

## A REVIEW ON POTENTIAL THERAPEUTIC USES OF *WITHANIA SOMNIFERA*

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Article Received on  
15 May 2017,

Revised on 05 June 2017,  
Accepted on 25 June 2017

DOI: 10.20959/wjpr20177-8882

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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 and indigenous medical systems for over 3000 years. Ashwagandha is a small, woody shrub in the Solanaceae family that grows about two feet in height. The roots of the plant are categorised as rasayanas, which are reputed to promote health and longevity by augmenting defence against disease, arresting the ageing process, revitalising the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing.<sup>[1]</sup> It is in use for a very long time for all age groups and both sexes and even during pregnancy without any side effects.<sup>[2]</sup> The

pharmacological effects of the roots of WS are attributed to the presence of withanolides, a group of steroidal lactones.<sup>[3]</sup> Its leaves are used in Ayurvedic and Unani systems for treatment of tumors and tubercular glands.<sup>[4]</sup> A number of withanolide steroidal lactones have been isolated from the leaves of *W. somnifera*.<sup>[5]</sup> And exhibit antibacterial, anti-fungal and antitumor properties.<sup>[6]</sup> Ashwagandha is used to calm the mind, relieve weakness and nervous exhaustion, build sexual energy and promote healthy sleep. The herb is termed a rasayana. in Ayurvedic practice, which means it acts as a tonic for vitality and longevity. It is also classified as an adaptogen.<sup>[7]</sup> Two varieties of Asgand have been mentioned in classical Unani literatue: 1) Asgand Nagori and 2) Asgand Dakani. Asgand Nagori is preferred for its more potential medicinal properties.<sup>[8]</sup>

### Scientific Classification

**Kingdom** : Plantae, Plants;

**Subkingdom** : Tracheobionta, Vascular plants;

**Super division** : Spermatophyta, Seeds plants;

**Division** : Angiosperma

**Class** : Dicotyledons

**Order** : Tubiflorae

**Family** : Solanaceae

**Genus** : Withania

**Species** : somnifera Dunal

**Vernacular names of *Withania somnifera*.**

**Gujarati** - Asam, Asoda, Ghodasoda, **Hindi** – Asgandh, **Canarese** - Amangura, Hirimaddina-gadde, Sogada-bery, **Marathi** - Asgundh, Kanchuki, Askandha, **Sanskrit** - Ashvagandha, Balada, Gandhpatri, Kamrupini, Vajini, **Bengali** – Ashvagandh, **Punjabi**- Asgand, **Tamil** – Asuragandi, **Telugu** - Asvagandhi, Penneru, **Urdu** – Asgandanagaori, **Kannada** – Keramaddinagaddi.

## INTRODUCTION

### Botanical description

*Withania somnifera* 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. Parts used: Whole plant, roots, leaves, stem, green berries, fruits, seeds, bark are used. *W. somnifera* has a chromosome number of  $2n=48$ .<sup>[9]</sup>



