 1000 mg/kg. Actual measurements of inflammation were not conducted [13].

Antitumor effect of ashwagandha [8]:

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 [14].11 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 [15]. The growth inhibitory effect of WS was also observed in Sarcoma 180 (S-180), a transplantable mouse tumor. 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 S180 and in Ehrlich ascites carcinoma. Antitumor and radiosensitizing effects of withaferin (a steroidal lactone of WS) were also seen in mouse Ehrlich ascites carcinoma in vivo. 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.These studies are suggestive of antitumor activity as well as enhancement of the effects of radiation by WS [16].

Estrogenic Activity of Ashwagandha [9]**:**

The effect of Ashwagandharoot extract on Osteoporosis. The ethanolic root extract contains oestrogen-like withanolides for anti-osteoporotic activity. The author observed significant increase in serum (ALP) levels and excretion of urinary Ca and P in withanolide in tested group. Khazal et al. (2013) studied the effect of Ashwagandha root extract on Estrogen Receptor-Positive Mammary Carcinomas. The authors found that in treated group the rate of cell division, in the mammary tumours was significantly reduced [17].

Effects of Ashwagandha on the Alzheimer's disease [10]:

The effect of withanoside IV in mice with spinal cord injury (SCI) it was found that in SCI the myelin levels in axons, white matter, gray matter and CNS is decrease. Treatment with withanoside IV (10 µmole/kg body) resulted in increase axonal density with increase myelin levels in peripheral nervous system (PNS); the loss of CNS myelin was not affected. The authors suggest that oral administration of withanolide IV may ameliorate locomotors function by facilitating both axonal regrowth and increase in PNS myelin levels. Konar et al. (2011) reported that administration of scopolamine resulted in down regulation of the expression of BDNF and GFAP in dose and time dependent manner [18]. Treatment with alcoholic extract of ashwagandha leaf markedly attenuated these effects. Similarly effects was noted in IMR32 neuronal and C6 glioma cells the authors concluding that scopolamine besides the blocking cholinergic receptors, may induce memory loss by causing oxidative stress; leaf extract of ashwagandha and withanone may serve as potential preventive and therapeutic agents.

Effects of Ashwagandha on the Endocrine System:

The efficacy of ashwagandha in regulating thyroid function and based on the observations author suggested that ashwagandha provides protection from free radical damage in the mouse liver. In another study ashwagandha root extract were given to mice (1.4 g/kg, daily for 20 days) and it was noted that 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. Ashwagandha significantly reduced hepatic LPO and increased the activity of SOD and catalase [19]. The results suggest that ashwagandha stimulates thyroidal activity and also promotes hepatic antioxidant activity.

Hemopoetic Effect of Ashwagandha:

Administration of ashwagandha extract was found to significantly reduce leukopenia induced by cyclophosphamide (CTX) treatment in Swiss albino mice (Davis and Kuttan, 1998). Total white blood cell count was in normal range in CTX-plus-Ashwagandha group. In the CTX-plus-Ashwagandha mice, the cellularity of the bone marrow was significantly increased compared to the CTX-alone treated group. Similarly, the number of alpha-esterase positive cells in the bone marrow of the CTX-plus-Ashwagandha mice increased compared to the CTX alone mice. The major activity of ashwagandha may be the stimulation of stem cell proliferation. These studies indicated that ashwagandha reduced CTX-induced toxicity and may prove useful in cancer chemotherapy [20].

Immunomodulatory Activities of Ashwagandha:

The use of Ashwagandha as a general tonic to increase energy balance and prevent disease may be partially related to its effect on the immune system. Ghosal et al. (1989) evaluated the immunomodulatory and central nervous system effects (antistress, memory, and learning) of glycowithanolides and a mixture of sitoindosides IX and X isolated from ashwagandha in Swiss mice and Wistar rats. The author observed that both extracts produced statistically significant mobilization and activation of peritoneal macrophages, phagocytosis, and increased activity of the lysosomal enzymes; it also produced significant anti-stress activity in mice and rats and augmented learning acquisition and memory retention in both young and old rats [21].

Effects of Ashwagandha on Nervous System:

Total alkaloid extract (ashwagandholine, AG) of Ashwagandha roots has been studied for its effects on the central nervous system. AG exhibited a taming effect and a mild depressant (tranquilizer) effect on the central nervous system in monkeys, cats, dogs, rats and mice. AG had no analgesic activity in rats but increased Metrazol toxicity in rats and mice, amphetamine toxicity in mice, and produced hypothermia in mice [22]. It also potentiated barbiturate, ethanol, and urethane induced hypnosis in mice.

Chemical composition [11]:

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. Apart from these contents plant also contain chemical constituents like withaniol, acylsteryl glucosides, starch, reducing sugar, hantreacotaneand ducitol, a variety of amino acids including aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, cystine, tryptophan, and high amount of iron.The biologically active chemical constituents of Withania somnifera (WS) include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins. Sitoindosides and acylsterylglucosides in Ashwagandha are anti-stress agents [23].Active principles of Ashwagandha, for instance the sitoindosides VII-X and Withaferin-A, and have been shown to have significant anti-stress activity against acute models of experimental stress. Many of its constituents support immunomodulatory actions. The aerial parts of Withania somnifera yielded 5-dehydroxy withanolide-R and withasomniferin-A.

Components of withania somnifera:

- Alkaloids
- Tannins
- Carbohydrates
- Steroids
- Saponins
- Flavonoids

1.4Introduction ToEthosomes:

Skin is the largest human organ and consists of three functional layers:epidermis, dermis, and subcutaneous [24].It has a wide variety of functions: one major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical environments. The protective properties are provided by the outermost layer of the skin.

Transdermal drug delivery can be used as an alternative delivery of drug into the systemic circulation .Transdermal drugdelivery offers many advantages as compared to traditional drug delivery better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens.

Advantages clamied are increased patient acceptability,avoidance of first pass metabolisam,predictable and extended duration of activity,minimizingside effects and utility of short half life of drugs ,improving physiological and pharmacological response,avoiding the fluctuation in drug levels .The barrier function govern by stratum corneum is main problem for delivery of drugs across the skin [25].The strateum corneum consists of corneocytes surrounded by lipid layers ,which play an essential role in the barrier properties of the strateum corneum.

In order to increase the number of drugs administered via transdermal route,novel drug delivery systems have to be designed.These systems include use of physical means,such as iontophoresis,sonophoresis,microneedles,etc,and chemical means like penetration enhancers and biochemical means using liposomes,niosomes,transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum.The vesicles have been well known for their importance in cellular communication and particle transportation for many years.Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities ,which would to tag the vesicle for cell specificity.one of the major advances in vesicle research was the findinga vesicle derivatives known as an ethosomes [26].

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