Vol. 11/1 (2011) 1-13

JOURNAL OF NATURAL REMEDIES

A Comprehensive Review on *Withania somnifera* Dunal

Vivek K. Vyas[*1], Pratik Bhandari [2], Radheshyam Patidar[3]

1. Institute of Pharmacy, Nirma University, S.G. Highway, Ahmedabad, 382 481, Gujarat, India.

2. Vinayaka Mission's College of Pharmacy, Vinayaka Mission University, Yercaud Main Road, Kondappanaickenpatty, Salem 636 008, Tamil Nadu, India.

3. Mahakal Institute of Pharmaceutical Studies, Ujjain 456 664, Madhya Pradesh, India.

Abstract

Withania somnifera is known as Ashwagandha, also commonly known in different parts of the world as Indian ginseng, Winter cherry, Ajagandhaand and Kanaje Hindi, a plant belonging to the Solanaceae family. Ashwagandha is a woody shrub or herb whose various parts (berries, leaves and roots) are used as folk remedies. Some traditional uses of ashwagandha are also invoked now a day, such as enhancing sexual function in men, increasing fertility in men or women, aiding sleep and enhancing sports performance. *Withania somnifera* is used as adaptogen, antiarthritic, antispasmodic, anti-inflammatory, nervine tonic, nerve soothing, sedative, hypotensive, antioxidant, immunomodulator, free radical scavenger, anti-stress and anti-cancer agent. Ashwagandha is called "Rasayana", which means powerful rejuvenator in Ayurvedic jargon as it increases hemoglobin (red blood count) and hair melanin. In this study we have critically reviewed recent advancements of *Withania somnifera* in an attempt to authenticate its use as a multi-purpose medicinal agent.

Key words: *Withania somnifera*, Solanaceae, Ashwagandha, Withanolides, Withaferin-A, Adaptogen.

1. Introduction

Withania somnifera Dunal (ashwagandha) is a commonly used herb in Ayurveda, Siddha and Unani system of medicine. The Indian name for *Withania somnifera* Dunal (ashwagandha) means "odor of the horse", probably the term refers the smell of horse originating from odor of its root. The name "*somnifera*" in Latin means "sleep-inducer" which probably refers to its general use as a remedy against stress. *Withania somnifera* is a main ingredient of many marketed formulations used for a variety of clinical conditions like arthritis and rheumatism and as a general tonic to improve health of the elderly and during pregnancy in women [1-4]. *Withania somnifera* also helps in conditions like chronic fatigue, weakness, dehydration, bone weakness, loose teeth, thirst, impotency, premature ageing and emaciation [5]. It is an

* Corresponding author
Email: vicky_1744@yahoo.com ,vivekvyas@nirmauni.ac.in

imperative herb in traditional medicine systems for over 3000 years. Traditionally, plant was used as aphrodisiac, anti-inflammatory agent, as an ingredient of liver tonic, rejuvenating agent and to treat insomnia. *Withania somnifera* has reported to cause increase in weights of testes, seminal vesicle and bulb urethral gland [6]. *Withania somnifera* is considered to promote youthful vigor, endurance, strength and general health. It is widely claimed to produce mild sedation, an effect potentially useful for those troubled by anxiety [7]. The leaves of *W. somnifera* are bitter in taste and used as an antihelmantic. Bruised leaves and fruits are locally applied to tumors and tubercular glands, carbuncles and ulcers. The roots are used in constipation, loss of memory, loss of muscular energy and spermatorrhoe [8, 9]. The medicinal properties of *W. somnifera* is attributed to several classes of withanolides, a group of naturally occurring C-28 steroidal lactone triterpenoids, in which C-22 and C-26 are suitably oxidized to form a six-membered lactone ring [10]. The purpose of this article is to review recent literature regarding *W. somnifera* in an attempt to establish a scientific basis for therapeutic use of *W. somnifera*.

1.1 Botanical description of W. somnifera [11]

W. somnifera is an erect branching shrub that attains height between 30 and 150 cm, covered in a woolly pubescence. The ovate leaves are 10 cm long and 2.5–5 cm wide, entire margins arranged in an alternate fashion. The flowers are green or yellow and fruits are red in colour when mature. The roots are fleshy and cylindrical in shape, epidermis is light brown and medulla is white in colour.

1.2 Geographical description of W. somnifera [12]

W. somnifera grows effectively in dry regions of South Asia, Central Asia and Africa, particularly in India, Pakistan, Bangladesh, Sri Lanka, Afghanistan, South Africa, Egypt, Morocco, Congo and Jordon. In India, it is cultivated on a commercial scale in the states of Madhya Pradesh, Uttar Pradesh, Punjab, Gujarat and Rajasthan.

2. Phytochemistry

Phytochemistry of *W. somnifera* is extensively studied, over 35 chemical constituents are identified, extracted and isolated [13].

2.1 Active Chemical Constituents

Phytochemistry of *Withania* species is extensively studied and various chemical constituents such as steroidal lactones, alkaloids, flavonoids, tannin etc. are identified, extracted and isolated [14-19]. At nearby, more than 12 alkaloids, 40 withanolides and several sitoindosides (a withanolide containing a glucose molecule at C-27) are reported from aerial parts, roots and berries of *Withania* species. The major chemical constituents of *Withania* species, withanolides are mainly contained in leaves [14-20]. Withanolides are a group of naturally occurring C-28 steroidal lactones built on an intact ergostane structure, in which C-22 and C-26 are oxidized to form a six-membered lactone ring [21-26]. Withaferin A (Figure 1) was the first member of withanolides, isolated from *W. somnifera* [21, 27-29]. Withanolides are main chemical constituents responsible for multiple medicinal applications of ashwagandha. It stimulates activation of immune system cells such a lymphocytes. It inhibits inflammation and restores memory. At present, more than 125 withanolides from Solanaceae genera are well known, generally occurring in free form, but in a few cases present as glycosides [21]. Leaves are reported to contain five unidentified alkaloids (0.09%), chlorogenic acid, calystegines, withanone, tannin and flavonoids. Four types of peroxidases is purified and characterized

from *W. somnifera* roots [30]. Different chemical constituents present in *Withania* species are 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) [29] .