*Fig. W. somnifera:*

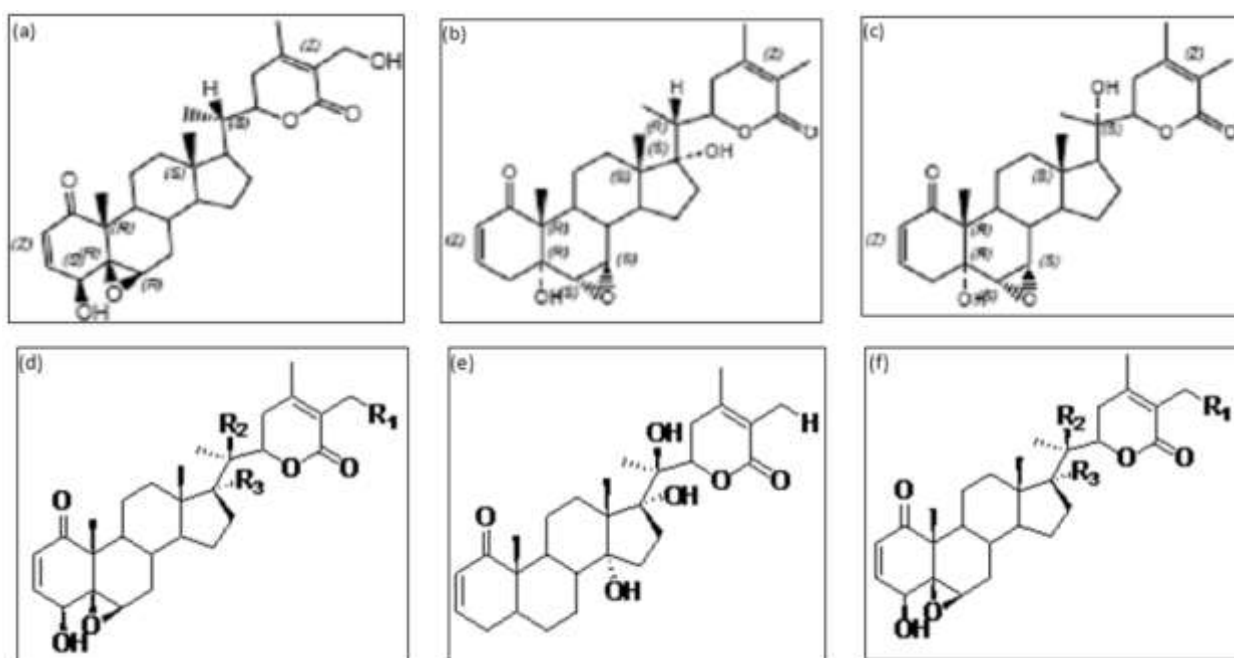
### Geographical distribution

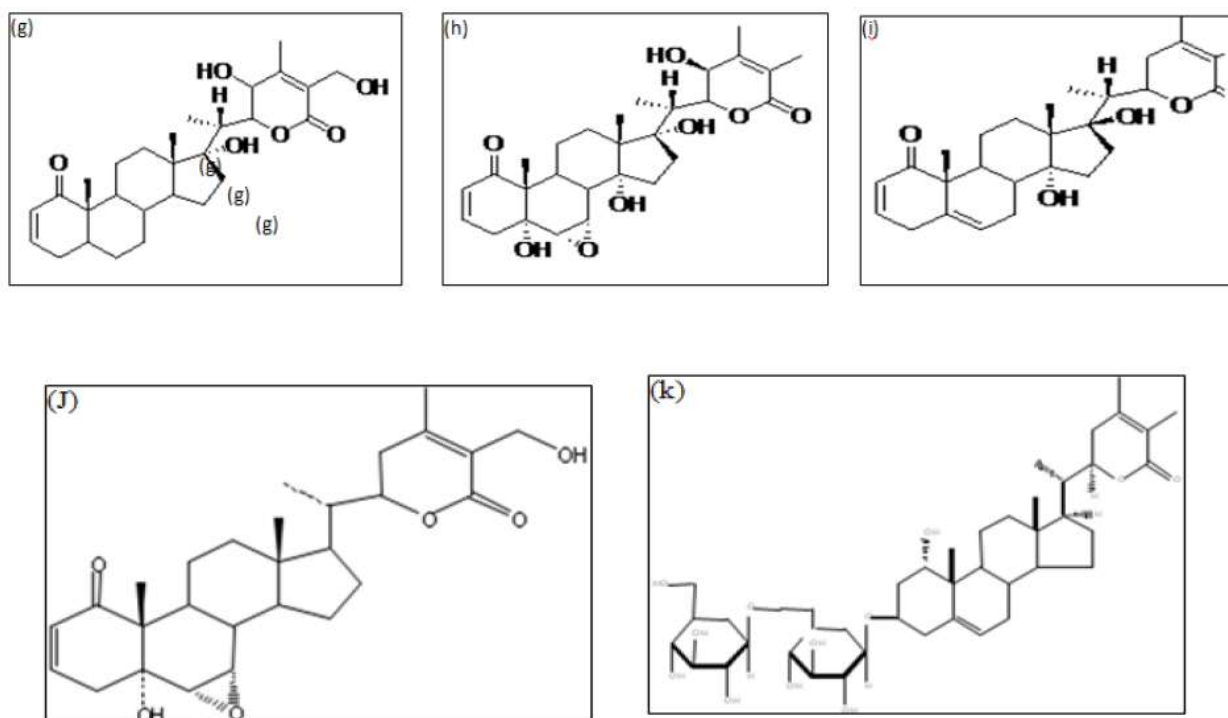
*W. somnifera* is widely distributed in the drier parts of tropical and sub tropical zones, ranging from the Canary Islands, The Mediterranean region and Northern Africa to Southwest Asia including Israel, Jordan, Egypt, Sudan, Iran, Afganistan, Baluchistan, Pakistan and India. In India the plant grows wild in North Western regions extending to mountainous regions of Punjab, Himachal Pradesh and Jammu up to an altitude of 1500 m (Singh and Kumar, 1998). It grows successfully in sandy loam or light red soils. A soil pH range of 7.5 to 8 is ideal. It is cultivated in an area of about 5000 hectares in India mainly in drier parts of Rajasthan, Madhya Pradesh andhra Pradesh and Uttar Pradesh.<sup>[10]</sup>

