Available online on 15.04.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Withania somnifera: A potential rejuvenator of medicinal system for healthcare

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Article Info:

Article History:

Received 08 Feb 2024
Reviewed 04 March 2024
Accepted 01 April 2024
Published 15 April 2024

Cite this article as:

Sharma V, Sehgal R, Gupta R, *Withania somnifera*: A potential rejuvenator of medicinal system for healthcare, Journal of Drug Delivery and Therapeutics. 2024; 14(4):145-154

DOI: http://dx.doi.org/10.22270/jddt.v14i4.6536

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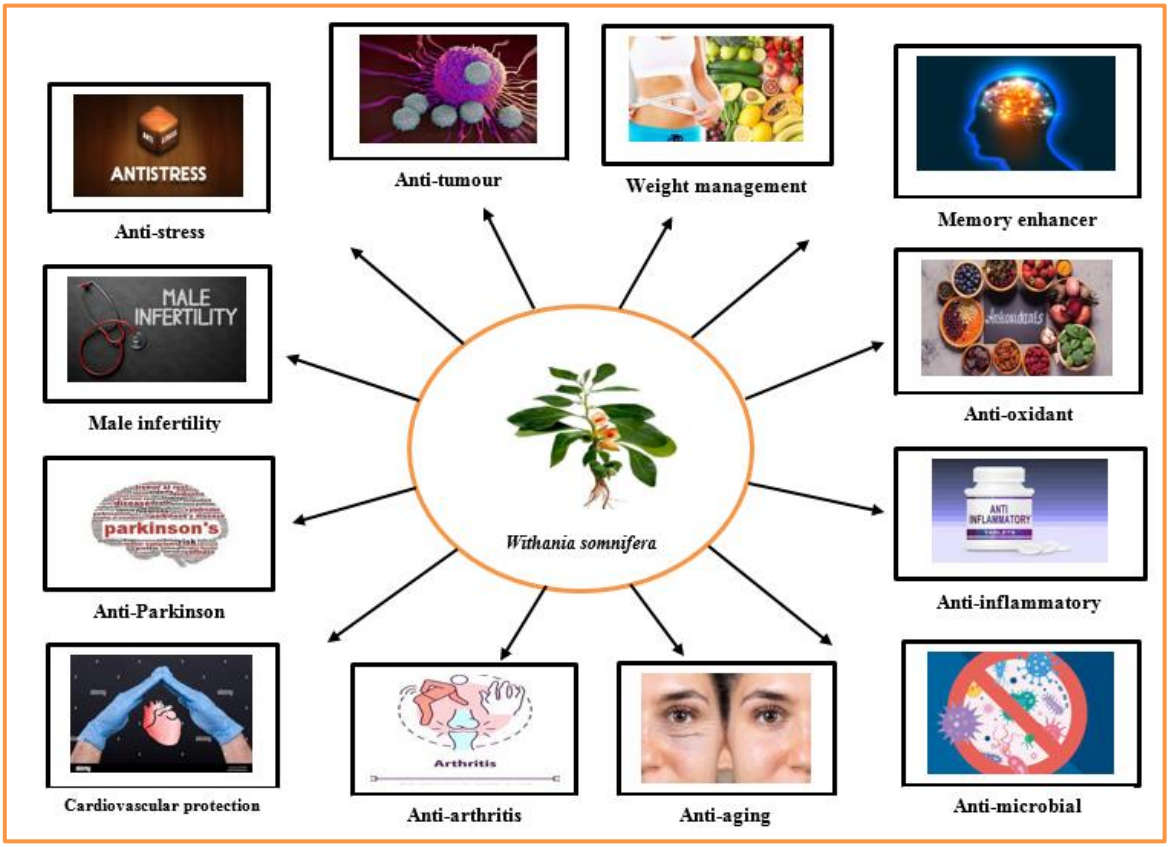
Abstract

Medicinal herbs have been used since the time of the Vedas. The plants have therapeutic qualities in every part. Secondary metabolites of extensive variety are present in medicinal plants and are utilised in the production of medications as well as in the treatment of many different ailments. *Withania somnifera* is a medicinal plant, have various properties. 'Ashwagandha' is the popular name of *Withania somnifera*. It is offered as churna, a finely sieved powder that can be combined with ghee, water or honey. It has memory-enhancing, anti-oxidant, anti-stress, anti-venom, anti-inflammatory and anti-tumor effects. It is employed to treat a variety of clinical problems. In addition to being used as a suppressant in HIV/AIDS patients, *Withania somnifera* is used to treat ulcers, emaciation, colds, coughs, diabetes, conjunctivitis, insomnia, senile dementia, epilepsy, leprosy, Parkinson's disease, nervous disorders, rheumatism, arthritis, intestinal infections, bronchitis and asthma. The review article concentrates on the *Withania somnifera* plant's different pharmacological qualities.

Keywords: *Withania somnifera*, Ayurveda, Anti-oxidant, Anti-inflammatory, Anti-tumour

Graphical abstract



Introduction

From the beginning of time, medicinal plants have been utilised to heal a variety of ailments. The World Health Organization (WHO) estimates that around 70–80 percent of the world's population currently relies on traditional medicine for their basic healthcare requirements[1]. The creation of indigenous medicines and the utilisation of medicinal plants to treat a variety of ailments have significant economic advantages. Most people, especially those in rural areas, are still obliged to use traditional treatments for their common ailments because there are not many communication options, very few educational opportunities, less money and lack of new medical facilities[2].

