



A Systematic and Comprehensive Review on *Withania somnifera* (L.) Dunal- An Indian Ginseng

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Authors' contributions

This work was carried out in collaboration between all authors. Author AB designed the study, wrote the protocol, and wrote the first draft of the review manuscript. Author NS managed the literature searches with author AB. Authors HSD and VS managed the process of review article and identified the plant species. All the authors read and approved the final manuscript for publication.

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Review Article

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ABSTRACT

Present review article reveals the importance of species *Withania somnifera* (L.) Dunal, distributed in India and other parts of the world, this extensive research information on this species is highly significant for future researchers worldwide. In this article cytomorphological, phytochemical and biological activities inputs have been extensively recorded and discussed. As a part of our investigation on cytomorphological and phytochemical aspects for important medicinal plants from India, the aim of this pioneer attempt is to provide precise, truthful and detailed information of *W. somnifera* (L.). As per our knowledge, there is not even a single, combined, constructive review report available about this species, evaluated by using cytomorphological, phytochemical and biological activities based aspects.

Keywords: Ashwagandha, biological activities; cytomorphology; indian ginseng; phytochemistry; *Withania somnifera* (L.) Dunal.

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1. INTRODUCTION

Plants are one of the most important sources of medicines in world and the writing indicate their medicinal uses as old as 4000-500 B.C. Chinese were the first to use the herbal preparations as medicines. In India, Rig-Veda (written between 3500-1600 B.C.) have earliest references of use of plants as medicine and later the properties and therapeutic uses of medicinal plant were recorded in Ayurveda [1]. World Health organization has listed more than 20,000 species of medicinal plants which are used globally [2]. According to WHO, for primary health care more than 80% of World's population relies on traditional herbal medicines [3]. Various drugs and chemicals derived from various parts of the plants and they continue to be possible sources of new drugs and chemicals [4,5]. *Withania somnifera* (L.) Dunal is an important medicinal plant and used in Ayurvedic medicines for the treatment of many diseases and it is also used in other parts of world [6,7]. In Ayurveda it is known as 'Rasayana' because it promote health and longevity, arrest ageing process, increase capability of individual to resist adverse environmental conditions [8]. The steroidal lactones (withanolides) obtained from its roots are mainly responsible for its therapeutic activities and general health maintenance like immunomodulation, combating infectious agents, anti-cancer, anti-epileptic, anti-ageing, anti-oxidant, hypoglycemic, hypocholesterolemic activities, memory enhancer and in common an effective adaptogen. These compounds also

work as "marker compounds/agents" for chemical standardization of Ashwagandha-based products [9-11]. *W. somnifera* (L.) Dunal commonly known as "Ashwagandha", "Asgandh" and "Winter Cherry" belongs to family Solanaceae and widely distributed in warmer parts of the world. Genus *Withania* comprises 23 species including *W. somnifera* (L.) Dunal and *W. coagulans* (L.) Dunal having high medicinal value which are used as "Rasayana" in Ayurvedic formulations [12]. Ashwagandha attains the special name because its root smells like horse ("Ashwa") and believe to provide power like horse when consumed [11]. In Vedas it is described as herbal tonic and health food and considered as 'Indian Ginseng' because of its ginseng like health promoting effects [8,13]. Ashwagandha is as one of the ingredients in 74 Ayurvedic, 9 Siddha, 3 Unani and 126 herbal formulations [14]. Ashwagandha improves energy and also memory by enhancing the brain and nervous function; shows anxiolytic effects, has hepatoprotective property, raises hemoglobin level and red blood cell count, improve energy level; has potent antioxidant activity, improve the cell-mediated immunity; promotes vigor and vitality along with cheerful sexual life and reproductive equilibrium and act as powerful adaptogen [15-20]. As per our knowledge, there is not even a single, combined, constructive review report available about this highly recommended and utilized Indian species *W. somnifera* (L.) Dunal evaluated by using cytomorphological, phytochemical and biological activities based aspects from India and abroad.