### Chemical Composition

Laboratory analysis has revealed over 35 chemical constituents contained in the roots of *Withania somnifera*.<sup>[11]</sup> The biologically active chemical constituents are alkaloids (isopellertierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII) and withanoloides with a glucose at carbon 27 (sitonidoside XI and X). *Withania somnifera* is also rich in iron. The roots of *Withania somnifera* consist primarily of compounds known as withanolides, which are believed to account for its extraordinary medicinal properties. Chemical analysis of Ashwagandha shows its main constituents to be alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent. The other alkaloids are somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropine, choline, cuscohygrine, isopelletierine, anaferine andanahydrine. Two acyl steryl glucoside viz. sitoindoside VII and sitoindoside VIII have been isolated from root.<sup>[12]</sup>

The leaves contain steroidal lactones, which are commonly called withanolides. The withanolides have C28 steroidal nucleus with C9 side chain, with a six membered lactone ring.<sup>[13]</sup> Twelve alkaloids, 35 withanolides and several sitoindosides from *Withania somnifera* have been isolated and studied. Asitoindoside is a withanolide containing a glucose molecule at carbon 27. Much of Ashwaganda's pharmacological activity has been attributed to two main withanolides, withaferin A and withanolide D. Further chemical analysis has shown the presence of the following: Anaferine (Alkaloid), Anahygrine (Alkaloid), Beta-Sisterol, Chlorogenic acid (in leaf only), Cysteine (in fruit), Cuscohygrine (Alkaloid), Iron, Pseudotropine (Alkaloid), Scopoletin, Somniferinine (Alkaloid), Somniferiene (Alkaloid), Tropanol (Alkaloid), Withanine (Alkaloid), Withananine (Alkaloid) and Withanolides A-Y (Steroidal lactones).<sup>[14-15]</sup>





**Fig.1. some bioactive molecules and their chemical structures isolated from *Withania somnifera*. (A) Withaferin A, (B) Withanone, (C) Withanolide A, (D) Withanolide D, (E) Withanolide E, (F) Withanolide G, (G) Withanolide Q, (H) Withanolide R, (I) Withanolide P, (J) 7-Hydroxy withanolide B and (K) Withanoside VI.**

#### TRADITIONAL 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 Immunomodulation and Hematopoiesis.<sup>[16, 17]</sup>