Withania somnifera (WS) inhabits the most powerful position among the plants of ayurvedic rasayana. It is a xerophytic plant that is employed medicinally and grows over a large range, from the Atlantic Ocean to South East Asia and from the Mediterranean region to South Africa[3]. It is a member of the Solanaceae family. It develops into a small shrub that is 35 to 75 cm long with a central stem from which the branches radiate outward in the shape of stars (a feature known as stellation). The tomentose surface, which is made up of many thick woolly hairs, covers the entire plant. WS has tiny, green blooms and its mature fruit has an orange-red tint. Because the roots of the plant smell like a wet horse, it is known as ashwagandha. WS is a late-rainy-season kharif crop. It may be grown as a rain-fed crop in semitropical locations with 500 to 800 mm of rainfall. Root growth is improved by one or two rainfalls throughout the winter. The growth season for WS must be somewhat dry. It can withstand temperatures between 20 and 38°C and also as low as 10°C. The plant may be found 1500 metres above sea level. Fig. 1 depicts the sections of the *Withania somnifera* plant (ashwagandha)[4].

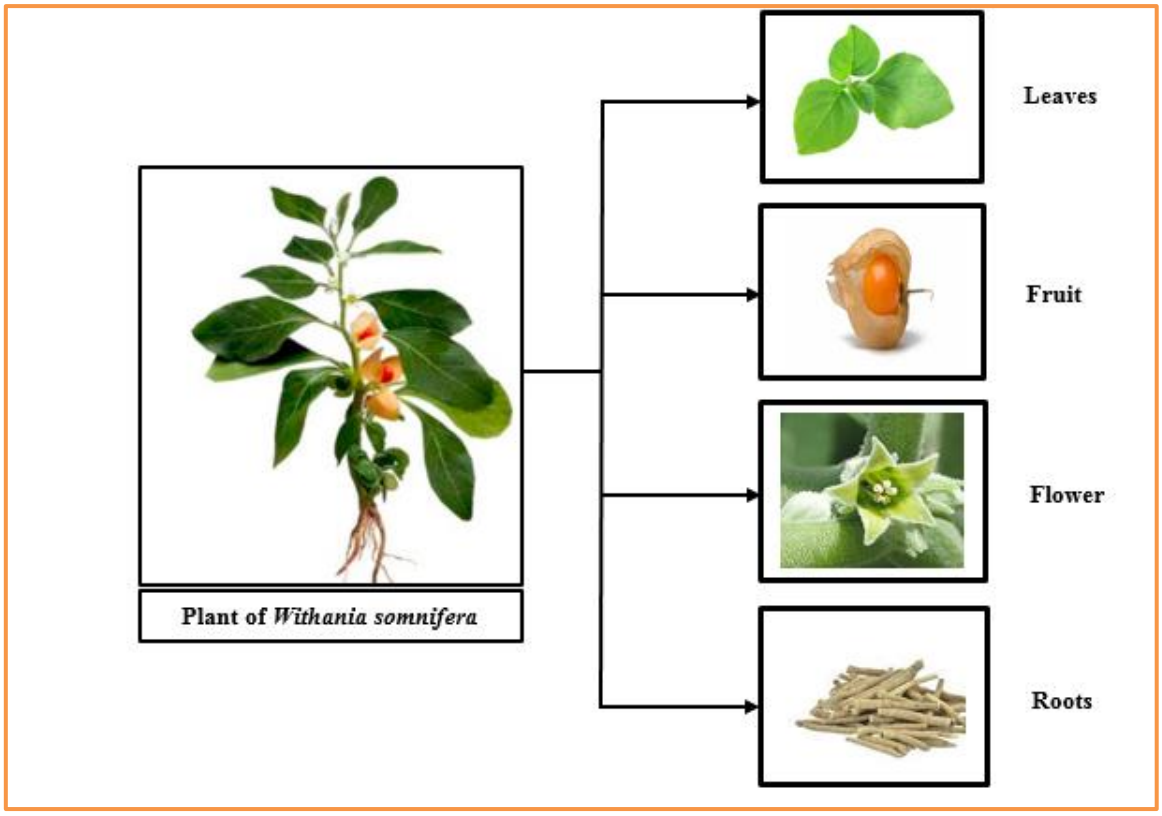


Figure 1: Plant of *Withania somnifera*

WS occupies the most influential position among the ayurvedic rasayana plants. It has been used for more than three thousand years in both Ayurveda and indigenous medical traditions as one of the key herbs. It is one of the 32 therapeutically important plants of India listed by National Bank for Agriculture and Rural Development (NABARD)[5]. By boosting the body's cell-mediated immunity, it strengthens the body's defences against illness[6]. Additionally, it has strong antioxidant qualities that guard against cellular damage brought on by free radicals. Rasayana is one of the eight sub-disciplines of Ayurveda. It is asserted that rasayana medications help to revitalise the tissues and even the mentality, maintaining human health. *Rasayana* is a metallic or herbal mixture that inspires pleasure, youthful mental and physical health. It possesses the potential to promote wellness and survival by boosting disease defence, slowing down the ageing process, improving the person's capacity to endure harmful environmental impacts, revitalising the body in poor situations and cultivating a feeling of mental well-being[7].