1.1 Botanical Classification		1.2 Vernacular Names	
Kingdom :	Plantae	Arabic :	Kaknaj-e-Hindi
Division :	Angiosperms	Bengali :	Ashvaganda, Asvagandha
Class :	Dicotyledoneae	English :	Winter cherry
Order :	Tubiflorae	Gujarati :	Asan, Asana, Asoda, Asundha Ghodaasoda,
Family :	Solanaceae	Malayalam :	Amukkiram, Pevetti
Genus :	<i>Withania</i>	Marathi :	Askandha, Kanchuuki, Tilli
Species :	<i>somnifera</i>	Odiya :	Asugandha
		Persian :	Kaknaj-e-Hindi, Asgand Nagaori
		Sanskrit :	Ashvagandha, Ash vakandika, Gandhapatri, Palashaparni
		Tamil :	Amukkira, Asubam, Asuvagandi
		Telugu :	Asvagandhi, Penneru, Pennerugadda, Dommadolu
		Urdu :	Asgand, Asgand Nagori [21-23]

1.3 Common Names

Winter cherry (Eng.); Bitterappelliefie, Geneesblaarbossie, Koorshout (Afr.); Bofepha (Sotho); Ubuvuma (Xhosa); Ubuvimbha (Zulu); Ashwagandha (Hindi).

1.4 Conservation Status

Raimondo and co-workers, described the status of *W. somnifera* as 'Least Concern' as it is not a threatened species [24].

1.5 Geographical Distribution

W. somnifera is widely distributed around the world from Southern Mediterranean regions to the Canary Island and from South to East Africa; from Palestine to North India covering Israel, Jordan, Egypt, Sudan, Iran, Afghanistan, Baluchistan and Pakistan. In India the plant can be seen growing wild in the North Western regions extending to the mountainous region of Punjab, Himachal Pradesh and Jammu up to an altitude of 1,500 m [14].

2. CYTOLOGICAL STATUS

W. somnifera is reported to have intraspecific chromosomal variations having diploid, $2n=2x=24$ [25], tetraploid, $2n = 4x = 48$ [26] and hexaploid, $2n=6x=72$ [27] cytotypes located in different parts of India. An aneuploid cytotype with $2n=42$ from a callus regenerated plant is also mentioned in some reports [28]. The plant shows more than 97% incompatibility between wild and cultivated accessions which may be due to self-pollinating nature of the plant [29]. This plant show high degree of variability with respect to growth, habit and morphological characteristics in different parts of India and five distinct morphotypes of this plant have been identified from India [30]. The comparative detailed cytological studies on different accessions from North India have also been reported [31].

3. MORPHOLOGICAL DESCRIPTION

W. somnifera is an erect, green, branched or unbranched herb with height up to 1.25m. The aerial parts like stem, leaves and calyx are covered with fine hairy tomentum. Its branches are rounded; leaves are simple, petiolate, ovate, entire, shiny smooth and opposite; flowers are inconspicuous, greenish or yellow, in axillary umbellate cymes, bisexual; fruit is a berry in persistent calyx and seeds are small, flat, yellow,

reniform, very light [14,32]. The plant prefers a sunny situation, seeds are sown during June or July and seedlings are transplanted at a distance of 60 cm x 30 cm [33]. It is susceptible to bacterial, fungal, viruses, phytoplasmas and pests infections [34]. Comparative morphological evaluations from wild accessions have also been extensively covered to find out new cytomorphotypes from North Indian wild germplasm [31].

4. CHEMICAL CONSTITUENTS

Withanolides and alkaloids are the major secondary groups characterized from *W. somnifera* and are of great medicinal interest [35]. Large numbers of withanolides have been isolated from its roots and leaves which attribute the medicinal property of this plant. Withaferin A represented the first natural lactone of the withanolide series isolated from its shoots [36]. Most of the pharmacological activities of this plant are due to two main withanolides, withaferine A and withanolide D [37]. Its roots are the major source of desired phytochemicals. Withanolides are characterized by the presence of C-28 basic skeleton with a nine carbon atom side chain in which C-22 and C-26 oxidized to form a six membered lactone ring (CS-8). According to biogenetic point of view, withanolides are considered to have a cholestane type structure with an extra methyl group at C-24 and various oxygenated groups or double bonds placed at different sites of the skeleton [14]. Five distinct chemotype of this plant, three from Israel and one from South Africa and India, were reported [38,39]. High performance liquid chromatography (HPLC) investigation of various organs of *W. somnifera* show a gradual decrease in content of withanolide A from aerial parts i.e., from young leaves to the root [40]. High-performance thin-layer chromatography (HPTLC) quantification of major bioactive withanolides like withaferine A, 1,2 deoxy-withastramonolide, withanolide A and withanolide B from the root has also been done for rapid validation of Ayurvedic product [41]. GCMS analysis of roots and callus confirm the presence of 17 alkaloids out of which maximum present in roots followed by callus [42]. Metabolic profiling of chemotype variant in *W. somnifera* fruits using GC-MS and NMR spectroscopy has identified 82 chemically diverse metabolites consisting of fatty acids, organic acids, aliphatic and aromatic acids, polyols, sterols, sugars, tocopherols, phenolic acids and withanamides. Squalene and tocopherol has been identified for the first time in

