ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2016; 7 (1): 1- 11

REVIEW ARTICLE

Studies of Ashwagandha (*Withania somnifera* Dunal)

Krutika J[1]*, Swagata Tavhare[2], Kalpesh Panara [3], Praveen Kumar A[4], Nishteswar Karra[5]

[1,3,4] MD (AYU), PhD (AYU) ,Dravyaguna Department, IPGT&RA, Gujarat Ayurved University, Jamnagar, Gujarat, India

[2] PhD scholar,Dravyaguna Department, IPGT&RA, Gujarat Ayurved University, Jamnagar, Gujarat, India

[5]Professor and X-HOD, Dravyaguna Department, IPGT&RA, Gujarat Ayurved University, Jamnagar, Gujarat, India

Received 07 Nov 2015; Revised 04 Feb 2016; Accepted 18 Feb 2016

ABSTRACT

Withania somnifera Dunal member of Solanaceae family popularly known as Ashwagandha, Indian ginseng, or winter cherry has been used in Ayurveda, Indian system of traditional medicine. It is classified as a Rasayana (rejuvenation) and accepted to increase longevity and vitality. It is a reputed health food and herbal tonic and used for cardiovascular diseases in ethnomedicine. It is available for human use either as a single herb or an ingredient of polyherbal or herbomineral formulations. Thorough review of Ayurvedic literature and scientific research journals and articles were executed and presented in concise manner. The review includes various activities of Ashwagandha in experimental models and clinical evaluation of the drug in various dosage forms. The drug is reported with anti-inflammatory, anti-arthritic, caridoprotective, anti-stress, trainquillizers type sedative activity, hypoglycemic, thyroprotective activity and proved to be an effective remedy in cancer cells and the malignant growth of different organs. The drug is studied in all the scientific aspects and proven to be the broad spectrum remedy in various experimental studies. This review may help for the further evaluation of the drug for the cure of the ailments which are threat to human being.

Key words: Ashwagandha, *Withania somnifera*, Withaferin A, Rasayana

INTRODUCTION

W. somnifera Dunal (Solanaceae), also known as Ashwagandha or winter cherry, is one of the most valuable plants in the traditional Indian systems of medicine. It is a small evergreen shrub that grows to roughly four to five feet tall. In India, it is cultivated, on a commercial scale, in the states of Madhya Pradesh, Uttar Pradesh, Punjab, Gujarat and Rajasthan [1]. This plant is used in more than 100 formulations in Ayurveda, Unani and Siddha [2]. Ashwagandha is one of the prime drugs of Ayurveda material medica. Acharya Charaka included it in Balya and Brimhana-gana [3]. It is attributed with Balya, Vrishya and Rasayana properties and suggested as substitute of Kakoli and Kshirakakoli.

The species name somnifera means 'sleep-inducing' in Latin, indicating that to it are attributed sedating properties, but it has been also used for sexual vitality and as an adaptogen. 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. Ethno-medicinally, decoction of the roots is used for colds and chills; and to increase the tone of uterus after miscarriage or birth. An infusion of the root bark has been used for asthma, a use also common to traditional herbal practices in India. In *Ayurvedic* medicine, its root is used as an anti-inflammatory drug for swellings, tumours, scrofula and rheumatism; and as a sedative and hypnotic in anxiety neurosis. Leaf possesses anti-inflammatory, hepatoprotective, antibacterial properties. Fruits and seeds are diuretic. The berries are used as a substitute for rennet, to coagulate milk in cheese making. Studies have proven that the activity of the Withania extract was approximately equal to the activity of the *Panax ginseng* extract. *Withania somnifera*, however, has an advantage over *Panax ginseng* in that it does not appear to result in ginseng- abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension, and insomnia [4].

***Corresponding Author:** Krutika Joshi, **Email:** vd.krutika@gmail.com

Large numbers of experimental and clinical study conducted on Ashwagandha to screen its safety and efficacy on various biological systems but its data are scattered. Many review papers are also drafted but most of it is focused only on pharmcognostic and pharmacological (*in vivo* or *in vitro*) profiles. Keep this in view, attempt has been made to review *Ashwagandha* with Ayurvedic, experimental and clinical aspects. Ayurvedic classical texts, compendia, lexicons, databases, texts and research journals on medicinal plants were reviewed critically and data acquired were presented in concise form.