Chemical constituents of *Withania somnifera*

WS has a variety of chemical components that are pharmacologically active, including steroidal substances such withasomniferin-A, withaferin A, steroidal lactones, withanolides A-y, withasomidienone, withasomniferols A-C, withanone, etc, alkaloids such as cuscohygrine, ashwagandhine, tropine, anahygrine, etc. and other components including withanolides with a glucose at carbon number 27 (sitoindoside IX and X) and saponins with an extra acyl group (sitoindoside VII and VIII)[8]. It contains a significant quantity of iron as well as chemical components including withaniol, acylsteryl glucosides, starch, hantreacotane, ducitol and a variety of amino acids like proline, tyrosine, aspartic acid, alanine, glycine, and cystine. Table 1 lists the different chemical components of *Withania somnifera*.

Table 1 Chemical constituents of *Withania somnifera*

Chemical component	Types	References
Alkaloids	Withania somniferaine	9
	Cuscohygrine	
	Anahygrine	
	Tropine	
	Withanine	
	Withasomnine	
	Visamine	
	Scopoletin	
	Pseudotropine	
	Cuscohygrine	
	Pseudowithanine	
	Tropeltigloate	
Steroids	Steroidallactones	10
	Withaferin-A	
	Withasomidienone	
	A-y Withanolides,	
	Withasomniferin-A,	
	Withanone	
	Withasomniferols A-C	
	Cholesterol	
	Diosgenin	
Saponins	VII Sitoindoside	11
	VIII Sitoindoside	
	IX Sitoindoside	
	X Sitoindoside	
Amino acids	Glycine	12
	Proline	
	Cystine	
	Tyrosine	
	Alanine	
	Aspartic acid	
	Glutamic acid	
	Tryptophan	
Flavonoids	Kaempferol	13
	Quercetin	
Glycosides	Sitondisides VII and VIII	13
Trace elements	Withanol	13
	Somnisol	
	Somnitol	

Humans rely on plants for their energy needs, which include carbohydrates, proteins, fibers, calcium, iron, etc. These nutrients are present in *Withania somnifera* in sufficient amount. The various nutrients present in *Withania somnifera* are shown in Fig. 2[3].

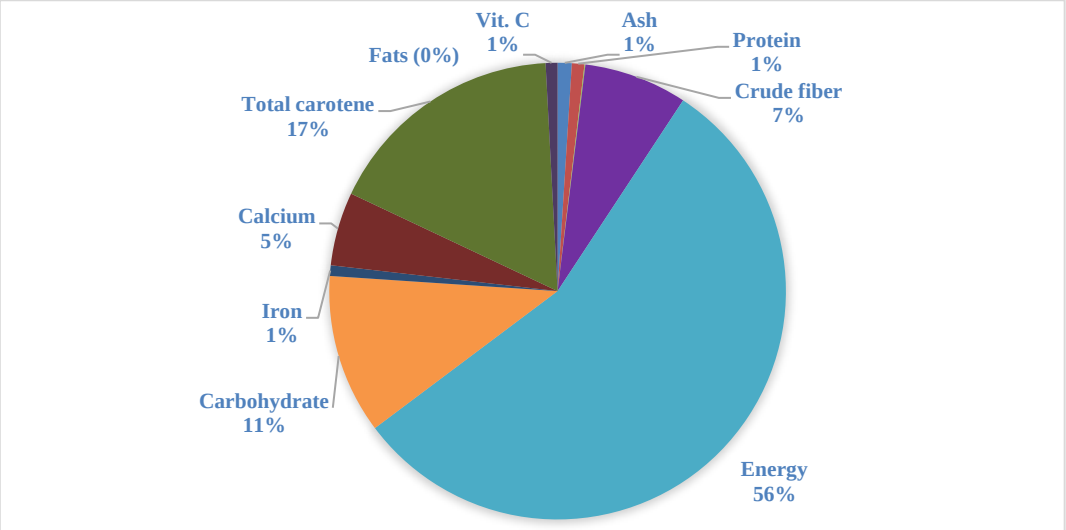


Figure 2: The nutrients in percent (w/v) present in *Withania somnifera*

Pharmacological properties of *Withania somnifera*

In Indian medicine systems, WS is a major herbal component of geriatric tonics[14]. In 'Ayurvedic system', this plant is declared to possess strong stimulating, life sustaining and reviving properties. Generally, it has regenerative and stimulating qualities and thus is used for treatment of skin problems, nervous exhaustion, insomnia, memory related conditions, potency issues, fatigue and coughing. It enhances memory capacity and learning ability[15].