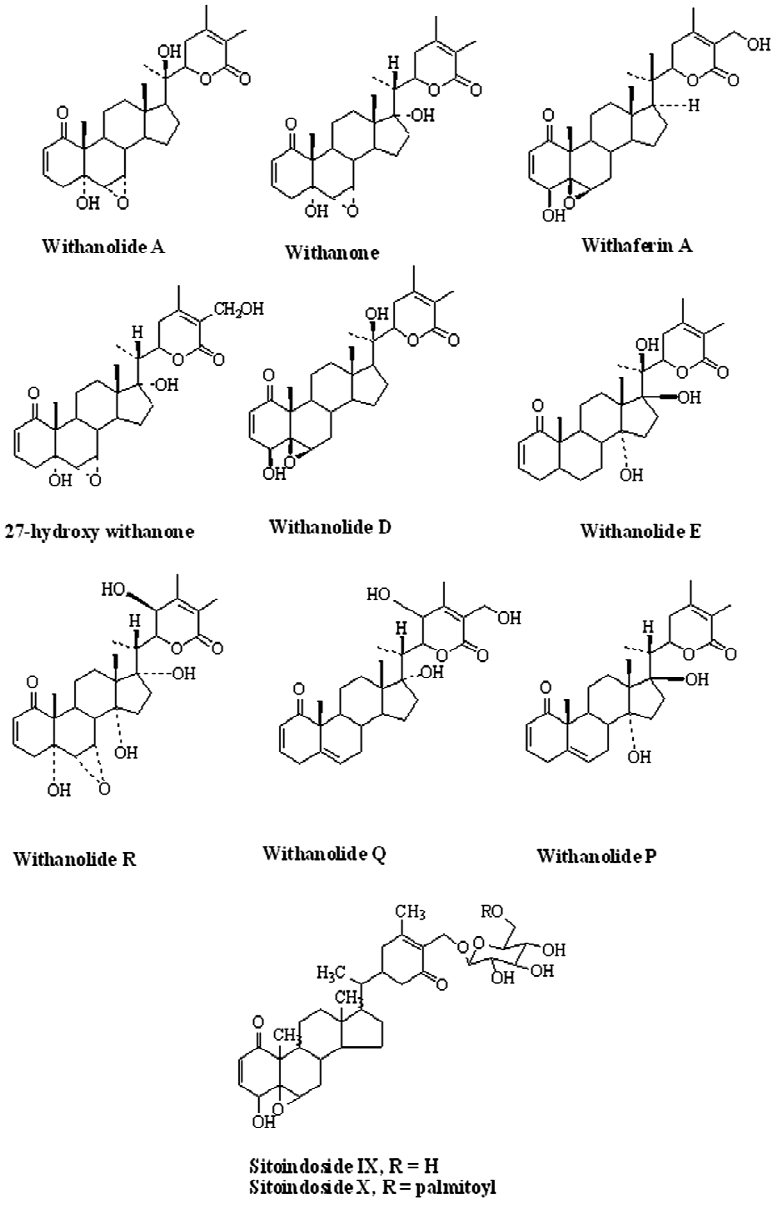

Fig. 1. Chemical Structures of Active Constituents of *W. somnifera*

Table 1: Medicinal use of different parts of *W. somnifera* Dunal [31-35]

S. No.	Disorders	Part used	Description
01	Digestive disorder (dyspepsiaand loss of appetite)	Roots	It corrects disorders processes of digestion.
02	Rheumatism	Roots	3 g/day in rheumatic arthritis
03	Female sterility	Roots	6 g/day with milk for 5 to 6 successive nights after menstruation.
04	Skin disorders, painful swelling inside the skin and syphilitic sores	Leaves	Ointment and cream of leaves is useful in ulcers and swelling
05	Sore eyes	Leaves	Fermented leaves can be applied to get relief
06	Brain tonic	Roots	Regular use improves stress tolerance and restores memory
07	General debility	Roots	2 g/day
08	Tuberculosis	Roots	Decoction of roots is used with long pepper and honey, in the treatment of scrofula (tuberculosis of lymph glands especially in the neck)
09	Insomnia	Roots	Produce deep sleep
10	Cough and cold	Roots	3 g/day in the form of decoction
11	Weak immune system	Roots extract	Immunomodulatory
12	Aging	Roots	Antioxidant

2.2 Different Species of Genus Withania

Twenty-three known *Withania* species are widely distributed in the drier parts of tropical and subtropical countries of the world, ranging from Canary Islands, Mediterranean region and Northern Africa to Southwest Asia [36-38]. The Genus *Withania* is further organized into groups including:

W. martiana , W. melanocystis , W. micrantha, W. microphysalis, W. mollis, W. monifera, W. morisonii, W. mucronata, W. novo-friburgensis, W. novofriburgensis, W. obtusifolia, W. origanifolia, W. orinocensis, W. peruviana, W. picta, W. picta var. parvifolia, W. picta var. subnuda, W. pogogena, W. pogogena var. glabra, W. pohliana, W. pyrifolia, W. qaraitica, W. ramosa, W. reichenbachii, W. riebeckii, W. schottiana, W. sicula, W. simonyaua, W. sinensis, W. sinica, W. somnifera, W. somnifera obtusifolia, W. sordida, W. sphaerocarpa, W. sphaerocarpa var. grisea, W. suberosa, W. subtriflora, W. villosa, W. wiebeckii, W. xalapensis and W. yunnanensis [39].