Indication described in Ayurvedic Medicine

In Ayurvedic classics, Ashwagandha is indicated for Murchha (syncope), Apasmara (epilepsy), Shosha(cachexia), Unmada (mania/psychosis), Karshya (emaciation), Arsha (piles), Pramehapidika (diabetic carbuncle), Arbuda (tumour), Gandamala (cervical lymphadenitis), Bhagandara (fistula-in-ano), Guhya-vrana (ulcer in genitalia), Vatarakta (gout), Kushtha (diseases of skin), Kilasa (vitiligo), Asthibhanga (bone fracture), Katigraha (stiffness in lumbo-sacral region), Gridhrasi (sciatica), Hanugraha (lockjaw), Janustabdhata (stiffness of the knee), Hrudgraha (cardiac failure), Yonidosha (disorders of female genital tract) and Vidradhi (abscess) [5, 6].

Formulation

It is used as an ingredient many formulations such as Shwagandhadi-churna, Ashwagandha-rasayana, Ashwagandha-ghrita, Ashwagandha-rishta, Ashwagandha-taila, Madhyamanarayana-taila, Brihat Ashwagandha-ghrita, Brihachchhagaladya-ghrita, Saraswata-churna, Pramehamihira-taila [7] Nagabala-ghrita. Ashwagandha-taila, Ashvagandha-rishata, Madhusnuhi-rasayana [8].

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 [9]. 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 [10]. 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 [11].

Steroidal compound:

Withanolides glycol with anolides and alkaloids. These include withaferin A, Withanolides G&D sitoindosides IX&X and with asomnine. These have been reported as active marker for standardization [12]. 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 CCl_4 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.

Experimental Pharmacology

Large number of in vitro and in vivo experiments has been conducted to evaluate it efficacy on different biological systems. Activities screened are presented in bellow tables.

Table 1: Activities screened on *In vitro* models

Effects/activity	Active constitutes	Author
Antioxidant	Withaferin –A	A. Bhattacharya *et al*,[13]
	Methanolic extract	A.russo *et al* [14]
Immunomodulatory	Withanolides	V.Bahr, R.Hansel *et al* [15]
	Aqueous extract	M.Gautam *et al* [16]
	Glycowithanolides	V.Bahr, R.Hansel *et al* [17]
	70% ethanolic extract	L.Davis, G.Kuttan *et al* [18]
Relaxant and antispasmodic effects and direct musculotropic action.	The total alkaloids of Aswagandha	The WOI -1982 [19]
Chondroprotective	aqueous extracts of *Withania somnifera* root powder	Venil N Sumantran. [20]
Anti-inflammatory		Somasundaram S [21]

Table 2: Activities evaluated on *In Vivo* models

S. No	Effects /activity	Part used	Author
1	Depressant effect (tranquillizer-sedative type)	Total alkaloids	Rastogi RP [22]
2	Adaptogenic	50% methanolic extract and Sitoindosides – VII and VIII(root)	S.K.Bhattacharya *et al* [23]

