WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 598-612. Review Article ISSN 2277–7105

ASHWAGANDHA: NATURE"S BOON FOR A HEALTHY LIFE

Dr. Shrawan Kumar Sahu[1]*, Dr. Ashok Kumar Sinha[2] and Dr. Rahul Ghuse[3]

Research Officer (Ayu.), Regional Ayurveda Research Institute, Gangtok, Sikkim, India, 737102.

Article Received on
02 Sept. 2018,

Revised on 24 Sept. 2018,
Accepted on 15 October 2018

DOI: 10.20959/wjpr201818-13593

***Corresponding Author**
Dr. Shrawan Kumar Sahu
Research Officer (Ayu.),
Regional Ayurveda Research Institute, Gangtok, Sikkim, India-737102.

ABSTRACT

Attitude, behavior, concentration, dedication and enthusiasm are very much necessary for the continuation and successful completion of any task. Owing to day by day decline of these qualities, masses are in search of a safe agent which can help them in leading happy lives through accomplishment of their works smoothly. Ashwagandha is very much capable of meeting this demand of the people. It is classified as a Rasayana (rejuvenation-medicine) and accepted to increase longevity and vitality. The drug is reported with anti-inflammatory, anti-arthritic, caridioprotective, anti-stress, tranquillizer-like sedative activity, hypoglycemic, thyroprotective activity and proved to be an effective remedy in the malignant growth of different organs. Although many articles have been published on this wonderful drug, the holistic approach has not been addressed till date. This article is for serving that very purpose. The review includes various activities of Ashwagandha in experimental models along with clinical evaluation of the drug in various dosage forms. Thorough review of various books, scientific research journals, theses, articles etc. available on Ashwagandha along with internet was performed to bring about the article in present form. The classical literatures in Ayurveda, Unani & Allopathy on this natural gift were studied at fundamental level, interpreted and analyzed logically and are presented in this detail research article.

KEYWORDS: Ashwagandha, Rasayana, Ayurveda.

INTRODUCTION

Ashwagandha *(Withania somnifera*) has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. The roots of the plant are categorized as Rasayana i.e. having capability to promote health and longevity by augmenting defense

against disease, arresting the ageing process, revitalizing the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing.[1] It is in use for a very long time for all age groups and both sexes and even during pregnancy without any side effects.[2] The pharmacological effects of the roots of Ashwagandha are attributed to the presence of withanolides, a group of steroidal lactones.[3] Its leaves are used in Ayurvedic and Unani systems for treatment of tumors and tubercular glands.[4] A number of withanolide steroidal lactones have been isolated from the leaves of *Withania somnifera*[5] and these exhibit antibacterial, anti-fungal and antitumor properties.[6]

Ashwagandha (*Withania somnifera*) is one of the most revered plants in traditional Ayurvedic medicine in India. It is an erect, grayish, subshrub with inconspicuous yellow or greenish flowers followed by small, spherical, orange-red berries containing yellow, kidney-shaped seeds. It grows three-to-five feet tall, mainly on waste land, but is cultivated widely as the whole plant; most commonly the root and leaf are used medicinally.[7,8]

The importance of this wonder drug cannot be overemphasized, since there are *WITHANIA somnifera* standards monographs published in the Ayurvedic Pharmacopoeia of India (Vol. I, 1989)[9], Siddha Pharmacopoeia of India (Vol. I, 2008)[10], Unani Pharmacopoeia of India (Vol. I, 2007)[11], the World Health Organization (WHO) Monographs (Vol. 4, 2009)[12] as well as in the currently valid editions of the British Pharmacopoeia(BP 2012)[13], Indian Pharmacopoeia (IP 2010)[14] and United States Pharmacopeia (USP 36).[15]

The species is widely distributed in the northwestern Indian states of Gujarat, Madhya Pradesh, Maharashtra, Rajasthan, Uttar Pradesh, and the Punjab plains extending to the mountainous regions of Himachal Pradesh and Jammu.[16] It also is cultivated in parts of Madhya Pradesh and Rajasthan.[17] Northwest of India, its habitat extends into the Pakistani provinces of Sindh and Baluchistan, and on into Afghanistan. To the southeast of India, it occurs in Sri Lanka.[18]