3. Recent Advancements in Pharmacological activities of *W. somnifera* Dunal

W. somnifera is used for centuries to treat a wide range of diseases, showed great potential as a safe and efficacious multi-purpose medicinal agent. Beside its traditional uses several recent reports have demonstrated immunomodulatory, antitumor, hypolipidaemic and cardioprotective effect of ashwagandha [40-44] Moreover, various parts of plant are reported to possess antiserotogenic, anticancer and anabolic properties and have beneficial effects in the treatment of arthritis, stress and geriatric problems [45-48]. *W. somnifera* is used as home remedy to treat diseases in India as well as other parts of the world [49-50].

W.somnifera is claimed to produce beneficial effects in the conditions like anxiety and depression [51-54]. According to one study in animals, ashwagandha may raise thyroid hormone levels [55-58]. Fruits of *W. somnifera* have a milk-coagulating property, which is used in preparation of vegetable rennet ferment for cheese [59]. The fruits of plant are claimed to be sedative, emetic, stomachic, a blood-purifier, febrifuge, diuretic and bitter tonic in dyspepsia as well as a growth promoter in infants [60, 61]. The crude preparation of *W. somnifera* is found to be active against a number of pathogenic bacteria [62]. In recent years, several pharmacological investigations are carried to investigate different biological effects of chemical constituents of *W. somnifera* [63-67]. In animal studies, withaferin-A has showed significant anticancer activity. Majority of the anticancer drugs like vinblastine, vincristine and taxol are derived from green flora. Withanolides are under the great research potential for the treatment of cancer [68-69]. Experimental studies in animal models have extensively demonstrated GABA-mediated action of *W. somnifera* [70]. It is possible to formulate ashwagandha into pills, capsules and alcoholic extracts to create greater public acceptance. Gupta and Rana [71] have reviewed pharmacological activity of *W. somnifera* extracts. The intention of next section is to review the literature and articles to cover recent advances in pharmacological activities of *W. Somnifera.*

3.1 Antiparkinson's

Rajasankar S *et al*. (2009) proposed that *W. somnifera* root extract improves catecholamines and physiological abnormalities in Parkinson disease (PD). Results of this study suggested that *W. somnifera* is a potential drug in treating catecholamines, oxidative damage and physiological abnormalities in PD mouse [72]. In another study (2009) the authors evaluated effects of leaf extract of *W. somnifera* in PD mouse. This study revealed that *W. somnifera* is a agent in treating oxidative damage and physiological abnormalities in Parkinson disease [73]. Yadav CS *et al.* (2010) studied the effect of *W. somnifera*, on propoxur-induced acetylcholine esterase inhibition and impairment of cognitive function in rats. The authors suggested that oral administration of *W. somnifera* exerts protective effect and attenuates AChE inhibition and cognitive impairment caused by sub-chronic exposure to propoxur [74].

3.2 Antiproliferative

Abdeljebbar LH *et al*. (2009) studied antiproliferative effects of withanolides, extracted from *W. adpressa*. The bioassay-guided fractionation of *W. adpressa* plant extracts results in identification of novel withanolide (14α, 15α, 17β, 20β -tetrahydroxy-1-oxo-(22R)-witha-2, 5, 24-trienolide). Effects of previously identified withanolides (F and J) and novel withanolide extracts suggested that withanolides from *W. adpressa* has potential as antiproliferative agents [75]. Mirjalili MH *et al.* (2009) focused on two novel activities, tumor inhibition and antiangiogenic properties of withaferin A. The authors discussed most recent attempts in biotechnological production of withanolides [76]. Shah N *et al*. (2009) investigated growth inhibition and differentiation potential of alcoholic extract of ashwagandha leaves on cell lines. Withaferin-A, withanone, withanolide-A and alcoholic extract markedly inhibits proliferation of glioma cell lines in a dose-dependent manner [77]. Mulabagal V *et al.*(2009) evaluated methanolic extract of *W. somnifera* roots for bioactive constituents (withanolide sulfoxide and ashwagandhanolide with S-linkage). Isolation of withanolide sulfoxide from *W. somnifera* and its ability to