## PHARMACOLOGICAL ACTIVITY

### Anticancer activity

Withaferin A and withanolide D are reported to be significant anti-tumor and radiosensitizing withanolides.<sup>[18-21]</sup> 1-oxo-5 $\beta$ , 6 $\beta$ -epoxy-witha-2-enolide is another constituent of *W. somnifera* reported to reduce the skin carcinoma induced by UV radiations.<sup>[22]</sup> Withaferin A acts as a mitotic poison arresting the division of the cultured human larynx carcinoma cells at metaphase. It also produced a significant dose dependent retardation of the growth of Ehrlich ascites carcinoma, sarcoma 180 and sarcoma Black and E 0771 mammary adenocarcinoma.<sup>[23]</sup>

### Anti-Aging

In a double-blind clinical trial, ashwagandha was tested in a group of 101 healthy males, 50-59 years old, at a dosage of 3 grams daily for one year. A significant improvement in hemoglobin, red blood cell count, hair melanin and seated stature was observed. Serum cholesterol decreased and nail calcium was preserved. Erythrocyte sedimentation rate decreased significantly and 71.4 percent reported improvement in sexual performance.<sup>[24]</sup>

### Anti-arthritic effect

Ashwagandha is an analgesic that soothes nervous system from pain response.<sup>[25]</sup> The powerful anti-arthritic properties.<sup>[26,27]</sup> of Ashwagandha are now widely accepted and documented; it is furthermore found to be effective as antipyretic as well as analgesic also. Ashwagandha (1000 mg/kg/oral) produced significant analgesic activity for a rat experiencing heat analgesia induced by hot plate method. The peak analgesic effect of Ashwagandha was recorded as 78.03 percent at 2nd hour of administration. The involvement of pain mediators; prostaglandin and 5-hydroxytryptamine in analgesic activity of Ashwagandha was studied by pretreatment with paracetamol (100 mg/kg, ip) and cyproheptadine (10 mg/kg, ip). The analgesic activity of Ashwagandha was potentiated significantly by cyproheptadine, however, paracetamol failed to exhibit any significant change in its activity, suggesting the involvement of serotonin, but not prostaglandins in the analgesic activity of Ashwagandha.<sup>[28]</sup>

### Chronic Stress

Chronic stress (CS) can result in a number of adverse physiologic conditions including cognitive deficit, immunosuppression, sexual dysfunction, gastric ulceration, irregularities in glucose homeostasis and changes in plasma corticosterone levels. In a rat model of chronic



stress *Withania somnifera* and *Panax ginseng* extracts were compared for their ability to attenuate some effects of chronic stress. Both botanicals were able to decrease the number and severity of CS-induced ulcers, reverse CS-induced inhibition of male sexual behavior, and inhibit the adverse effects of CS on retention of learned tasks. Both botanicals also reversed CS-induced immunosuppression, but only the *Withania* extract increased peritoneal macrophage activity in the rats. The activity of the *Withania* extract was approximately equal to the activity of the *Panax ginseng* extract. *Withania somnifera*, however, has an advantage over *Panax ginseng* in that it does not appear to result in ginseng- abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension and insomnia.<sup>[29]</sup>

### Antibiotic Activity

The antibiotic activity of the roots as well as leaves has recently been shown experimentally. Withaferin A in concentration of 10µg/ml inhibited the growth of various Gram-positive bacteria, acid-fast and aerobic bacilli and pathogenic fungi. It was active against *Micrococcus pyogenes* var aureus 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*.<sup>[30]</sup> 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.<sup>[31]</sup> 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.<sup>[32]</sup>

### Immunomodulation and Hematopoiesis

A series of animal studies show *ashwagandha* to have profound effects on the hematopoietic system, acting as an immunoregulator and a chemoprotective agent.<sup>[33,34]</sup> In a mouse study, administration of a powdered root extract from *ashwagandha* was found to enhance 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.<sup>[35]</sup> Recent research suggests a possible mechanism behind the increased cytotoxic effect of macrophages exposed to *W. somnifera* extracts.<sup>[36]</sup> Nitric oxide has been determined

to have a significant effect on macrophage cytotoxicity against microorganisms and tumor cells. Iuvone et al demonstrated *Withania somnifera* increased NO production in mouse macrophages in a concentration-dependent manner. This effect was attributed to increased production of inducible nitric oxide synthase, an enzyme generated in response to inflammatory mediators and known to inhibit the growth of many pathogens.<sup>[37]</sup>