Preparations of various plant parts have been credited with the following actions: abortifacient, adaptogenic, alterative, analgesic, antiarthritic, antiasthmatic, antibiotic, antidyspeptic, anti-inflammatory, antimitotic, antiproliferative, antitumor, aphrodisiac, astringent, bactericide, carminative, contraceptive, depurative, diuretic, emetic, febrifuge, fungicidal, hypnotic, immune-modulating, laxative, proteolytic, tonic, and nervine

sedative.[19,20,21] Additionally, it may have cytotoxic, chemopreventative, and radiosensitizing actions.[20]

Some herbalists refer to Ashwagandha as Indian ginseng, since it is used in Ayurvedic medicine in a way similar to that ginseng is used in traditional Chinese medicine. Studies have proven that the activity of the Withania extract was approximately equal to the activity of the Panax ginseng extract. Withania somnifera, owever, has an advantage over Panax ginseng in that it does not appear to result in ginseng- abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension, and insomnia.[22]

Major Chemical Constituents

Phytochemical contents: Ashwagandha has been found to contain steroidal lactones called withanolides. Much of the pharmacological activities are attributed to the presence of these steroidal lactones.[23] In addition, the roots provide 18 fatty acids, beta-sitesterol, polyphenols and phytosterols. The root contains several alkaloids, including withanine, withananine, withananinine, pseudo-withanine, somnine, somniferine, somniferinine. The leaves of Indian chemotype contain withanolides, including withaferin A.[24] Withanine is sedative and hypnotic. The root extract contains an ingredient which has GABA mimetic activity. The free amino acids present in the root include aspartic acid, glycine, tyrosine, alanine, proline, tryptophan, glutamic acid and cystine.[25]

Steroidal compound: These include withaferin A, Withanolides G&D sitoindosides IX&X and withasomnine. These have been reported as active marker for standardization.[26] Withaferin A, a steroidal lactone is the most important withanolide isolated from the extract of the leaves and dried roots of Withania somnifera. Anti-inflammatory activity has been attributed to biologically active steroids, of which withaferin A is a major component. The activity is comparable to that of hydrocortisone sodium succinate. Withaferin A also showed significantly protective effect against CCl4 induced hepatotoxicity in rats. It was as effective as hydrocortisone dose. The curative properties of the leaves and roots are attributed to Withaferin A. Withaferin A is antitumour, antiarthritic and antibacterial.

Adaptogenic effect: Double blind clinical trial involving 60 healthy children (8-12 years age), oral intake of 2 g/day of root powder (in 100 ml milk) for 2months lead to increase body weight, total protein and Mean corpuscular hemoglobin. There was no toxic effect of any kind even after 8 months of daily consumption.[76] In a related clinical study, root

powder (3 gms. /day) was given to healthy male volunteers (age 50-59 years) for one year. There was a uniform significant increase in Hb, RBC improvement in hair melanin and seated stature.[27]

In a double-blind clinical trial, Ashwagandha root powder was tested in a group of 101 healthy males, 50-59 years old, at a dosage of 3 grams daily for one year. A significant improvement in haemoglobin, red blood cell count, hair melanin, and seated stature was observed. Serum cholesterol decreased and nail calcium was preserved. ESR decreased significantly and 71.4 percent reported improvement in sexual performance.[28]

In a double blind study shade dried roots of WS were powdered and made as tablets of 0.5 gms each and administered in the dose of 2 tabs 3 times a day with milk to healthy volunteers for a period of one year. Results have shown significant increase in haemoglobin, RBC, Hair melanin, and in seated stature in the treated group as compared to control group. Serum cholesterol and calcium level of nails have also been decreased in treated group.[29]

Anti-inflammatory Activity

Withaferin A exhibits fairly potent anti-arthritic and anti-inflammatory activities. Anti-inflammatory activity has been attributed to biologically active steroids, of which Withaferin A is a major component. It is as effective as hydrocortisone sodium succinate dose for dose.[30] It was found to suppress effectively arthritic syndrome without any toxic effect. Unlike hydrocortisone-treated animals which lost weight, the animals treated with Withaferin A showed gain in weight in arthritic syndrome. It is interesting that Withaferin A seems to be more potent than hydrocortisone in adjuvant-induced arthritis in rats, a close experimental approximation to human rheumatoid arthritis. In its oedema inhibiting activity, the compound gave a good doseresponse in the dose range of 12-25 mg/kg body weight of Albino rats intraperitoneally and a single dose had a good duration of action, as it could effectively suppress the inflammation after 4 hours of its administration.[31] Asgand (*Withania somnifera*) has been shown to possess anti-inflammatory property in many animal models of inflammations like carrageenan-induced inflammation, cotton pellet granuloma and adjuvant-induced arthritis Detailed studies were carried out to investigate the release of serum β-1 globulin during inflammation by two models of inflammations viz. primary phase of adjuvantinduced arthritis and formaldehyde-induced arthritis. The experiments showed interesting results as most of the APR wereinfluenced in a very short duration and also suppressed the degree of inflammation.[32]