the fruit and rated as the most potent naturally compounds with antioxidant properties [43]. Some research work on *W. somnifera* has already been done in our laboratories to identify cytomorphotypes and chemotypes by morphometric parameters, cytological studies and (HPTLC) High Performance Thin Layer Chromatography, (HPLC) High Performance Liquid Chromatographic techniques [13,44].

5. PHARMACOLOGICAL AND BIO-ACTIVITIES

W. somnifera (L.) (Ashwagandha) is widely used in Ayurvedic medicines and is an important ingredient prescribed for a variety of musculoskeletal conditions like arthritis, rheumatism and also used as general tonic to increase energy, improve overall health and longevity. Many pharmacological studies like immunomodulatory, cardioprotective, neuro-protective, anti-ageing and anti-oxidant etc. have been conducted to investigate the properties of Ashwagandha [45]. The information about various pharmacological activities have also been reviewed and given by few workers in their respective reviews [46,47]. It is one of the most important plants in Indian and world pharmacopoeia. The main aim of the present review is to collect all the possible information on *W. somnifera* so that it will become easy for other workers to retrieve the truthful information from this review.

5.1 Anti-cancerous Activity

Cancer is a hyper proliferative disorder that results in apoptosis, transformation and metastasis [48]. Millions of people suffer with various kind of cancer and die each year [49]. Ashwagandha a proud herb of Ayurveda has great anti-tumorigenic activity against various cancer cell lines due to the presence of withaferin A (WFA), a withanolide derived from this medicinal plant [50]. To investigate the anti-cancerous activity of *W. somnifera* various studies have been conducted. A study conducted on five human cancer cell lines of four different tissues that is PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung) and IMR (neuroblastoma) showed 0-98% *in vitro* cytotoxicity of 50% ethanol extract of root, stem and leaves depending on cell lines but 50% ethanol extract of leaves of *W. somnifera* showed maximum activity. Ethanol extract of leaves obtained from treatment T₂, T₃, T₄ and T₅ showed 80-90% growth inhibitor activity against PC-3 and HCT-

15 which is a strong activity, while 50% ethanol extract of leaves from T₁ treatment show minimal 39% growth inhibition against HCT-15 and T₃ showed a maximum of 98% growth inhibition against HCT-15 [51]. Water extract of Ashwagandha leaves (ASH-WSX) both by *in vitro* and *in vivo* assays show anti-cancerous activity and triethylene glycol (TEG) was identified as active anti-cancerous component. It was also found that ASH-WSX was selectively cytotoxic to cancer cells and results in *in vivo* tumor suppression. Molecular analysis showed activation of tumor suppression protein p53 and pRB in ASH-WEX and TEG treated cancer cells [52]. *W. somnifera* (leaves) flavonoid compounds show anti-cancerous activities on cell lines MCF-7, A549 and PA1. These readings showed that *W. somnifera* (leaves) shows efficient cytotoxicity on MCF-7 (10±1µg) than PA1 (13±1µg) and A459 (11±1µg) cancer cell lines [53]. A long term tumor genesis study on Swiss albino mouse model shows that roots of *W. somnifera* inhibit the benzo(a)pyrene-induced forestomach papillomagenesis and results in 60 and 92% inhibition in tumor incidence and multiplicity. Similarly it also inhibits the 7, 12-dimethylbenzanthracene-induced skin papillomagenesis by showing 45 and 71% inhibition in tumor incidence and multiplicity [54]. Squamous cervical cell line, SiHa treated with ethanolic extract of roots of *W. somnifera* show apoptosis which is an important step in cancer biology [55]. Withanolides are important for the treatment of cancer cells by suppressing the expression of oncoprotein Skp2 which is a member of the F-box family of substrate recognition subunits of SCF ubiquitin-protein ligase complexes which implicate in the ubiquitin-mediated degradation [56]. Similarly in another study it was observed that a bioactive withanolide tubocapsanolide A inhibits the proliferation of human lung cancer cells via repressing Skp2 expression [57]. Withaferin A enhances radiation-induced apoptosis in human renal cancer cells (Caki) through induction of ROS, Bcl-2 down regulation and Akt dephosphorylation [58]. Yu and co-workers, conducted an *in vitro* and *in vivo* study on pancreatic cancer cell to reveal that withaferin show *in vitro* antiproliferative activity against pancreatic cancer cell lines Pac-1, MiaPaCa and BxPc3 with IC₅₀ value of 1.24, 2.93, 2.78µ respectively. The study also investigated that withaferin A binds to Hsp90, inhibits its chaperone activity through an ATP-independent mechanism, results in its client protein degradation and exhibits *in vivo* anticancer