inhibit COX-2 enzyme and to suppress human tumor cell proliferation were reported first time in this study [78]. Aalinkeel R *et al*. (2008) highlighted role of JAK-STAT signaling in anti-proliferative action by genomic analysis. The authors investigated effects of ashwagandha in prostate cancer cells lines. This study hypothesized that immunomodulatory and anti-inflammatory properties of ashwagandha contributed to its overall effectiveness as an anti-carcinogenic agent. Main goal of this study was to gain insight into the general biological, molecular functions and immunomodulatory processes that is altered as a result of *W. somnifera* treatment in prostate cancer cells [79]. Stan SD *et al.* (2008) evaluated anticancer activity of withaferin-A against human breast cancer cell lines in culture and *in vivo*. Treatment with withaferin-A decreased viability of MCF-7 (estrogen-responsive) and MDA-MB-231 (estrogen-independent) human breast cancer cells in a concentration-dependent manner. Withaferin-A induced suppression of breast cancer cell viability was correlated with apoptosis induction characterized by DNA condensation, cytoplasmic histone-associated DNA fragmentation and cleavage of poly-(ADP-ribose) - polymerase [80]. Bolleddula J *et al.* (2009) isolated 12 withanolides, tested for their antiproliferative activity on lung, colon, central nervous system and breast tumor cell lines. The authors suggested that incorporation of withanolides in diet may prevent or decrease growth of tumors in the body [81]. Choudhary MI *et al.* (2010) isolated a chlorinated steroidal lactone (27-acetoxy-4β,6α-dihydroxy-5β-chloro-1-oxowitha-2,24-dienolide), a diepoxy withanolide (5β,6β,14α,15α-diepoxy-4β,27-dihydroxy-1-oxowitha-2,24-dienolide), and withaferin-A from aerial parts of *W. somnifera*. Isolated compounds showed cytotoxic activity against human lung cancer cell line with withaferin-A being the most potent among three compounds tested [82].

3.3 Immunostimulatory

Muralikrishnan G *et al.* (2010) tested efficacy of *W. somnifera* on immunomodulation in experimental azoxymethane induced colon cancer in mice. *W. somnifera* significantly altered the level of leucocytes, lymphocytes, neutrophils, immune complexes and immunoglobulins (Ig) A, G and M. The azoxymethane induced colon cancer and immune dysfunction was better controlled by *W. somnifera* [83]. Khan S *et al.* (2009) gave molecular insight into the immune up-regulatory properties of leaf extract of ashwagandha. This study demonstrated potential role of chemically standardized leaf extract of *W. somnifera* and its identified component in activating immune system [84].

3.4 Neuroprotective

Kumar P and Kumar A (2009) described neuroprotective effect of *W. somnifera* root extract. Huntington's disease (HD) is neurodegenerative disorder that results from the destruction of neurons in the basal ganglia. The study was designed to investigate the effects of *W. somnifera* root extract against 3-nitropropionic acid (3-NP) induced gait abnormalities, oxidative stress and mitochondrial dysfunction. Chronic treatment with *W. somnifera* root extracts (100 and 200 mg/kg) for a period of 2 weeks, dose-dependently improved 3-NP-induced behavioral, biochemical and enzymatic changes. [85]. Bhatnagar M , *et al.* (2009) proposed possible mechanism of neuroprotective action of root extract of *W. somnifera*. This study was focused on *W. somnifera* mediated inhibition of nitric oxide production, which is known to produce neurodegeneration during stress. *W. somnifera* root extract could be developed as a potential preventive or therapeutic drug for stress induced

neurological disorders[86]. Kumar S *et al.* (2010) investigated neuroprotective properties of an aqueous extract of *W. somnifera* root as a novel approach to treat dementia, especially dementia of the Alzheimer's type (AD) [87]. Jayaprakasam B *et al.* (2010) tested two major withanamides (A and C) for their ability to protect PC-12 cells and rat neuronal cells from damage caused by beta-amyloid (inducer of Alzheimer disease) [88].

3.5 Hypoglycaemic and Hypolipidaemic

Hoda Q *et al.* (2010) evaluated aqueous extract of *W. coagulans* fruits, for its effect on blood glucose, lipid profile and body weight in type-2 diabetic rats. Aqueous extract showed significant decrease in blood glucose, triglyceride, total cholesterol, LDL and VLDL level. *W. coagulans* was found slightly superior to metformin for its antihyperglycemic effect [89]. Udayakumar R *et al.* (2009) investigated hypoglycaemic and hypolipidaemic effect of *W. somnifera* root and leaf extracts on alloxan-induced diabetic rats. The levels of urine sugar, blood glucose, serum lipids except high density lipoprotein-bound cholesterol (HDL-c) and tissues like liver, kidney and heart lipids were significantly increased, however hemoglobin, total protein, albumin, albumin:globulin (A:G) ratio, tissues protein and glycogen were significantly decreased in alloxan-induced diabetic rats [90]. In another study (2010) the authors determined orally administrated phenolic and flavonoid compounds from extracts of *W. somnifera* root and leaf extracts to reduce levels of urine sugar, blood glucose and liver glycogen in diabetic rats. This study revealed that *W. somnifera* root and leaf extracts and their antioxidant activity may play a vital role in reduction of blood glucose level in alloxan-induced diabetic rats [91]. Anwer T *et al.* (2008) showed effect of an aqueous extract of *W. somnifera* on insulin sensitivity. Study suggested that aqueous extract of *W. somnifera* normalizes hyperglycemia in NIDDM rats by improving insulin sensitivity [92].

3.6 In hypothyroidism

Jatwa R , *et al.* (2009) investigated possible ameliorative role of two plant extracts (*W. somnifera and Bauhinia purpurea*) on an antidiabetic drug-induced hypothyroidism in type-2 diabetic animals. The findings of this study revealed that evaluated plant extracts have a potential to ameliorate metformin-induced hypothyroidism in type-2 diabetic subjects [93].

3.7 Antifungal protein

Ghosh M (2009) purified 30 KDa monomeric acidic lectin-like proteins leaves of *W. somnifera* by a series of gel filtration and affinity chromatography methods. Antifungal activity of protein was compared with standard lectins like concanavalin-A, phytohemagglutinin and wheat germ agglutinin [94].