Analgesic effect

This study was done to evaluate the analgesic effect and tolerability of single oral dose (1000mg) of standardized aqueous extract of *Withania somnifera* using Hot Air Pain model in healthy human volunteers as per ICH GCP Guidelines. Subjects were randomised to receive either single oral dose of 1000mg standardize aqueous extract of *Withania somnifera* or identical placebo in a double blind manner. Mean Pain Threshold Time at baseline and 3hrs after drug administration were noted. Washout period of 10-14 days was given for cross-over between the two treatments. Safety assessments were conducted before and at end of study in total twelve subjects were enrolled. In the study, treatment with standardized aqueous extract of *Withania somnifera* produced significant increase in Pain Threshold time compared baseline and placebo.[33]

Rejuvenating Effect

A double-blind, placebo-controlled study was conducted to evaluate the efficacy an ethanolic extract of Aswagandha (*Withania somnifera*), in patients with ICD-10 anxiety disorders comprised 39 subjects, of whom 20 received the drug and 19 received placebo. At 6 weeks, significantly more patients met a priori response criteria in the drug group (88.2%) as compared with the placebo group (50%). Results indicated that ethanolic extract has useful anxiolytic potential.[34]

Antistress effect

The safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots to reduce stress and anxiety was studied on 64 subjects for 60 days with prospective, double-blind, randomized, placebo-controlled design. In the study drug treatment group, each capsule contained 300 mg of high-concentration full-spectrum extract from the root of the Ashwagandha. The treatment group exhibited a significant reduction ($P<0.0001$) in scores on all the stress-assessment scales compare to the placebo group. The serum cortisol levels were substantially reduced ($P=0.0006$) in the Ashwagandha group, relative to the placebo group. The study suggest that a high-concentration full-spectrum Ashwagandha root extract safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life.[35]

In another clinical trial, the effect of standardized WS root and leaf extract (WSE) was evaluated in chronically stressed humans Participants who were randomly assigned to WSE (125 mg QD, 125 mg BD, or 250 mg BID) or placebo groups. Stress levels were assessed at

days 0, 30 and 60 using a modified Hamilton anxiety (mHAM-A) scale. Biochemical and clinical variables were measured at days 0 and 60. 130 subjects enrolled 98 completed the study. Between days o and 60 the WSE 125 mg QD group decreased significantly more than placebo for mean mHAM- A score, serum cortisole, serum C-reactive protein, pulse rate and blood pressure. The consumption of WSE significantly reduces experiential and biochemical reduction of stress without adverse effects.[36]

A study conducted by the Institute of Basic Medical Sciences at Calcutta University examined the effects of Ashwagandha on chronic stress in rodents. For a period of 21 days, the animals received a mild electric shock to their feet. The resulting stress on the animals produced hyperglycemia, glucose intolerance, increase in plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression.[37] Researchers using *Withania somnifera* discovered the animals given the herb an hour before the foot shock experienced a significantly reduced level of stress. This research confirms the theory that Ashwagandha has a significant anti-stress effect.[38]

Cardiovascular protection

Withania somnifera may be useful as a general tonic, due in part to its beneficial effects on the cardiopulmonary system, as reported in the following studies. The effect of WS was studied on the cardiovascular and respiratory systems in dogs and frogs.[39] The alkaloids had a prolonged hypotensive, bradycardiac, and respiratory stimulant action in dogs. The study found that the hypotensive effect was mainly due to autonomic ganglion blocking action and that a depressant action on the higher cerebral centers also contributed to the hypotension. The alkaloids stimulated the vasomotor and respiratory centers in the brain stem of dogs. The cardio-inhibitory action in dogs appeared to be due to ganglion blocking and direct cardiodepressant actions. The alkaloids produced immediate predominant but short-lived cardio-depressant effects and a weak but prolonged cardiotonic effect in isolated normal and hypodynamic frog hearts. In another study, Left ventricular dysfunction was seen as a decrease in heart rate, left ventricular rate of peak positive and negative pressure change and elevated left ventricular end-diastolic pressure in the control group was recorded. *Withania somnifera* showed strong cardioprotective effect in the experimental model of isoprenaline-induced myonecrosis in rats. Augmentation of endogenous antioxidants, maintenance of the myocardial antioxidant status and significant restoration of most of the altered haemodynamic parameters may contribute to its cardioprotective effect.[40]