activity against pancreatic cancer [59]. A novel bioactive compound withanolide sulfoxide obtained from the methanol extract of *W. somnifera* roots has been shown to inhibit nuclear transcription factor-kappa-B, cyclooxygenase and tumor cell proliferation against the human breast (MCF-7) cancer cell lines [60]. It has also shown that leaf extract of *W. somnifera* produce antiproliferative activity against MCF-7 human breast tumor cell lines [51]. Anticancerous activity of *W. somnifera* was also confirmed by various workers [61-64].

5.2 Immunomodulatory Activity

A series of studies conducted on animals showed that *W. somnifera* has a profound effect on hematopoietic system by acting as an immunoregulator and chemoprotective agent [1, 65]. Extract of this plant experimentally in normal mice records the increased cell mediated immunity (CMI) and root extract known to enhance the level of interferon gamma (IFN- γ), interleukin (IL-2) and granulocyte macrophages colony stimulating factor (GM-CSF) in mice. This suggests their immunoprotective and myeloprotective effect. Ashwagandha increases the microbes killing power of these immune cells by enhancing nitric oxide synthetase activity of the macrophages [66]. For increasing the phagocytic activity, it activates and mobilizes macrophages, potentates the activity of lysosomal enzymes and acts as an anti-stress molecule and anti-inflammatory agent in mice and rat [67]. Ethanolic extract of *W. somnifera* enhances humoral immune response in Swiss albino mice on 7th day of administration by 12% as compare to control cyclophosphamide (54%). Cell mediated immune response was enhanced to 19.27% in comparison with control cyclosporine (37.63%). In tumor bearing mice, the effect of methanolic extract on hematological parameter shows an increase in number of RBCs and a decrease in WBCs compared to the control mice [33]. Treatment with five doses of *Withania* root extract (20mg/dose/animal; i.p.) in Babl/c mice showed an enhancement of the total WBC count (17125 cells/mm on 10th day), increase in bone marrow cellularity (27x10 cells/femur) and significant increase ($P < 0.001$) in α -esterase positive cell number (1800/4000 cells). Administration of *Withania* extract along with antigen (SRBC) showed enhancement in circulating antibody titer, maximum number of plaque forming cells PFC (985 PFC/10 on fourth day) in spleen and inhibition of delayed type of hypersensitivity in mice. It also showed an

enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cells/200) when compared to control (31.5/200cells) [68]. *W. somnifera* is an excellent immunomodulator because in the absence as well as in presence of cyclophosphamide it influences T-cell production, enhances neutrophil counts and produces significant humoral response against sheep RBCs. The immunomodulatory activities may be due to withaferin A and withanolide D [69]. Extract of *W. somnifera* shows immunomodulatory effects on azoxymethane induced colon cancer in Swiss albino mice when treated with plant extract of 400 mg/kg body weight once a week for four weeks orally [64]. The levels of IFN γ , IL-2 and GM-CSF was reversed to approximately normal in cyclophosphamide treated mice when administrated with *W. somnifera* extract. This also lower the levels of tumor necrosis factor- α and this indicate the immunopotentiating and myeloprotective effect of *W. somnifera* [70].