Traditionally, the plant, WS was used to enhance energy, strength, endurance, youthful vigour, improves health, increase cell production, key body fluids like semen muscle fat, lymph, blood and nourish the body's physiological components[16]. It helps in preventing dehydration, weakness, thirst, debility, long-term fatigue, loose teeth, impotency, bone weakness, convalescence, muscle tension and emaciation due to early ageing. It helps in reviving the reproductive organs and energize the body[6]. There are variety of pharmacological properties of different parts of WS. The presence of various alkaloids, steroids and other compounds contribute to its pharmacological characteristics. Some of the pharmacological properties of *Withania somnifera* are shown in Fig. 3 and described as follows

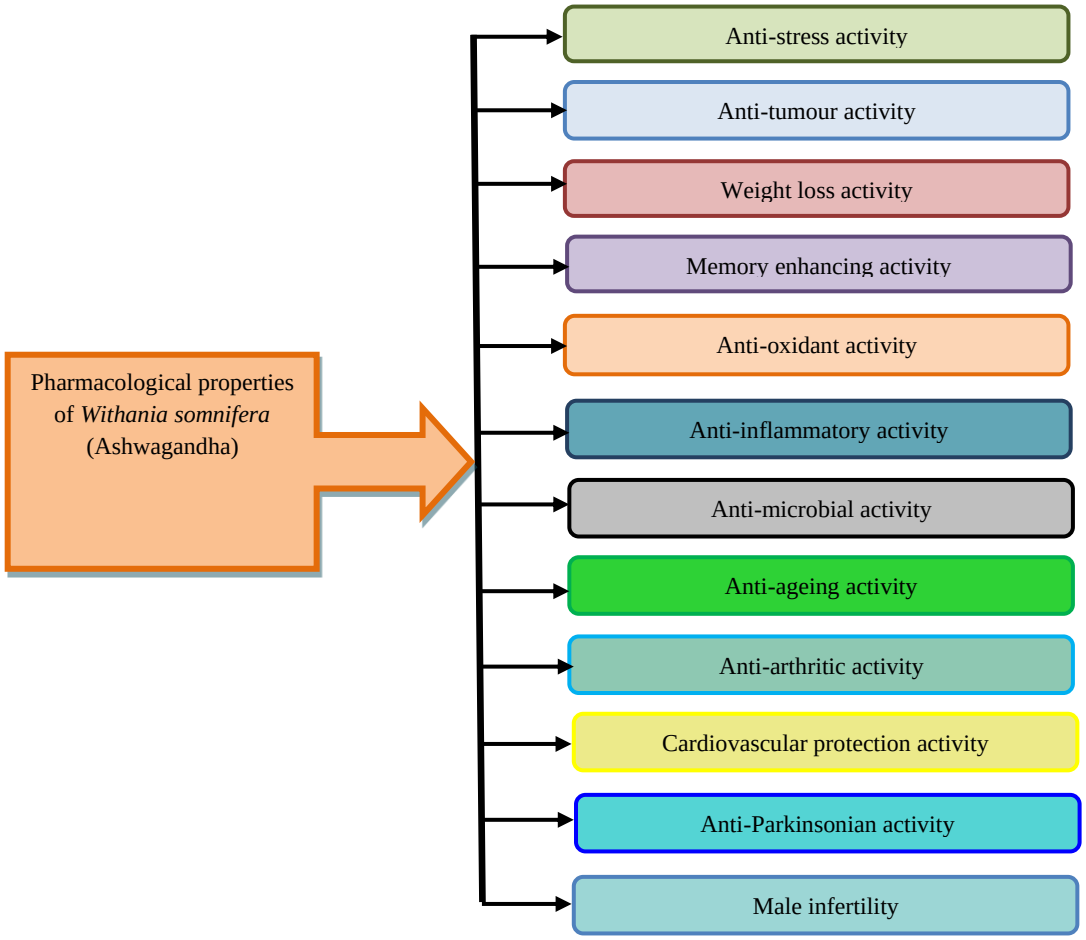


Figure 3: Various pharmacological properties of *Withania somnifera*[17]

1. Anti-stress activity

Today's lifestyle is particularly frustrating owing to the hectic schedules of everyone from school-age children to the elderly. As a result, there is a sizable market for pharmaceuticals that treat stress and psychosis globally. Stress is a major contributor to a wide range of illnesses, from psychological conditions to endocrine problems including, diabetes mellitus, hypothyroidism, male sexual dysfunction, hypertension, ulcerative colitis, peptic ulcer, etc. Chronic stress may have extremely negative impacts on our health, but acute stress can be exhilarating and keep us attentive and active[18].

The plant, *Withania somnifera* shows activities like Gamma-aminobutyric acid (GABA), which may contribute for the anti-anxiety and anti-stress effects of herbs[19,5]. Neuronal excessive activity may lead to insomnia and restlessness; however, GABA inhibits a large number of brain nerve cells that gets activated. The function of GABA is to lessen the activity of neurons and to inhibit the nerve cells from over activating, which further generates a soothing impact. It uplift mood, induce sleep and reduce stress and anxiety[20]. The anti-stress activities of WS have demonstrated to be highly efficient in boosting stamina (physical endurance) (Fig. 4).