Hypoglycemic and hypocholesterolemic effect

In a study, hypoglycemic, diuretic and hypocholesterolemic effects of roots of *Withania somnifera* were assessed on human subjects. Six mild NIDDM subjects and six mild hypercholesterolemic subjects were treated with the powder of roots of WS for 30 days. Suitable parameters were studied in the blood and urine samples of the subjects along with dietary pattern before and at the end of treatment period. Decrease in blood glucose was comparable to that of an oral hypoglycemic drug. Significant increase in urine sodium, urine volume, significant decrease in serum cholesterol, triglycerides, LDL (low density lipoproteins) and VLDL (very low density lipoproteins) cholesterol were observed indicating that root of WS is a potential source of hypoglycemic, diuretic and hypocholesterolemic agents.[41]

Anti-carcinogenic activity

Ashwagandha is reported to have anti-carcinogenic effects. Research on animal cell cultures has shown that the herb decreases the levels of the nuclear factor kappaB, suppresses the intercellular tumor necrosis factor, and potentiates apoptotic signalling in cancerous cell lines.[42] In one study, the herb was evaluated for its anti-tumor effect in urethane-induced lung tumors in adult male mice.[43] Following administration of Ashwagandha over a period of seven months, the histological appearance of the lungs of animals which received the herb was similar to those observed in the lungs of control animals.

Anti-tumor effect Effect on Chinese Hamster Ovary (CHO) cells carcinoma

Withania roots caused the inhibitory effect of about 49% on colony forming efficiency of CHO cells. It inhibits the cell growth and prevents the cell attachment. It induced long term growth inhibition of CHO cells which was dependent on the cell density and duration of Ashwagandha exposure.[44]

Adjuvant to chemotherapy

Fifty patients were recruited to each group, with a median age of 51 years (range 36–70 years) in the WITHANIA somnifera plus chemotherapy group and 50.5 years (range 30–82 years) in the control group. Eight patients had stage I, 33 stage II, 44 stage III, and 15 stage IV breast cancer. Fifteen patients were offered palliative chemotherapy and 85 were offered adjuvant chemotherapy. Patients in the group treated with WITHANIA somnifera root extract and chemotherapy had less fatigue than did those in the control group (PFS $p < 0.001$ and SCFS $p < 0.003$). QoL was significantly better ($p = 0.0001$) than in the control group. There

was no difference in the haematological parameters or 24-month overall survival for all stages [study 74% versus control 56% (p = 0.174)]; however, there was a trend for longer survival in the patients treated with WITHANIA somnifera root extract plus chemotherapy. Addition of WITHANIA somnifera to chemotherapy could have a positive effect on fatigue and improve QoL in patients with breast cancer. The effectiveness and toxicity of chemotherapy were not altered. Thus further study with a large sample size, uniform tumour criteria, and risk stratified patients with breast cancer could help to validate our preliminary outcome.[45]

Effect on neurodegenerative diseases such as Parkinson's, Huntington's and Alzheimer's diseases-In patients with Alzheimer's disease, neuritic atrophy and synaptic loss[46] are considered the major causes of cognitive impairment, as based on the results of neuropathological post-mortem studies of the brain.[47] In the brains of patients suffering from other neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Creutzfeldt- Jakob disease, the atrophy of neurites has also been observed as a significant part of the etiology. There are dozens of studies that show that Ashwagandha slows, stops, reverses or removes neuritic atrophy and synaptic loss. Therefore Ashwagandha can be used to treat Alzheimer's, Parkinson's, Huntington's and other neurodegenerative diseases at any stage of the disease, even before a person has been diagnosed and is still in the state of mild forgetfulness, etc. Glycowithanolides withaferin- A and sitoindosides VII–X isolated from the roots of Ashwagandha significantly reversed ibotenic acid induced cognitive defects in Alzheimer's disease model.[48]

GABA-mimetic effect on neurodegeneration and neuroregenerative potential

Behavioral experiments have lent support to the GABA-mimetic activity of Ashwagandha root extract. GABAergic neurodegeneration due to neuroleptic-induced excitotoxicity and oxidative stress is one of the etiopathological mechanisms in the pathophysiology of tardive dyskinesia[49] and GABA agonists are shown to be effective in ameliorating the symptoms of tardive dyskinesia. The beneficial effect of Ashwagandha root extract might be due to its GABA mimetic activity. Ashwagandha, its constituents and the metabolites of its constituents promote the growth of nerves after taking it for 7 days.