5.3 Cardioprotective Activity

Myocardial infraction is the most lethal manifestation of cardiovascular diseases and it is one of the most important subjects of intense investigation by scientists [71]. Now a day there is an increased realization that herbs can maintain the balance of body and can influence heart diseases and its treatment by providing nutritional substances [72-73]. Although the therapeutic properties of this plant like immunomodulatory, adaptogenic, antioxidant, hypoglycemic and anti-cancerous are well known [74,75], but very few studies are available, which assess its cardioprotective potential [9]. Cardioprotective effect of hydro-alcoholic extract of *W. somnifera* was studied on the basis of haemodynamic, histopathological and biochemical parameters in the isoprenaline-(isoproterenol) induced myocardial necrosis in rats and was compared with vitamin E, a known cardioprotective antioxidant. Both the drugs restore the myocardial antioxidant status and maintain membrane integrity by evidently reducing the malonyldialdehyde levels. Cardioprotective effect of these drugs was also confirmed by histopathological examinations. *W. somnifera* at 50 mg/kg dose shows maximum cardioprotective effect [76].

5.4 Neuroprotective Activity

Ashwagandha can be used for the treatment of neurodegenerative disorders like Alzheimer,

Parkinson, Huntington and other neurodegenerative disorders at any stage of disease because it can significantly reverse the neurotrophic atrophy, synaptic loss, along with GABA mimetic effect and promotes formation of dendrites due to therapeutic activity of glycowithanolides withaferin A VII-X present in roots of ashwagandha [77-80]. Scientists of the institute of Natural Medicine at the Toyama Medical and Pharmaceutical University of Japan, by using the valid model of damaged nerve cell and impaired nerve signaling pathway, showed that the plant supports significant regeneration of the axon and dendrites of nerve cells. Its extracts supported the reconstruction of synapses or networks of the nervous system and it may act as potential treatment for neurodegenerative diseases such as Alzheimer, Parkinson etc. [18]. At the same institute during another study researcher found that Ashwagandha help in growth of nerve cell dendrites which suggests that Ashwagandha help in healing the brain tissue changes that accompany dementia [81]. Parkinson's disease 6-Hydroxydopamine rat models were pretreated with 100, 200 and 300 mg/kg dose of *W. somnifera* extract for 3 weeks. *W. somnifera* extract significantly reverse all the parameters (glutathione content, activities of glutathione-S-transferase, glutathione reductase, glutathione peroxidase etc.) to normal in dose dependent manner and demonstrate that it is helpful in protecting the neuronal injury in Parkinson's disease [80]. Ashwagandha root extract increases cortical muscarinic acetylcholine receptor capacity by affecting mainly the cortical and basal forebrain cholinergic signal transduction cascade which leads to cognition- enhancing and memory improving effect in animals and humans [77]. The pre-treatment of *W. somnifera* results in attenuation of cerebral ischemia-reperfusion and long-term hypoperfusion induced alterations in rats which confirm the neuroprotective effect of *W. somnifera* [82]. In another study female albino rats were subjected to immobilization stress for 14h and then treated with the root extract of *W. somnifera* which results in significant reduction (80%) in the number of degenerative cells in hippocampal sub-regions of rat [83]. Sankar and co-workers studied the influence of root extract of *W. somnifera* on Parkinsonism in MPTP-intoxicated mice [84]. Oral treatment resulted in significant improvement in behavior, antioxidant status and a significant reduction in level of lipid peroxidation. Malhotra and co-workers have also studied the neuroprotective effect of this plant on the central nervous system [85].