3.8 Cardioprotective

Mohanty IR *et al.* (2009) described cardioprotective effect of *W. somnifera* in setting of ischemia and reperfusion (IR) injury. Antioxidant and anti-apoptotic properties of *W. somnifera* contributed to cardioprotective effects of *W. somnifera* [95].

3.9 Antistress

Gupta GL and Rana AC (2009) described effects of root extract of *W. somnifera* and diazepam in social isolation induced behavior such as anxiety and depression in rats. Investigations supported use of *W. somnifera* as a mood stabilizer [96]. Shah PC *et al.* (2006) evaluated antidepressant action of *W. somnifera* as well as its interaction with conventional antidepressant drugs. The authors explained possible mechanism of antidepressant action

W. somnifera using forced swimming mice model [97].

3.10 Anticatalepsy

Nair V *et al.* (2009) evaluated anticataleptic effect of *W. somnifera* extract on haloperidol-induced catalepsy in albino mice. The authors believed that antioxidant effect of *W. somnifera* contributed its anticataleptic effect [98]

3.11 Antibacterial

Arora S. *et al.* (2004) evaluated methanolic, hexane and diethyl ether extracts of *W. somnifera* (leaves and roots) for antibacterial activity. Antibacterial activity was evaluated using agar plate disc-diffusion assay against *S. typhimurium* and *E.coli* [99].

3.12 Anticonvulsant

Kulkarni SK *et al.* (2008) studied effect of *W. somnifera* root extract alone and in combination with exogenous GABA or with diazepam against pentylenetetrazol (PTZ) induced seizure threshold in mice. GABAA ergic modulation was thought to be involved in anticonvulsant effect of *W. somnifera* [100].

3.13 Anti-malarial

Dikasso D et al. (2006) investigated *in vivo* antiplasmodial activity of *W. somnifera.* Leaves and root extracts of *W. somnifera* showed parasite suppressive effect and a protective effect on packed cell volume in dose-dependent manner [101].

3.14 Herbicidal

Javaid A *et al.* (2010) studied herbicidal activity of *W. somnifera* against *Phalaris minor* Retz. Study described bioassays of aqueous, methanolic and n-hexane extracts of roots and shoots of *W. somnifera*. Extracts in different solvents exhibited markedly variable herbicidal activities against germination and seedling growth of target weed species [102].

3.15 Nephroprotective

Jeyanthi T *et al.* (2009) investigated protective effect of *W. somnifera*. Root extract of three different doses of *W. somnifera* showed nephroprotective effect in gentamicin-induced nephrotoxic rats [103]. In another study (2010) the authors investigated protective effect of *W.somnifera* root powder on lipid peroxidation and antioxidant status in gentamicin-induced nephrotoxic rats [104].

3.16 GABA mimetic activity

Bhattarai JP *et al.* (2010) examined effect of methanolic extract of *W. somnifera*on gonadotropin releasing hormone (GnRH) neuron. The results of this study showed that methanolic extract of *W. somnifera* affects neuronal activities by mediating GABA(a) receptor, and suggested that *W. somnifera* contains an ingredient with possible GABA mimetic activity [105].

3.17 Some Other Latest Research with W. somnifera

Kasture S (2009) showed that morphine withdrawal induces spine reduction in nucleus accumbens shell. Study showed that pretreatment with *W. somnifera* protects from structural changes induced by morphine withdrawal [106]. Ahmad MK *et al.* (2009) investigated *W. somnifera* roots on semen profile, oxidative biomarkers and reproductive hormone levels of infertile men [107]. Ahuja A *et al*. (2009) studied glycowithanolides accumulation of shoot cultures of *W. somnifera* [108]. Baldi A *et al*. (2009) explained biotechnology based methodology for large-scale production of withaferin cell suspension cultures of *W. somnifera* [109]. Oza VP *et al.* (2009) identified *W. somnifera* as a potential source of enzyme L-asparaginase[110].

Benjumea D *et al.* (2009) reported diuretic activity of several extracts of *W. aristata* [111]. Xu YM *et al.* (2009) formulated prodrug (2,3-Dihydrowithaferin A-3beta-O-sulfate) of withaferin-A [112]. Pramanick S *et al.* (2008) analyzed n-butanol fraction of methanolic extract *W. somnifera* (leaves) by reverse-phase preparative HPLC [113]. Mandal C *et al.* (2008) demonstrated that how withaferin-A induces apoptosis by exhibits a strong growth inhibitory effect on several human leukemic cell lines and on primary cells from patients withymphoblastic [114]. Murthy HN *et al.* (2008) established hairy root cultures of *W. somnifera* for the production of withanolide-A [115]. Park HJ *et al.* (2008) showed that withaferin-A acts on adipocytes to reduce cell viability and adipogenesis and also induce apoptosis [116].

4. Conclusion

W. somnifera is used for centuries in Ayurvedic medicine to increase longevity and vitality. *W. somnifera* is the most important medicinal plant, extensively used in herbal formulations. Aswagandha, chemically rich with its diverse content of active compounds, such as withanolides, sitoindosides and many useful alkaloids, constitutes a wide range of active constituents as a multi-purpose medicinal agent. In this study, we have reviewed literature pertaining to *W. somnifera* and its botanical constituents as antitumor, antiparkinson, immunostimulatory, cardioprotective hypoglycaemic and hypolipidaemic agents. *W. somnifera* exhibit varying degrees of therapeutic value some of which useful in the treatment of fungal, malaria and bacterial infections. These data suggested that *W. somnifera* is a polypharmaceutical, and under intensive investigation in an attempt to authenticate its use as a multipurpose medicinal agent. More clinical trials require to be carried out to support its therapeutic potential as multipurpose medicinal agent.