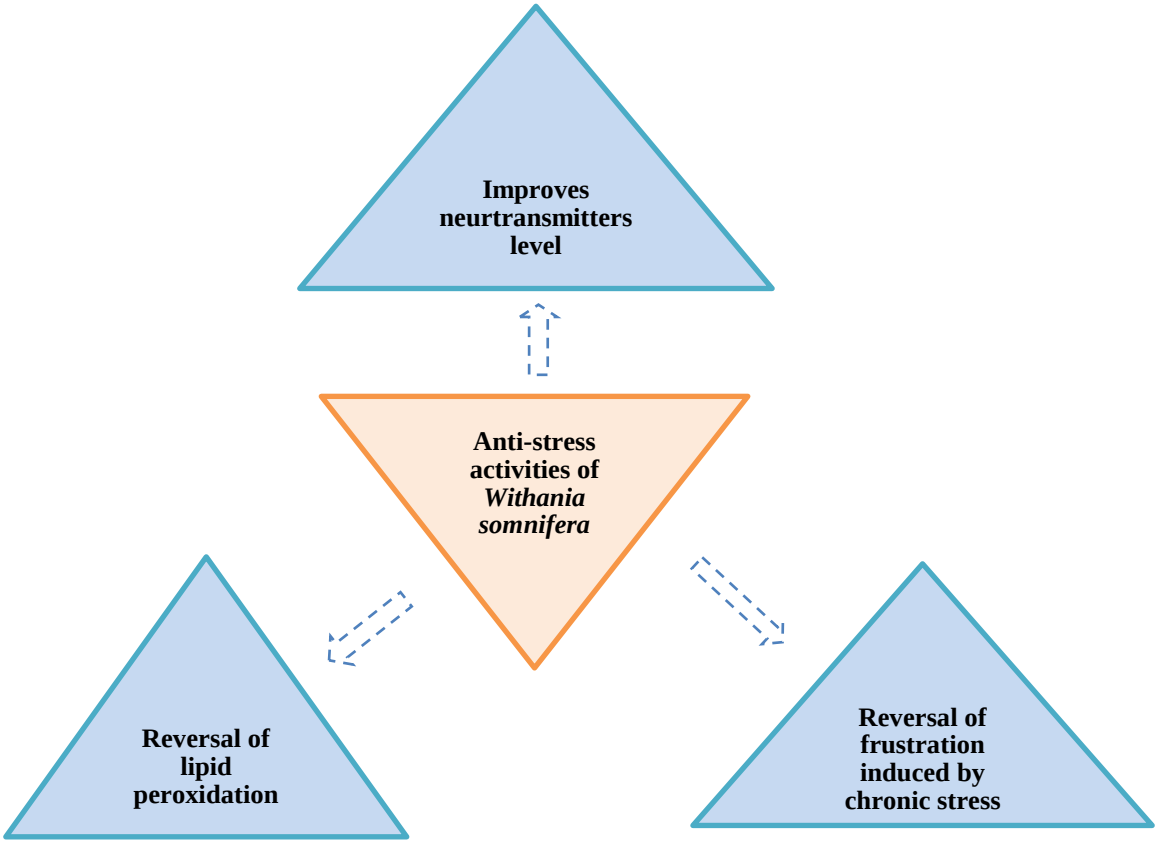


Figure 4: Anti-stress activities of *Withania somnifera*[21]

The vast research on the anti-stress and adaptogenic effects of WS in biological model animals has demonstrated its effectiveness in strengthening the stamina and minimizing stress induced stomach ulcer, hepatotoxicity induced by carbon tetrachloride (CCl_4) and chances of death[22]. Taking 240 mg of WS extract daily can lessen the 'Hamilton anxiety rating scale (HAM-A) (DASS-21)' and stress scale-21. In a recent study, dehydro-epiandrosterone and morning cortisol levels were also found to be decreased. Men only showed a little rise in testosterone in relation to this study[23].

2. Anti-tumour activity

Cancer incidences are increasing at a very high pace and need a very efficacious quick fix for its proper management. A lot of anti-cancerous drugs are used today and are derived from plants which specifically target tumour cells rather than healthy ones. In India, 'Ayurveda' is one of the safe ancient science branches of medicinal practices, with clinical outcomes and minimum side effects. WS, being an ayurvedic plant, has been tested in different studies and found to exhibit considerable anti-tumor properties targeting a number of factors that enhance tumor formation[24]. It works in a pleiotropic manner, concurrently attacking many carcinogenic pathways which help cancer patients to live better. The active components of the plant specifically target the oncogenic mediators MMP-9, NF-kB, PI3K/Akt pathway, MMP-2 and JAK/STAT system, all of which contribute to the activation of epithelial to mesenchymal transition (EMT) and hence encourage invasion and metastasis[25]. Fig. 5 depicts the anti-tumor efficacy of *Withania somnifera.*