### Antioxidant effect

The brain and nervous system are relatively more susceptible to free radical damage than other tissues because they are rich in lipids and iron, both known to be important in generating reactive oxygen species. Free radical damage of nervous tissue may be involved in normal aging and neurodegenerative diseases, e.g., epilepsy, schizophrenia, Parkinson's, Alzheimer's, and other diseases. The active principles of WS, sitoindosides VII-X and withaferin A (glycowithanolides), have been tested for antioxidant activity using the major free-radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) levels in the rat brain frontal cortex and striatum. Decreased activity of these enzymes leads to accumulation of toxic oxidative free radicals and resulting degenerative effects. An increase in these enzymes would represent increased antioxidant activity and a protective effect on neuronal tissue. Active glycowithanolides of WS were given once daily for 21 days, dose-related increased in all enzymes were observed; the increases comparable to those seen with deprenyl (a known antioxidant) administration. This implies that WS does have an antioxidant effect in the brain, which may be responsible for its diverse pharmacological properties.<sup>[38]</sup> In another study, an aqueous suspension of WS root extract was evaluated for its effect on stress-induced lipid peroxidation (LPO) in mice and rabbits. LPO blood levels were increased by lipopolysaccharides (LPS) from *Klebsiella pneumoniae* and peptidoglycans (PGN) from *Staphylococcus aureus*. Simultaneous oral administration of WS extract prevented an increase in LPO.<sup>[39]</sup> Apart from hepatic lipid peroxidation (LPO), the serum enzymes, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase, were assessed as indices of hepatotoxicity. Silymarin (20 mg/kg, p.o.) was used for comparison. Iron overload induced marked increase in hepatic LPO and serum levels of the enzymes, which was attenuated by glycowithanolides (WSG) in a dose-related manner and by silymarin.<sup>[40]</sup>



### Cardiovascular Protection

Hypoglycemic, diuretic and hypocholesterolemic effects of ashwagandha root were assessed in human subjects, in which six type 2 diabetes mellitus subjects and six mildly hypercholesterolemic subjects were treated with a powder extract for 30 days. A decrease in blood glucose comparable to that of an oral hypoglycaemic drug was observed. Significant increases in urine sodium, urine volume and decreases in serum cholesterol, triglycerides, and low-density lipoproteins were also seen.<sup>[41]</sup>

### Anti-inflammatory effect due to Withaferin

Withaferin A and 3-b-hydroxy-2,3-dihydrowithanolide F isolated from *Withania somnifera* show promising antibacterial, antitumoral, immunomodulating and anti-inflammatory properties.<sup>[42]</sup>

### Immunity

*W. somnifera* show an immuno-potentiating and myeloprotective effects know roots by enhancing the levels of interferon (IFN)- $\gamma$ , interleukin (IL)-2 and granulocyte macrophage colony stimulating factor in normal and cyclophosphamide-treated mice.<sup>[43]</sup> As the plant is rich in iron, it contributes to red blood cell count. The effect of *W. somnifera* on the immune system is subtler than simply suppressing the immune/ inflammatory response. The active compound (withanolide A) in the roots of *W. somnifera* significantly increases the expression levels of T-helper 1 (Th1) cytokines, as well as CD4 and CD8 counts. It also enhances natural killer (NK) cell activity in a dose dependent manner with a faster recovery of CD4+ T cells in immune suppressed animals.<sup>[44,45]</sup> Apart from the above activated macrophage functioning indicated by enhanced secretion of nitrile, IL-2 and TNF-2, decreases moderately IL-4 with no effect on IL-10 suggesting that it only influenced Th1 profile of the cytokines. Root powder of this plant is also reported to stimulate the cell-mediated immunity, IgM and IgG and a prominent enhancement in proliferation and differentiation of lymphocytes as indicated by lymphocyte surface markers of T cells (CD3+, CD4+ and CD8+) and B cells (CD19+).<sup>[46]</sup>