References

1. Anonymous. (1976) In *the Wealth of India,* (*Raw Materials*). CSIR: New Delhi, India; 10:580-585.
2. Kirson I, Glotter E, Lavie D, Abraham A. (1971) *J. Chem. Soc.* C, 2032-2044.
3. Chatterjee A, Pakrashi SC. (1995) *The Treatise on Indian Medicinal Plants* 4: 208-212.
4. Bone K. (1996) *Clinical Applications of Ayurvedic and Chinese Herbs. Monographs for the Western Herbal Practitioner*. Phytotherapy Press: Australia; 137-141.
5. Mishra LC, Singh BB, Dagenais S. (2000) *Altern. Med. Rev.* 5: 334-346.
6. Rastogi RA, Mehrotra BN. (1995) *Compendia of Indian Medicinal Plants vol. 5* CDRI Lucknow, National Institute of Science and communication New Delhi, India; 889-891.
7. Nadkarni KM. (1976) *Indian Materia Medica,* Popular Prakshan Limited: Bombay, India; 1291.
8. Williamson EM. (2002) *Major Herbs of Ayurveda,* Churchill Livingstone: London, UK; 322-323.
9. Kapoor LD. (2001) *Handbook of Ayurvedic Medicinal Plants,* CRC Press: London, UK; 337-338.
10. Srivastava SK, Iyer SS, Ray GK. (1960) *Indian J. Pharm.* 22: 94.
11. Dash B, Manfred J. (1983) *A Handbook of Ayurveda,* Concept Publishing: New Delhi,

India; 329-330

12. Ven Murthy MR , Ranjekar PK, Ramassamy C, Deshpande M. (2010) *Cent. Nerv. Syst. Agents Med. Chem.* 10: 238-246.

13. Brekhman II, Dardymov IV. (1969) *Annu. Rev. Pharmacol*. 9: 419- 430.

14. Bhatnagar M, Sisodia SS, Bhatnagar R. (2005) *Ann. N. Y. Acad .Sci*. 1056: 261-278.

15. Nittala SS, Lavie D. (1981) *Phytochemistry* 20: 2741-2748.

16. Bandyopadhyay M, Jha S, Tepfer D. (2007) *Plant Cell Rep*. : 599-609.

17. Velde VV, Lavie D. (1981) *Phytochemistry* 20: 1359-1363.

18. Danishefsky I. (1980) *Biochemistry for Medical Sciences*, Little, Brown and Company: Boston, USA; 232.

19. Uma DP, Akagi K. (1996) *Int. J. of Radiation Biol*. 69:193-197.

20. Kapoor LD. (2001) *Handbook of Ayurvedic Medicinal Plants*, CRC Press: London, UK; 337- 338.

21. Christen P. (1986) *Acta Helv*. 61: 242-246.

22. Glotter E. (1991) *Nat. Prod. Rep*. 8: 415-440.

23. Tursunova RN, Maslennikova VA, Abubakirov NK. (1977) *Chem. Nat. Comp*. : 13:131-138.

24. Alfonso D, Bernardinelli G, Kapetanidis I. (1993) *Phytochemistry* 34: 517-521.

25. Alfonso D, Kapetanidis I. (1994) *Phytochemistry* 36: 179-183.

26. Fuska J, Proska B, Williamson JS, Rosazza J. (1987) *Folia Microbiol*. 32: 112-115.

27. Gupta AP, Verma RK. (1996) *J. Med. Arom. Plant Sci*. 18: 788-790.

28. Devi PU, Akagi K, Ostapenko V, Tanaka Y, Sugahara T. (1996) *Int. J. Radiation Biol*. 69: 193-197.

29. Kulkarni SK, Dhir A. (2008) *Prog. Neuro-Psychopharmacol. Biol. Psych*. 32: 1093-1105.

30. Johri S, Jamwal U, Rasool S, Kumar A, Verma V, Qazi GN. (2005) *Plant Sci*. 169: 1014-1021.

31. Puri HS. (2002) *Simple Ayurvedic Remedies*, UBSPD: New Delhi, India.

32. Singh N, Nath R, Lata A. (1982) *Int. J. Crude Drug Res*. 20: 29-35.

33. Kirtikar KR, Basu BD.(1991) *Indian Medicinal Plants Vol. 3*, Shiva Publishers: Dehradun, India; 1783.

34. Charaka Samhita, (1997) Chikitsa Sthana Second Chapter, Chowkambha Publishers, 38.

35. Devi PU, Sharada AC, Solomon FE. (1995) *Cancer Lett*. 95: 189-193.

36. Hepper FN. (1991) In*:* Hawkes, JG, Lester RN, Nee M, Estrada E. (Eds.) *Solanaceae III: taxonomy, chemistry, evolution*, Royal Botanic Gardens: Kew, UK; 211-227.

37. Warrier PK, Nambiar VPK, Ramankutty C. (1996) *Indian Medicinal Plants: A Compendium of 500 species*. Orient Longman: Hyderabad, India; 5: 409.

38. Hunziker AT. (2001) *Genera Solanacearum: The Genera of The Solanaceae Illustrated, Arranged According to A New System*, Gantner Verlag Ruggell, Liechtenstein.