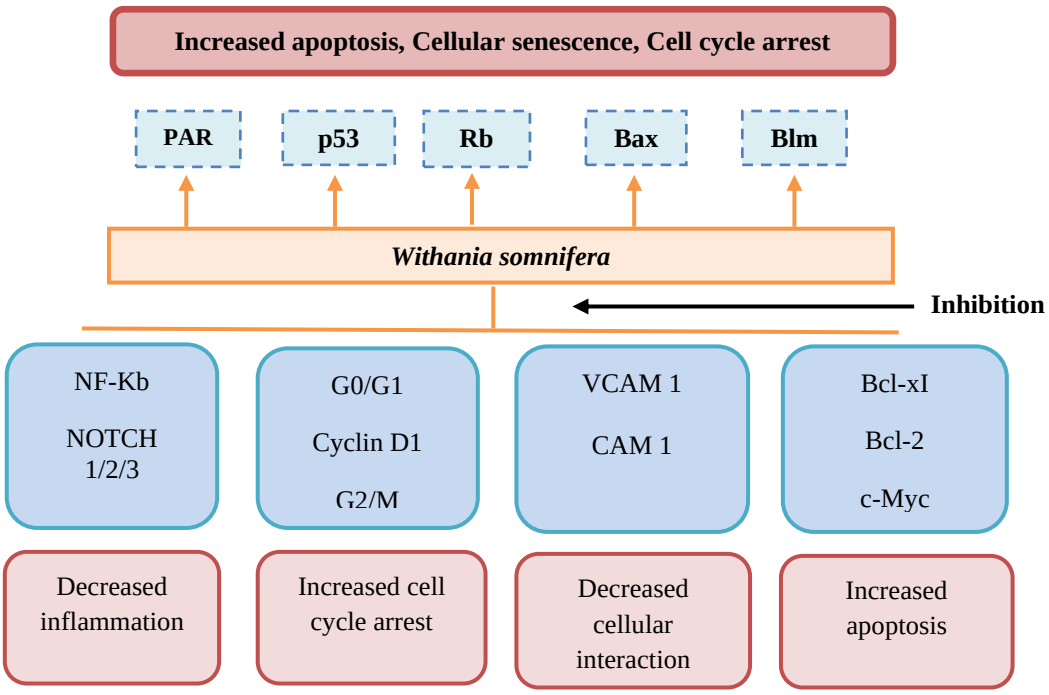


Figure 5: Anti-tumour activity of *Withania somnifera*[25]

An analysis stated that WS contains a lot of withanone (WN), which is an active anticancer component[26]. In a review, numerous plants for their ability to treat different ailments were examined and it was concluded that an extract from WS leaves has considerable potential for treating three different malignancies, including ovary, breast, and lung cancers[27]. By administering WS root extract to cancer trial participants, it was investigated that the fatigue brought on by chemotherapy in breast cancer patients[28]. The results of a full trial that spanned a few years showed that WS has the potential to help cancer patients live better lives and recover from the weariness imposed on by their disease. A prior study evaluated the anticancer effects of methanolic and aqueous extracts of WS against breast cancer cell lines (MCF-7) using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay. *In-vitro* extract concentrations ranged from 2.5µg/ml to 25µg/ml. The results demonstrated that all plant extracts suppressed breast cancer cell proliferation in a dose-dependent manner. The methanolic and aqueous extracts of WS have stronger anticancer activity, with IC50 values of 14.20 and 17.00 µg/ml, respectively[29].

3. Weight loss activity

The adaptogenic effects of WS, may help in encouraging the weight loss when used with other dietary supplements for reducing weight[29]. A chemical known as an adaptogen aids in reducing dietary changes brought on by stress. People who either overeat or undereat as a result of environmental stress, may find WS to be beneficial. Additionally, it could aid in enhancing metabolism and eliminating gastrointestinal abnormalities. Since it contains natural antioxidants, it could enhance general health and encourage more effective fat burning. Research on the root extract of WS has demonstrated a strong effect for reducing stress and stress-induced eating, which may subsequently result in weight reduction. In a recent study, it was found that obese people with high stress level, who took 300 mg of WS root extract twice daily for eight consecutive weeks experienced significant improvements in body weight, hormone levels related to stress and the dramatic drop in stress-related feeling and eating[30].

4. Memory enhancing activity

Learning can be defined as a behaviour change brought on by experience that enables someone to adjust to current living instances[31]. It is a method by which the brain accumulates new knowledge about the activities happening in the environment[32]. Memory is a fundamental mental ability. Without memory, humans are only capable of rudimentary reflexes and stereotyped behaviours. It is the ability to store and recall feelings, impressions and ideas[33]. As a result, one of the topics in neuroscience that has received the most attention is learning and memory.

WS plant has the ability to bind to calcium, which makes it a potential therapeutic candidate for treating Alzheimer's illness and memory related issues[34]. Acetylcholinesterase and butylcholinesterase are known to be dose-dependently inhibited by withanoloids. According to reports, WS root extract may have a positive impact because of its GABA mimic action. After consuming it for seven days, its components and the metabolites promote the development of nerves. Axonal, dendritic and synaptic losses as well as memory problems brought on by amyloid peptide A were shown to be mitigated in mice by continuous oral treatment of withanoside IV[6]. Withanoside IV was converted into sominone in mice after oral dosing, resulting in significant recovery of neurites and synapses, increased dendritic and axonal outgrowth and synapse formation. After withanoside IV treatment was ceased, the effects remained for at least 7 days. These results suggest that withanoside IV and sominone, a derivative, may be clinically useful as anti-dementia drugs.

5. Antioxidant activity

The brain and nervous system are more vulnerable to free radical damage than other tissues because they contain a high concentration of lipids and iron, both of which are known to be crucial in the formation of reactive oxygen species[12]. Oxygen radicals damage the nervous system that can cause normal ageing and neurodegenerative illnesses including, Parkinson's, epilepsy, schizophrenia, Alzheimer's and other conditions. It can also contribute to neuronal death in cerebral ischemia. To identify anti-oxidant activity, the main free-radical scavenging enzymes i.e., catalase (CAT), superoxide dismutase

(SOD) and glutathione peroxidase (GPx) are utilised. The decreased activity of these enzymes causes harmful oxidative free radicals to build up and cause neurodegenerative damage. Increased antioxidant activity and a protective impact on neural tissue would be represented by an increase in the levels of these enzymes[35]. WS contain antioxidant phytochemicals such as polyphenols, sitoindosides VII–X, withaferin A and glycowithanolides which helps in maintaining and increasing the activity of these enzymes[36]. A dose-dependent rise in all enzymes was seen after receiving active glycowithanolids of WS once daily for 21 days. This suggests that WS have a brain-related anti-oxidant impact. Fig. 6 displays the anti-oxidant properties of *Withania somnifera*.