An intriguing study demonstrated that chronic oral administration of withanoside IV attenuated the axonal, dendritic and synaptic losses and memory deficits induced by amyloid peptide Aβ(25–35) in mice 21.[50] After oral administration in mice, withanoside IV was

metabolized into sominone, which induced marked recovery in neurites and synapses and also enhanced axonal and dendritic outgrowth and synaptogenesis. These effects were maintained for at least 7 days after discontinuing withanoside IV administration. These data suggest that withanoside IV, and its metabolite, sominone, may have clinical usefulness as antidementia drugs.

Immunomodulatory Activity

Asgand showed a significant modulation of immune reactivity in animal models. Administration of Asgand was found to prevent myelo-suppression in mice treated with three immunosuppressive drugs viz. cyclophosphamide, azathioprin, and prednisolone. Treatment with Asgand was found to significantly increase Hb concentration, RBC count, platelet count, and body weight in mice.[51] Administration of Asgand extract was found to significantly reduce leucopenia induced by cyclophosphamide (CTX) treatment. Administration of Asgand extract increased the number of β-esterase positive cells in the bone marrow of CTX treated animals, compared to the CTX alone treated group.[52] Administration of Asgand extract was found to significantly reduce leucopenia induced by sub-lethal dose of gamma radiation.[52] Withaferin A and Withanolide E exhibited specific immunosuppressive effect on human B and T lymphocytes and on mice thymocytes. Withanolide E had specific effect on T lymphocytes whereas Withaferin A affected both B and T lymphocytes.[53]

The growth-promoting effect

The growth-promoting effect of WS was studied for 60 days in a double-blind study of 60 healthy children, age 8-12 years, who were divided into five groups of 12. Group 1 was given purified and powdered WS 2 g/day fortified in 100 cc of milk (no details about purification and powdering methods were disclosed). Similarly, Group 2 received 2 g daily of a mixture of equal parts WS and Punarnava (Boerhaavia diffusa), Groups 3 and 4 were given ferrous fumarate 5 mg/day and 30 mg/day, respectively, and Group 5 received placebo. Group 1 experienced a slight increase in haemoglobin, packed cell volume, mean corpuscular volume, serum iron, body weight, and hand grip, and significant increases in mean corpuscular haemoglobin and total proteins ($p<0.01$) at the end of 60 days when compared to the initial level and the placebo group. Group 2, treated with WS and Punarnava, showed a significant increase in the level of haemoglobin at the end of 30 days compared to the initial value. Marked increases in the levels of haemoglobin, packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin, serum iron, and hand grip were also observed at the

end of 60 days when compared to initial levels. It was noted that 13 of 15 children had an increase in body weight, 10 children had an increase in haemoglobin and packed cell volume, and 11 children had an increase in serum iron. The study demonstrated that WS may be useful as a growth promoter and hematinic in growing children.[54]

Anti-arthritic effect

In a double-blind, placebo-controlled cross-over study, 42 patients with osteoarthritis were randomized to receive a formula containing Ashwagandha (Ashwagandha, turmeric, boswellia and zinc complex) or placebo for three months. The herbal formula significantly reduced the severity of pain ($p<0.001$) and disability ($p<0.05$) scores, although no significant changes in radiological appearance or SED (Erythrocyte sedimentations) rate were noted.[55]

Rasayana effect: Randomized Placebo-Controlled Adjunctive Study of an Extract of Withania somnifera for Cognitive Dysfunction in Bipolar Disorder was assessed. Sixty euthymic subjects with DSM-IV bipolar disorder were enrolled in an 8-week, double-blind, placebo-controlled, randomized study of WSE (500 mg/d) as a precognitive agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder.