39. Kuang K, Lu AM. (1978) *Reipubl. Popularis Sin*. 67: 1-175.

40. Agarwal R, Diwanay S, Patki P, Patwardhan B. (1999*) J. Ethanopharmocol*. 67: 27-35.

41. Marderosion AD. (2001) *The Review of Natural Products, Facts and Comparisons*, St. Louis: MI: USA; 630-632.

42. Sharad AC, Soloman FE, Devi PU, Udupa N, Srinivasan KK. (1996) *Acta Oncol*. 35: 95-100.

43. Budhiraja RD, Sudhir S. (1987) *J. Scientific Ind. Res*. 46: 488-491.

44. Asthana R, Raina MK. (1989) *Indian Drugs* 26: 199-204.

45. Gandhi A, Majumdar AM, Patwardhan B. (1994) *J. Ethnopharmacol.* 44:131-135.

46. Davis L, Kuttan G. (2000) *Cancer Lett*. 148: 4-17.

47. Singh B, Saxena AK, Chandan BK, Gupta DK, Bhutani KK, Anand KK. (2001) *Phytother. Res.* 15: 311-318.

48. Prakash J, Gupta SK, Kochupillai V, Gupta YK, Joshi S. (2001) *Phytother. Res.* 15: 240-244.

49. Patwardhan B, Panse GT, Kulkarni PH. (1998) *J. Natl. Integrated Med. Assoc*. 30: 7-11.

50. Sharma K, Dandiya PC. (1991) *Indian Drugs* 29: 247-250.

51. Parker V, Morinan A. (1986) *Neuropharmacology* 25: 663-664.

52. Dong E, Matsumoto K, Tohda M, Kaneko Y, Watanabe H. (1999) *Neurosci. Res*. 33: 171-177.

53. Dong E, Matsumoto K, Watanabe H. (1999) *Life Sci.* 65: 1561-1568.

54. Dong E, Matsumoto K, Uzunova V, Sugaya I, Takahata H, Nomura H, Watanabe H, Costa E, Guidotti A. (2001) *Proc. Natl. Acad. Sci. USA* 98: 2849-2854.

55. Karim A, Arslan MI. (2000) *Bangladesh Med. Res. Counc. Bull.* 26: 27-32.

56. Guidotti A, Dong E, Matsumoto K, Pinna G, Rasmusson AM, Costa E. (2001) *Brain Res*. 37: 110-115.

57. Ago Y, Matsuda T. (2003) *Nippon. Yakurigaku Zasshi* 122: 135-140.

58. Hirani K, Sharma AN, Jain NS, Ugale RR, Chopde CT. (2005) *Psychopharmacol*. 180: 267-268.

59. Atal, CK, Sethi PD. (1963) *Indian J. Pharm.*25: 163-164.

60. Ziauddin M, Phansalkar N, Patki P. (1996) *J. Ethnopharmacol*. 50: 69-76.

61. Watt GA. (1972) *Dictionary of The Economic Products of India Vol. 6*, Cosmo Publication: New Delhi, India; 308-309.

62. Khan MTJ, Ashraf M, Tehniyat S, Bukhtair MK, Ashraf S, Ahmad W. (1993) *Fitoterapia* 64: 367-370.

63. Atta-ur-Rahman SAJ, Choudary MI, Asif I. (1991) *Phytochemistry* 30: 3824-3825.

64. Atta-ur-Rahman SAJ, Dur-e-Shawar ASJ, Choudhary MI. (1993) *J. Nat. Prod*. 53: 1000-1006.

65. Choudary MI, Abbas S, Jamal AS, Atta-ur-Rahman SAJ. (1996) *Heterocycles* 42: 555-563.

66. Khan PM, Ahmad S, Rubnawaz H, Malik A. (1999) *Phytochemistry*, 51: 669-671.

67. Begum VH, Sadique J. (1988) *Indian J. Exp. Biol.* 26: 877-882

68. Devi PU. (1996) *Indian J. Exp. Biol.* 34: 927- 932.

69. Uma DP, Akagi K. (1996) *Int. J. of Radiation Biol.* 69: 193-197.

70. Mehta AK, Binkley P, Gandhi SS, Ticku MK. (1991) *Indian J. Med. Res.* 94: 312-315.

71. Gupta GL, Rana AC. (2007) *Phcog. Rev*. 1: 129-136.

72. Rajasankar S , Manivasagam T, Sankar V, Prakash S, Muthusamy R, Krishnamurti A, Surendran S.(2009*) Ethnopharmacol*. 125: 369-373

73. Rajasankar S , Manivasagam T, Surendran S.(2009)*Neurosci. Lett* . 17: 11-15.

74. Yadav CS , Kumar V, Suke SG, Ahmed RS, Mediratta PK, Banerjee BD. (2010) *Indian J. Biochem. Biophys.* 47: 117-120.

75. Abdeljebbar LH , Benjouad A, Morjani H, Merghoub N, Haddar S, Humam M, Christen P, Hostettmann K, Bekkouche K, Amzazi S. (2009) *Therapie* . 64: 121-127.

76. Mirjalili MH , Moyano E , Bonfill M , Cusido RM , Palazón J . (2009) *Molecules* 3: 2373-2393.

77. Shah N , Kataria H, Kaul SC, Ishii T, Kaur G, Wadhwa R. (2009) *Cancer Sci* . 100: 1740-1747.

78. Mulabagal V , Subbaraju GV, Rao CV, Sivaramakrishna C, Dewitt DL, Holmes D, Sung B, Aggarwal BB, Tsay HS, Nair MG.(2009) *Phytother. Res* . 23: 987-992.