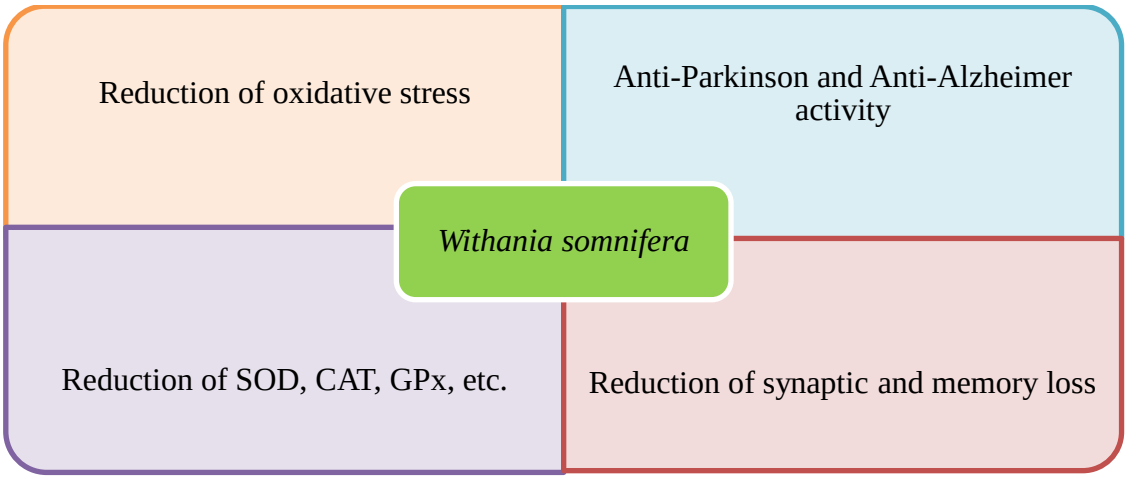


Figure 6: Anti-oxidant activities of *Withania somnifera*[21]

The impact of an aqueous solution of WS root extract on stress-related lipid peroxidation (LPO) in mice and rabbits was examined by observing the rise in the level of LPO in previous research. A rise in lipid peroxidation was stopped by oral treatment of WS extract (100 mg/kg)[37].

6. Anti-inflammatory activity

Human skin is composed of multiple layers having different components such as keratinocytes. Keratinocytes are also a significant source of inflammatory mediators including the interleukin (IL) and tumour necrosis factor (TNF) families[38]. An inappropriate inflammatory response may result from the overproduction of pro-inflammatory molecules. Therefore, these inflammatory mediators can be suppressed by possible anti-inflammatory drugs[39]. The roots of WS are useful in treating scabies, leucoderma and ulcers. Additionally, they have been used topically to treat wounds and relieve swelling[40]. In humans, roots extracts may increase the activity of natural killer cells which fight against infections[41]. WS tea was found to boost the activity of natural killer cells, which may be related to several tea constituents' effects on cytokine release[42]. According to a study, applying WS root extract topically to the skin may modify the expression of cytokines.

7. Anti-microbial activity

The discovery of antibiotics in the early 20th century provided progressively important tools to combat bacterial diseases[43]. Antibiotics can occasionally have negative side effects on the host, such as increased sensitivity, weakened immunity and allergic responses[44]. In this context, naturally occurring medicinal plants with active components that exhibit antibacterial action may offer a large study field. Plant-based antimicrobials have a huge medicinal promise. In previous research, many Gram-negative bacteria were suppressed by extracts of WS using agar well diffusion assay, demonstrating its anti-microbial potential. These bacteria included *Citrobacter freundii, Salmonella typhi, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa,* etc.[45]. WS flavonoids have an extremely strong anti-fungal activity against *Candida albicans*[46].

8. Anti-ageing activity

Shortening of telomeres is considered as the main factor that increase the rate of ageing of cells and also promotes the degeneration process[47]. With each DNA replication, the telomeres get noticeably shorter, eventually reaching an extremely short length. Telomerase is a major enzyme which plays role in the protection of ends of chromosomes and repair from shortening during DNA duplication, consequently prevent the catastrophic loss of DNA and promote the maintenance of healthy functioning of cell[48]. DNA damage or telomere shortening can be caused by two basic factors.

(i) Exogenous factors include bad food and lifestyle, radiation, environmental pollutants and mental stress[49].

(ii) Endogenous factors include chemical instability (removing impurities), chronic inflammation, spontaneous mistakes during DNA replication, maintenance and oxidative stress.

Natural remedies and conventional medications with the ability to postpone or halt ageing are being looked for due to the limited efficacy of conventional therapies as anti-ageing modulators. Chemical constituents found in roots of WS may significantly increase telomerase activity, thereby provide protection against telomere loss and potentially delay aging. WS claim to arrest degenerative changes, facilitate healthy ageing and have the capacity to rejuvenate cells and tissues[50,51]. Anti-aging properties of root powder extract have been found to increase the longevity of *Caenorhabditis elegans* roundworms by 20%[52].