Fifty-three patients completed the study (WSE, n = 24; placebo, n = 29). Compared to placebo, WSE provided significant benefits for 3 cognitive tasks: digit span backward (P = .035), Flanker neutral response time (P = .033), and the social cognition response rating of the Penn Emotional Acuity Test (P = .045). Mood and anxiety scale scores remained stable, and adverse events were minor. In preliminary level, WSE appears to improve auditory-verbal working memory (digit span backward), a measure of reaction time, and a measure of social cognition in bipolar disorder. Given the paucity of data for improving cognitive capacity in bipolar disorder, WSE offers promise, appears to have a benign side-effects profile, and merits further study.[56]

Drug Interactions: *Withania somnifera* given in combination with a diazepam produces an additive effect. The combination when used in status epilepticus was able to reduce significantly the effective dose of diazepam to offer complete protection with no subsequent mortality. Administration of *Withania somnifera* markedly alters the plasma levels and pharmacokinetics of Amikacin resulting in the modification of the dosage regimen of Amikacin in healthy buffalo calves which clearly indicated their safe and effective therapeutic use with promising antimicrobial polypharmacy.[57]

Immunopotentiation on oral feeding of standardized aqueous extract of *Withania somnifera* (Linn. Dunal, Family Solanaceae) was evaluated in laboratory animals immunized with DPT (Diphtheria, Pertussis, Tetanus) vaccine. Reduced mortality accompanied with overall improved health status was observed in treated animals after intracerebral challenge of B. pertussis indicating development of protective immune response. Present study indicates application of the test material as potential immunopotentiating agent possible applications in immunochemical industry. The test material also offers direct therapeutic benefits resulting in reduced morbidity and mortality of experimental animals.[58]

REFERENCES

1. Weiner, M.A, Weiner.J Ashwagandha (India ginseng). In: Herbs that Heal. Mill Valley, CA: Quantum Books, 1994; 70-72.
2. S. Sharma, S. Dahanukar, S.M. Karandikar. Effects of long-term administration of the roots of ashwagandha and shatavari in rats. Indian Drugs, 1985; 133-139.
3. Budhiraja RD, Sudhir S. Review of biological activity of Withenolides (Antibacterial Antitumor, Immunomodulating, Antiinflammatory and insect anti feedcent). J Sci Ind Res., 46: 488-91.
4. Chopra, R.N. Glossary of Indian Medicinal Plants. New Delhi: Academic Publishers India, 1994.
5. Glotter E, Kirson I, Abraham A, Lavie D. Constituents of Withania somnifera Dun—13. The withanolides of chemotype III. Tetrahedron, 1973; 29(10): 1353–1364.
6. Devi PU, Sharada AC, Solomon FE. Antitumor and radios ensitizing effects of Withania somnifera (Ashwagandha) on a transplantable mouse tumor, Sarcoma- 180. Indian J Exp Biol., 1993; 31(7): 607-11.
7. Williamson EM, Hooper M. Major Herbs of Ayurveda. Edinburgh: Churchill Livingstone, 2002.
8. Kapoor LD. CRC Handbook of Ayurvedic Medicinal Plants. Boca Raton, FL: CRC Press, 1990.
9. Ayurvedic Pharmacopoeia Committee. Asvagandha. In: The Ayurvedic Pharmacopoeia of India, Part I, Volume I. New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), 1989.

10. Siddha Pharmacopoeia Committee. Siddha Pharmacopoeia of India, Part I, Vol. I, First Edition. New Delhi, India: Govt. of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), 2008.
11. Unani Pharmacopoeia Committee. The Unani Pharmacopoeia of India, Part I, Volume I, New Delhi, India: Government of India, Ministry of Health and Family Welfare, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), 2007; 7-8.
12. World Health Organization. Radix Withaniae. In: WHO Monographs on Selected Medicinal Plants, Volume 4. Geneva, Switzerland: World Health Organization, 2009; 373-391.
13. British Pharmacopoeia Commission. Withania Somnifera for use in THMP. In: British Pharmacopoeia 2012. London, UK: The Stationery Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA), 2012.
14. Government of India Ministry of Health and Family Welfare. Indian Pharmacopoeia 2010. Ghaziabad, India: The Indian Pharmacopoeia Commission, 2010.
15. United States Pharmacopeia Convention. Ashwagandha Root; Powdered Ashwagandha Root; and Powdered Ashwagandha Root Extract. In: United States Pharmacopeia, 36th Revision (USP 36). Rockville, MD: United States Pharmacopeial Convention, 2013; 1336-1341.
16. Indian Drug Manufacturers' Association. Indian Herbal Pharmacopoeia, Revised New Edition 2002. Mumbai, India: Indian Drug Manufacturer's Association, 2002; 467-478.
17. Siddha Pharmacopoeia Committee. Amukkara (Root). In: Siddha Pharmacopoeia of India, Part I, Vol. I, First Edition. New Delhi, India: Govt. of India, Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), 2008; 1-3.
18. Central Council for Research in Unani Medicine. Asgand. In: Standardisation of Single Drugs of Unani Medicine, Part III. New Delhi, India: Govt. of India, Central Council for Research in Unani Medicine, 1997; 9-14.
19. Nadharni KM. Indian Materia Medica, Vol. 1. Bombay: Popular Prakashan, 1976.
20. Bone K, Mills S. Principles and Practice of Phytotherapy: Modern Herbal Medicine. Edinburgh: Churchill Livingstone, 2013.
21. Duke J, ed. Handbook of Medicinal Herbs. Boca Raton, FL: CRC Press, 1985.
22. Bone K. et al; Clinical applications of Ayurvedic and Chinese herbs-Monographs for the Western Herbal Practitioner. Australia: Phytotherapy Press, 1996; 137-141.