79. Aalinkeel R , Hu Z, Nair BB, Sykes DE, Reynolds JL, Mahajan SD, Schwartz SA. (2008) *Evid Based Complement. Alternat. Med.* 7: 177-187

80. Stan SD , Hahm ER , Warin R , Singh SV . (2008) *Cancer Res* .68: 7661-7669.

81. Bolleddula J, Zhang Y, Seeram NP, Nair MG. (2003) *Life Sci. 74: 125-132*.

82. Choudhary MI , Hussain S, Yousuf S, Dar A, Mudassar, Atta-ur-Rahman SAJ. (2010) *Phytochemistry* 71: 2205-2209.

83. Muralikrishnan G , Dinda AK, Shakeel F. (2010) *Immunol. Invest.* 39: 688-698.

84. Khan S , Malik F , Suri KA , Singh J . (2009) *Vaccine* 27: 6080-6087.

85. Kumar P , Kumar A . (2009) *J. Med. Food* 12: 591-600.

86. Bhatnagar M , Sharma D , Salvi M . (2009) *Neurochem. Res* . 34: 1975-1983.

87. Kumar S , Seal CJ, Howes MJ, Kite GC, Okello EJ. (2010) *Phytother. Res.* 24: 1567-1574.

88. Jayaprakasam B , Padmanabhan K, Nair MG. (2010) *Phytother. Res.* 24: 859-863.

89. Hoda Q , Ahmad S, Akhtar M, Najmi AK, Pillai KK, Ahmad SJ. (2010) *Hum. Exp. Toxicol.* 29: 653-658.

90. Udayakumar R , Kasthurirengan S, Mariashibu TS, Rajesh M, Anbazhagan VR, Kim SC, Ganapathi A, Choi CW. (2009) *Int. J. Mol. Sci* . 10: 2367-2382.

91. Udayakumar R , Kasthurirengan S, Vasudevan A, Mariashibu TS, Rayan JJ, Choi CW, Ganapathi A, Kim SC. (2010) *Plant Foods Hum. Nutr.* 65: 91-98.

92. Anwer T , Sharma M, Pillai KK, Iqbal M. (2008) *Basic Clin. Pharmacol. Toxicol* .102: 498-503.

93. Jatwa R , Kar A. (2009) *Phytother. Res* . 23: 1140-1145.

94. Ghosh M .(2009) *Fitoterapia* 80: 91-95.

95. Mohanty IR , Arya DS, Gupta SK. (2008) *Clin. Nutr.* 27: 635-642.

96. Gupta GL , Rana AC. (2007)*Indian J. Physiol. Pharmacol.* 51: 345-353.

97. Shah PC , Trivedi NA, Bhatt JD, Hemavathi KG. (2006) *Indian J. Physiol. Pharmacol* . 50: 409-415.

98. Nair V , Arjuman A, Gopalakrishna HN, Nandini M.(2008) *Phytother. Res.* 22: 243-246.

99. Arora S, Dhillon S, Rani, G Nagpal A. (2004) *Fitoterapia* 75: 385-388.

100. Kulkarni SK , Akula KK , Dhir A . (2008) *Indian J. Exp. Biol* . 46: 465-469.

101. Dikasso D , Makonnen E, Debella A, Abebe D, Urga K, Makonnen W, Melaku D, Kassa M, Guta M.(2006) *Ethiop. Med. J* .44: 279-285.

102. Javaid A , Shafique S, Shafique S. (2010) *Nat. Prod. Res.* 24: 1457-1468.

103. Jeyanthi T , Subramanian P. (2009) *Ren. Fail* 31: 814 - 821.

104. Jeyanthi T , Subramanian P. (2010) *J. Basic Clin. Physiol. Pharmacol.* 21: 61-78.

105. Bhattarai JP , Ah Park S, Han SK. (2010) *Phytother Res.* 4: 1147-1150.

106. Kasture S , Vinci S , Ibba F , Puddu A , Marongiu M , Murali B , Pisanu A , Lecca D , Zernig G , Acquas E . (2009) *Neurotox. Res* . 16: 343-355.

107. Ahmad MK , Mahdi AA, Shukla KK, Islam N, Rajender S, Madhukar D, Shankhwar S N,

Ahmad S. (2010) *Fertil. Steril* . 94: 989-996.

108. Ahuja A , Kaur D, Sharada M, Kumar A, Suri KA, Dutt P.(2009) *Nat. Prod. Commun*. 4: 479-482.

109. Baldi A , Singh D, Dixit VK. (2008) *Appl. Biochem. Biotechnol* . 151: 556-564.

110. Oza VP , Trivedi SD, Parmar PP, Subramanian RB. (2009) *J. Integr. Plant. Biol* . 51: 201-206.

111. Benjumea D, Martín-Herrera D , Abdala S , Perez-Paz P . (2007) *J. Ethnopharmacol* . 113: 487-491.

112. Xu YM , Marron MT , Seddon E , McLaughlin SP , Ray DT , Whitesell L , Gunatilaka AA . (2009) *Bioorg. Med. Chem* . 17: 2210-2214.

113. Pramanick S , Roy A, Ghosh S, Majumder HK, Mukhopadhyay S. (2008) *Planta Med*. 74: 1745-1748.

114. Mandal C , Dutta A , Mallick A , Chandra S , Misra L , Sangwan RS , Mandal C . (2008) *Apoptosis* 13: 1450-1464.

115. Murthy HN , Dijkstra C , Anthony P , White DA , Davey MR , Power JB , Hahn EJ , Paek KY . (2008) *J. Integr. Plant Biol* . 50: 975-998.

116. Park HJ , Rayalam S, Della-Fera MA, Ambati S, Yang JY, Baile CA.(2008) *Biofactors* 33: 137-148.