5.5 Anti-oxidant / Anti-aging Activity

There are many herbal plants which contain the antioxidant compounds and protect the cells from degenerative effect of Reactive Oxygen Species (ROS) [86,87]. Now research is going on to reveal potential phytochemical antioxidant because they are safer to health and have better antioxidant activity than synthetic antioxidants [88]. *W. somnifera* acts as a powerful antioxidant by increasing the level of three naturally occurring antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase in the brain of rats [9]. Active principles present in the root of *W. somnifera* have powerful antioxidant effect like anti-stress, cognition-facilitating, anti-inflammatory and anti-aging [89]. Antioxidant protects the body against free radical damage. An *in vitro* antioxidant activity of extract of different parts of *W. somnifera* shows that these are the potential scavengers of radicals and protector of lipid membrane in order of: leaves > fresh tubers > dry tubers. The antioxidant activity may be due to withanolides, glycowithanolides and sitoindosides VII-X. So the study indicates that Ashwagandha could be proved as natural source of safe anti-oxidative agent [90]. GEN-treated rat showing nephrocytotoxicity when administrated with *W. somnifera* (500mg/kg) significantly reverses the signs of tubular necrosis. Overall results suggest that nephroprotective effect of *W. somnifera* could be due to enhanced antioxidant activity with natural antioxidants and scavenging free radicals present in it [91]. Root powder of this plant prevents Cadmium- induced oxidative stress in chickens and lead induced oxidative damage in mouse [92-94]. A study was conducted to identify the antioxidant activity of extracts from *W. somnifera* by using various *in vitro* methods like 2, 2-diphenyl, 1-picryl hydrazyl (DPPH) radical scavenging activity, reducing capacity, competition with DMSO, hydroxy group reducing capacity, estimation of total phenol and estimation of ascorbic acid. The highest percentage (%) of DPPH (83.07) scavenging activity was found in polar flavonoid extract [87]. Similarly, free radical scavenging activity of ethanolic and aqueous extract of *W. somnifera* leaves was studied by DPPH and NBT methods and the results indicate that leaf possess antioxidant activity which may be due the presence of flavonoids and tannins in the leaf extract [95]. A double blind clinical trial conducted on 101 healthy male (50-59) for one year to test the anti-aging property of Ashwagandha showed a significant improvement

in hemoglobin, red blood cell count, hair melanin, seated stature, decreased serum cholesterol and preserved nail calcium in subjects. Sexual performance was also increased in 70% of subjects [37,89].

5.6 Antistress / Adaptogenic Activity

Traditionally, Ashwagandha is used to stabilize the mood of patients having behavioral disturbances and experimentally, it has also known to produce more anti-depressant and anti-anxiety effects as compared to drugs imipramine (anti-depressant) and lorazepam (anti-anxiety) [96]. Ashwagandha in India widely used as tranquilizer, improving reproductive and nervous system, rejuvenating body, improving vitality and recovery after chronic illness, so it hold an important position similar to ginseng in China [37,97]. Anti-stress activity of *W. somnifera* was conducted in rats using cold water swimming stress treatment and it was found that the drug treated animals show better stress tolerance [96]. Similarly, a withanolide free aqueous extract of roots show dose dependent anti-stress activity in mice [98]. Department of Pharmacology, University of Texas Health Science Center conducted a research on extract of Ashwagandha and these extracts were known to produce GABA-like activity which may be responsible for its anti-anxiety effects [99]. GABA is an inhibitory neurotransmitter in brain, decrease neuron activity, inhibit nerve cells from over firing, thus produces a calming effect. Two new acylsterylglucosides, sitoindoside VII and VIII isolated from root of *W. somnifera* show anti-stress activity and the preliminary toxicity also indicate the low order of acute toxicity of compounds [97]. In a passive rat experiment model, animals were subjected to multiple stress of cold, hypoxia, restrain (C-H-R) and treated with aqueous root extracts of *W. somnifera* and an active compound X isolated from it. C-H-R stressed rats treated with *W. somnifera* extract and compound X can better withstand the stress than control group [100]. A standardize *W. somnifera* root and leaf extract (WSE) reduces stress related parameters in chronically stressed humans. It was found that WSE treatment show greater dose-dependent response in parameters (mHAM-A score, serum cortisol, serum C-reactive protein, pulse rate, blood pressure and mean serum DHEAS and hemoglobin) and also show significantly greater responses in mean fasting blood glucose, serum lipid as compared to placebo [101]. To study the adaptogenic activity of *W. somnifera*, chronic stress (CS)

was induced in Wistar rats through mild, unpredictable foot shock stress procedure once daily for 21 days. The significant conditions induced by CS like hyperglycaemia, glucose intolerance, increase in plasma cortisol levels, gastric ulcerations, male sexual dysfunction, cognitive defects, immunosuppression and mental depression were attenuated by WS (25 and 50 mg/kg) and *Panax ginseng* (100 mg/kg) which were given 1h before foot shock for 21 days [16]. In another study adaptogenic activity of a novel withanolide free aqueous fraction from roots of *W. somnifera* was conducted on various parameters like hypoxia time, antifatigue effect, swimming performance time, swimming induced gastric ulceration, hypothermia, immobilization induced gastric ulceration, autoanalgesia and biochemical changes in adrenal gland. The extract has shown activity in dose related manner [102].