9. Anti-arthritic effect

The analgesic effect of WS calms the neurological system's pain reflex[53]. Its potent anti-arthritic qualities are well established and known; in addition, it has been proven to be useful as an analgesic and antipyretic[54]. The constituents like withaferin A and 3-β-hydroxy-2, 3-dihydrowithanolide F, known to have anti-inflammatory properties, are used as anti-arthritis compounds to treat osteoarthritis[55]. WS (1000 mg/kg/oral administration) significantly reduced pain in a rat with thermal analgesia brought on by the hot plate method. The second hour after delivery, WS's highest analgesic efficacy was measured at

78.03%. Pretreatment with paracetamol (100 mg/kg, ip) and analysis of the analgesic action revealed that prostaglandin and 5-hydroxytryptamine, two pain mediators, were involved. Cyproheptadine considerably increased the analgesic efficacy of WS, but paracetamol had little effect, indicating that serotonin, rather than prostaglandins, is involved in the analgesic activity of WS[6].

10. Cardiovascular protection

WS has positive effects on the heart and circulation system, which may contribute to its efficacy as a natural remedy for cardioprotective effect[56]. Increased endogenous antioxidants, preservation of the myocardial antioxidant state and significant restoration of the majority of the altered haemodynamic parameter can all be linked to its cardioprotective effects.

Dogs and frogs were used to study how WS affected their cardiovascular and pulmonary systems[12]. Dogs subjected to the alkaloids from WS experienced persistent bradycardia, hypotension and respiratory excitement. The research found that the autonomic ganglion inhibiting action was solely accountable for the hypovolemic impact, however a depressive action on the upper cerebral centres also had an impact. The canine brain stem's vasomotor and pulmonary areas were stimulated by the alkaloids of WS. Dog's cardio-inhibitory behaviour appears to be a consequence of immediate cardio depressant effect and ganglion plugging. In isolated hypodynamic and normal frog heart, the early, predominately short-lived cardio-depressant effects of the alkaloids were followed by a moderate, long-lasting cardiotonic effect. In different research, an elevation in left ventricular end-diastolic pressures, a decrease in heart rate and a left ventricular rate of maximum positive and negative pressure changes were used to diagnose left myocardial damage[57].

11. Anti-Parkinsonian activity

Parkinson's disease is a chronic ailment that impairs the nervous system's ability to manage both the body's physical functions and the neurological system. Parkinson's disease (PD) is the second most common neurodegenerative illness after Alzheimer's, affecting 1% of persons by the age of 65 and 4-5% by the age of 85[58,59]. Parkinson's disease has a fundamental cause that may be traced to the death of dopaminergic neurons in the substantia nigra pars compacta region of the midbrain[60]. This loss ultimately results in a decrease in the amount of dopamine. Age, genetics and environmental stressors are only a few of the factors that might affect the onset and progression of this disease[61].

6-Hydroxydopamine (6-OHDA) is one of the most often utilised rat models for Parkinson's illness The literature is loaded with proof that 6-OHDA triggers oxidative stress in order to cause its hazardous symptoms. WS extract has been found to have anti-parkinsonian advantages because of its potent, antiperoxidative, free radical quenching and antioxidant properties in diverse clinical situations. In a study, the WS extract was given orally to rats as a pretreatment for three weeks. 6-OHDA was administered intravenously into right striatum on day 21, whereas the control group was given placebo. Rats were tested for neurodevelopmental function three weeks after the injections of 6-OHDA and killed five weeks later in order to assess the levels of lipid peroxidation, reduced levels of glutathione, activities of glutathione-S-transferase, glutathione reductase, glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase activity, catecholamine content, tyrosine hydroxylase expression and dopaminergic D2 receptor binding. WS extract significantly reversed all these parameters in a dose dependent manner[62].

12. Male infertility

WS aids in sustaining male fertility. The aphrodisiac root extract raises the levels of the sex hormones cortisol and testosterone. Moreover, it raises sperm concentration, sperm motility and semen volume. For the treatment of leucorrhoea brought on by endometritis and puerperal backache, the powdered plant is combined with ghee, sugar and milk[63].

Conclusion

The medicinal plant *Withania somnifera* is mostly found in North America and India. In Indian medical systems, it has several clinical uses. It is a significant source of several medicinally and pharmacologically significant compounds, including withaferins, sitoindosides and numerous practical alkaloids. This herbal supplement is a rejuvenator of both physical and mental health due to its many health advantages. In addition to being useful as an anti-tumor, anti-inflammatory, anti-microbial, anti-arthritic and anti-aging agent, it also helps to preserve the body's strength so that it can withstand stress. It has also been found to be considerably beneficial in reducing body weight. Toxicity tests of *Withania somnifera* revealed no harmful or adverse effects, indicating that it may be used safely in the treatment of acute and chronic sick conditions in humans.

Acknowledgements

The financial support from Department of Biotechnology, Ministry of Science and Technology, Govt. of India, to Department of Biotechnology, Himachal Pradesh University, Shimla, India, is thankfully acknowledged.

Declarations

Ethical approval: Not applicable

Competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author's contributions: Vibhuti Sharma: Original draft writing and preparation, review and editing, Figures preparation, Conceptualization; Rutika Sehgal: Validation, Visualization, Data curation, Investigation; Reena Gupta: Supervision, Validation

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