### Effect on Energy levels and Mitochondrial Health

The effect of Ashwagandha on glycosaminoglycan synthesis in the granulation tissue of carrageenin-induced air pouch granuloma was studied. Ashwagandha is shown to exert significant inhibitory effect on incorporation of ribosome -35S into the granulation tissue. The uncoupling effect on oxidative phosphorylation (ADP/O ratio reduction) was also observed in the mitochondria of granulation tissue. Further, Mg<sup>2+</sup> dependent ATPase activity

was found to be influenced by Ashwagandha. Ashwagandha also reduced the succinate dehydrogenase enzyme activity in the mitochondria of granulation tissue.<sup>[47]</sup>

### Effect on nervous system

Ashwagandha is reported to have the sedative rather than stimulative action on the central nervous system, making it a superior medicine in exhaustion with nervous irritability. Ashwagandha alters the concentration of neurotransmitters that are known to play an important role in brain processes such as memory. The effects on nervous system are associated with Ashwagandholine (root extracts). It potentiates barbiturate-, ethanol- and urethane- induced hypnosis in mice and caused relaxant and antispasmodic effects against various agents that produce smooth muscle contractions in intestinal, uterine, tracheal and vascular muscles.<sup>[48]</sup> The bioactive compounds are reported to preferentially influence the events in the cortical and basal forebrain cholinergic-signal transduction cascade. The cognition and memory enhancing effects of *W. somnifera* extracts can be partly explained by the drug-induced enhancement of cortical muscarinic acetylcholine receptor capacity.<sup>[49]</sup> In general, Ashawagandha has been used traditionally as a tonic and nootropic agent.<sup>[50]</sup> It has also been associated with improvements in scopolamine-induced memory deficits in mice.<sup>[51]</sup> *W. somnifera* extracts also show an antiparkinsonian effect on neuroleptic-induced catalepsy by inhibiting haloperidol or reserpine-induced catalepsy attributed to potent antioxidant, antiperoxidative and free radical quenching properties.<sup>[52]</sup>

### Hypothyroidism

Animal studies reveal ashwaganda has a thyrotropic effect. An aqueous extract of dried Withania root was given to mice via gastric intubation at a dose of 1.4 g/kg body weight daily for 20 days. Serum was collected at the end of the 20- day period and analyzed for T3 and T4 concentrations and lipid peroxidation was measured in liver homogenate via antioxidant enzyme activity. Significant increases in serum T4 were observed, indicating the plant has a stimulatory effect at the glandular level. No changes in T3 levels were observed. Withania may also stimulate thyroid activity indirectly, via its effect on cellular antioxidant systems. Withania extract significantly decreased lipid peroxidation in the liver homogenate and significantly increased catalase activity, promoting scavenging of free radicals that can cause cellular damage. These results indicate ashwaganda may be a useful botanical in treating hypothyroidism.<sup>[53, 54]</sup>

### Side Effects and Toxicity

Ashwagandha is generally safe when taken in the prescribed dosage range. Large doses have been shown to cause gastrointestinal upset, diarrhea and vomiting.<sup>[55]</sup>

### CONCLUSION

*Withania somnifera* (Ashwagandha) is a plant used in medicine from the time of Ayurveda, the ancient system of Indian medicine. The plant has also been widely studied for their various pharmacological activities like antioxidant, anxiolytic, adaptogen, memory enhancing, antiparkinsonian, antiinflammatory, antitumor properties. Various other effects like immunomodulation, hypolipidemic, antibacterial, cardiovascular protection, sexual behaviour, have also been studied. While *Withania somnifera* has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use.<sup>[56]</sup>

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