23. Elsakka M, E Grigoreseu, U Stanescu, V Dorneanu; New data referring to chemistry of Withania somnifera species, Rev Med Chir Soc Med Nat lasi, 1990; 94(2): 385-387.
24. C. P. Khare, Indian Medicinal Plants - An Illustrated Dictionary. ISBN, 978-0-387-70637-5 Springers edition, 2007; 717.
25. Anonymous, Database on medicinal plants used in Ayurveda. CCRAS, New Delhi, 2001; 3: 88.
26. Santvani khyati et al - A preliminalry physicochemical assay of Ashwagandha granules–A pilot study. WWWITHANIAIJRAP.net, IJRAP, 2011; 2(4): 1026-1032.
27. Sukha Dev, A Selection of Prime Ayurvedic Plant Drugs Ancient-Modern Concordance. Anamaya Publishers, New Delhi, 2006; 448.
28. Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Monographs for the Western Herbal Practitioner. Australia: Phytotherapy Press, 1996; 137-141.
29. Kupparanjan K, et al. Effect of ashwaganda (Withania somnifera Dunal) on the process of aging in human volunteers. J Res Ayurveda Siddha, 1980; 1: 247–258.
30. Khare CP. Indian Medicinal Plants–An Illustrated Dictionary. First Indian Reprint, Springer (India) Pvt. Ltd., New Delhi. Kirtikar KR, Basu BD. Indian Medicinal Plants, 2007; 2: 717-718.
31. Rastogi RP, Mehrotra BN. Compendium of Indian Medicinal Plants. 2nd Reprint, Central Drug Research Institute, Lucknow and National Institute of Science Communication, Council of Scientific and Industrial Research, New Delhi, 1998; 1: 434-436; Vol. 2: 708-710; Vol. 3: 682-684; Vol. 4: 765-766; Vol. 5: 889-891; Vol. 6: 148.
32. Anabalagan K, Sadique J. Withania somnifera, a rejuvenating herbal drug which controls alpha-2 macroglobulin synthesis during inflammation. Intl J Crude Drug Res., 1985; 23: 177-183.
33. P.Usharani, P.Nalini, K.Manjunath. N.K.Sunil Kumar Reddy. Evaluation of the analgesic activity of standardized aqueous extract of Withania somnifera in healthy human volunteers using Hot Air Pain Model. Research Journal of Life Sciences (May- 2013), 01(02): 1-6 ISSN 2052-5176.
34. Chittaranjan Andrade, Anitha Aswath, S.K. Chaturvedi, M. Srinivasa & R. Raguram: A double-blind, placebocontrolled evaluation Of the anxiolytic.
35. Chandrasekhar K, Kapoor J, Anishetty S.A prospective, randomized double-blind,placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med., 2012; 34: 255-62.