5.7 Anti-diabetic Effect

Sarangi and co-workers conducted an investigation to explore the possibilities of using leaf and root extracts of *W. somnifera* against diabetes mellitus (DM) and also to examine their hypoglycaemic and hypolipidaemic effects on streptozotonic-induced diabetic rats [103]. The extract possess hypoglycaemic and hypolipidaemic properties and hence useful in diabetes mellitus. Another study show significant positive anti-diabetic activity of *W. somnifera* on diabetic rats when compared with Glibenclamide standard drug. Anti-diabetic activity may be due to increase in hepatic metabolism, increased insulin release from pancreatic β -cells or insulin sparing effect [104]. *W. somnifera* root (WSREt) and leaf (WSLEt) extract show hypoglycaemic and hypolipidaemic effect on alloxan-induced diabetic rats [105]. Andallu and Radhika (2000), studied the hypoglycemic, diuretic and hypocholesterolemic effect of roots of *W. somnifera* on six mild NIDDM and six mild hypercholesterolemic human subjects. Their studies indicate that the plant can be a potential source of hypoglycemic, diuretic and hypocholesterolemic drugs. No adverse effects were observed during clinical observations [106].

5.8 Anti-inflammatory Activity

Anti-inflammatory activity of *W. somnifera* has been attributed to the naturally occurring steroids, of which withaferin A is a major component and as effective as hydrocortisone sodium succinate dose, an anti-inflammatory

drug [98]. Rats treated with powder of *W. somnifera* orally 1h before the injection of inflammatory agent for 3 days produces anti-inflammatory responses which are comparable to hydrocortisone sodium succinate [107]. In another experiment it was found that WS causes dose-dependent suppression of α 2-macroglobulin which is an indicator for anti-inflammatory drugs in the serum of rats inflamed by sub-plantar injection of carrageenan suspension. The doses of WS root powder (500, 1000, 1500 or 1200 mg/kg) were given orally 3-4h prior to induction of inflammation and it was found that maximum effect (about 75%) was seen at 1000 mg/kg [108]. Withaferin A was found to suppress the arthritic syndrome effectively without any toxic effect. In arthritic syndrome animals treated with hydrocortisone show weight loss while animal treated with withaferin A show gain in weight [109,110].

6. CONCLUSION

W. somnifera (L.) Dunal (Ashwagandha) has several health benefits, so is the most important 'Rasayana' in Indian Ayurveda. The plant has the ability to boost the immune functions, enhance the longevity and facilitate the restoration of homeostasis by reducing the stress. The manifestations can be made on the basis of this comprehensive perusal of literature, that the *W. somnifera* is being used traditionally, due to their immense therapeutic potential to treat/cure various diseases. Important withanolides particularly withaferin-A extracted from root and leaf of *W. somnifera* play an important role in inhibiting the growth of human cancer cells. The roots of this plant are effective against the entire health problems already discussed here. We can say that the consumption of various parts of this plant as a dietary supplement may prevent or decrease the growth of tumors in cancer patients but can also protect the body from health conditions. Cytomorphological data reveals that there is an immense need to find out new cytomorphotypes for further germplasm maintenance and evaluation, because till today nobody is working on these important aspects. As per reported phytochemical data, it is concluded that there is a need to identify few more chemotypes for further herbal and allopathic drugs formations. There is huge need and possibilities to isolate new active components from untouched cytomorphotypes of the Genus *Withania* from India. Many studies demonstrated significant anti-inflammatory, anti-cancer, anti-diabetic, immunomodulatory and

anti-bacterial activities etc. which are reported in the extracts of different parts and from its phytoconstituents. These pharmacological activities and identified compounds provide solid scientific evidence for some of the traditional therapeutically claims. A variety of phytoconstituents has been isolated from the different parts of various species. It could be rightly said that due to its wide pharmacological activities, *W. somnifera* is considered as an important multi-purpose medicinal agent and an important component of various polyherbal preparations. Thus the plant has immense practical applicability in biomedicine as well as veterinary medicine focusing its potent role in the maintenance of sound health but more clinical trials should be conducted to support its therapeutic uses. Thus, there remains a wide scope for further scientific exploration of *W. somnifera* to establish their therapeutic efficacy and commercial exploitation. In this review article we have made a constructive, detailed survey of literature for the species *W. somnifera* from Indian origin, which will definitely help researchers from India and abroad.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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