36. A standardized WS extract significantly reduces stress related parameters in chronically stressed humans: A double blind, Randomized, Placebo-controlled study. JANA, 2008; 2(8).
37. Bhattacharya SK; Muruganandam AV; Adaptogenic activity of Withania somnifera: an experimental study using a rat model of chronic stress. Pharmacol Biochem Behav, 2003; 547-555.
38. Bhattacharya A, Ghosal S, Bhattacharya SK. Anti-oxidant effect of Withania somnifera glycowithanolides in chronic footshock stress-induced perturbations of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. J Ethnopharmacol, 2001; 74: 1-6.
39. Malhotra CL, Das PK, Dhalla NS, Prasad K. Studies on Withania ashwagandha, Kaul. III. The effect of total alkaloids on the cardiovascular system and respiration. Indian J Med Sci., 1981; 49: 448-460.
40. Mohanty I, Arya DS, Dinda A, Talwar KK, Joshi S, Gupta SK. Mechanisms of cardioprotective effect of Withania somnifera in experimentally induced myocardial infarction. Basic Clin Pharmacol Toxicol, 2004; 94(4): 184-190.
41. Andallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (Withania somnifera, Dunal) root. Indian J Exp Biol., 2000; 38(6): 607-09.
42. Ichikawa H, Takada Y, Shishodia S, Jayaprakasam B, Nair MG, Aggarwal BB. Withanolides potentiate apoptosis, inhibit invasion, and abolish osteoclastogenesis through suppression of nuclear factor-kappaB (NF-kappaB) activation and NF-kappa B-regulated gene expression. Mol Cancer Therap, 2006; 1434-45.
43. Jayaprakasam B, Zhang Y, Seeram N Nair. Growth inhibition of human tumor cell lines by withanolides from Withania somnifera leaves. M. Life Sci., 2003; 74: 125-32.
44. Sumanran VN, Boddul S, Madhuri D. Differential growth inhibitory effects of Withania somnifera root on CHO cells. Phytother Res., 2007; 21: 1-4.
45. B.M. Biswal et al AOS14 Phase II clinical study of combination chemotherapy with herb Withania somnifera (ashwagandha) in breast cancer Eu. J.of Cancer, 2012; 48(4): S8-S9.
46. Dickon TC, Vickers JC. The morphological phenotype of b-amyloid plaques and associated neuritic changes in Alzheimer's disease. Neuroscience, 2001; 105: 99-107. [PubMed]
47. Dekosky S, Scheff SWITHANIA Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Ann Neurol, 1990; 27: 457-464. [PubMed]

48. Bhattacharya SK, Kumar A, Ghosal S. Effects of glycowithanolides from Withania somnifera on animal model of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. Phytother Res., 1995; 9: 110-113.
49. Gunne LM, Andren PE. An animal model for coexisting tardive dyskinesia and tardive parkinsonism: A glutamate hypothesis for tardive dyskinesia. Clin Neuropharmacol, 1993; 16: 90-95. [PubMed]
50. Kuboyam A T, Tohda C, Komatsu K. Withanoside IV and its active metabolite, sominone, attenuate A beta(25-35)-induced neurodegeneration. Eur J Neurosci, 2006; 23(6): 1417-1426. [PubMed]
51. Ziauddin M, Phansalkar N, Patki P, Diwanay S, Patwardhan B. Studies on the immunomodulatory effect of Asgandh. J Ethnopharmacol, 1996; 50(2): 69-76.
52. Davis L, Kuttan G. Suppressive effect of cyclophosphamideinduced toxicity by Withania somnifera extract in mice. J Ethnopharmacol, 1998; 62(3): 209-214.
53. Kuttan G. Use of Withania somnifera Dunal as an adjuvant during radiation therapy. Indian J Exp Biol., 1996; 34(9): 854-856.
54. Venkataraghavan S, Seshadri C, Sundaresan TP; The comparative effect of milk fortified with Aswagandha and Punarnava in children – a double-blind study. J Res Ayur Sid., 1980; 1: 370-385.
55. Kulkarni RR, Patki PS, Jog VP; Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. J Ethnopharmacology, 1991; 33: 91-95.
56. K. N. Roy Chengappa et al Randomized Placebo-Controlled Adjunctive Study of an Extract of Withania somnifera for Cognitive Dysfunction in Bipolar Disorder J Clin Psychiatry, 2013; 74(11): 1076-1083.
57. Dahikar et al., Effect of Withania somnifera (Ashwagandha) on the Pharmacokinetics of Amikacin: A Future Antimicrobial Polypharmacy. J Drug Metab Toxicol, 2013; 4: 1 http://dx.doi.org/10.4172/2157- 7609.1000142.
58. M Gautam et al Immune response modulation to DPT vaccine by aqueous extract of Withania somnifera in experimental system. International Immunopharmacology, 2004; 4(6): 841-84.