3		Withnolide free WSE fraction of root	B.Singh *et al* [24]
4		*W.somnifera* sitoindosides –VII & VIII	S.K. Bhattacharya *et al*
5	Anabolic	Root powder	S Sharma *et al* [26]
6	Analgesic effect(Hyperalgesia in DM neuropathy)	Ashwagandha -mixed rat pellet	Mohsen khalili *et al* [27]
7	anti-inflammatory	Withaferin A (stainless steel implant induced inflammation)	S.Shivamani *et al* [28]
		Root powder (1 g/kg suspended in 2% gum acacia)	Anbalagan *et al*, [29]
		A set of 57 compounds from WS	Sathi N *et al* [30]
		Root powder (1000 mg/kg)	Begum *et al* [31]
		Methanol extract	Hindawi *et al* [32]
		Total extract of root , 100 mg/mL	Agarwal *et al* [33]
8	Anti-depressant	Fat extract (Ashwagandha ghrutha)- in mice.	Jayanthi MK *et al* [34]
		Extract of root – in Rats.	Bhattacharya A *et al* [35]
9	Antimicrobial activity	Bioactive compounds from leaf	Nabil Al Ani *et al* [36] Alam *et al* [37]
10	Anti bacterial	Ethanol root extract of WS	Mohamed El-Sayed El-Boshy [38]
11	Antiparkinson's	*W. somnifera* root extract	Rajasankar S [39]
12	Antipyretic	Alchoholic extract of WS (Intraperitonial administration)	CCRIMH
13	Cardioprotective	WS root extracts	J.N.Dhuley [40] I.Mohanty *et al* [41]
14	Antistress activity to mice (comparative study between finely powdered roots of WS and *Panax ginseng)*	Root powder	Grandhi A [42]
15	hypotensive, bradycardiac and respiratory stimulant activities(in dogs.)	Total alkaloid fraction of root extract	Rastogi RP [43]
16	Immunomodulatory	Ashwagandha churna (including SRBC methods)	M.Suresh Gupta *et al* [44]
		Aqueous extract(WS root)	Mohammad ziauddin *et al* [45]
17	neuroprotective action	Hydromethanolic root extract (Lead induced)	Sadhana Sharma *et al* [46]
		Root	Jain S.K [47]
		Root extract of WS	Mahdeep Bhatnagar. [48]
18	Sedation in mice, dogs, monkeys rabbits, and rats.	Ethanolic extract of the roots	S.K.Bhattacharya [49]
19	Thyrotropic effect.	Root extract of WS	Andallu B *et al* [50]
20	*Hypoglycaemic and Hypolipidaemic*	aqueous extract of *W. coagulans* fruits	Hoda Q [52]
21	Anti-malarial	*W. somnifera.* Leaves and root extracts	Dikasso D [53]
22	Nephroprotective	*W. somnifera*. Root extract	Jeyanthi T [54]

Table 3: Experiment carried out to screen anticancer activity

Activity	Part used	Author
Chemo protective		M.A. Akbarsha [55]
	WS extract	Prakash J [56]
As an effective and a novel source of L-asparaginase.	Root extracts	Oza V. [57]
Colon cancer	WS root extract(induced by azoxymethane and its immune dysfunction)	Muralikrishnan [58]
	Withaferin-A (WA)	Koduru [59]
Cytotoxic properties against lung, colon, central nervous system, and breast cancer cell lines	Root extracts of WS	Jayaprakasha B [60]
Dose dependent inhibition of metastatic lung nodules in breast cancer metastasis mouse model,	WFA	Thaiparambil JT *et al* [61]
Breast and colon cancer cell growth	Withaferin A,	Jayaprakasham B [62]
Lung cancer in mice (benzo(a)pyrene-induced)	The combination of paclitaxel with WS	Senthilnathan [63]
Control proliferative cells and nontoxic to normal lymphocytes	Withanolide D; a pure herbal compound isolated from WS	Mondal S [64]
Skin Carcinogenasis in mice	Root of ws	Padmavathi B [65]
Skin carcinoma in rat induced by ultra violet radiation	Chemical constituent isolated from root of WS	Mathur [66]
Skin cancer (7,12-dimethylbenz a]anthracene (DMBA)- induced) in Swiss albino mice	WS hydroalcoholic root extract (WSRE)	Prakash J [67]
Antiproliferative activity on MCF-7 (breast) human tumor cell lines.	Leaf extract	Yadav B [68]
Fibrosarcoma tumours in Swiss albino mice (20- methylcholanthrene induced)	Hydro-alcoholic extract of roots	Davis L [89]
Pancreatic cancer *in vitro* and *in vivo*	A steroidal lactone occurring in WS	Yu V [70]

Preclinical Safety Data

Acute toxicity:

Animal toxicity studies suggest that Ashwagandha and its constituents are safe even when administered in high doses. The approximate LD50 was reported as 1750 ± 41 mg po in albino mice (weighing 20- 25 g) [71]. Another study reported no deaths of albino mice up to 1000 mg/kg po of sitoindosides IX and X administration. LD_{50}s of ip administrations of these compounds were reported as 518 ± 34 mg/kg and 808 ± 68 mg/kg for sitoindosides IX and X. [72] The acute toxicity study showed that all

the extracts of *W.somnifera* were safe upto 200 mg/kg body weight. [73]

LD50 was recorded in rats - 465 mg/kg (332-651 mg/kg) and in mice - 432 mg/kg (299-626mg/kg) in two-percent suspension of ashwagandholine (total alkaloids from the roots of WS). [74] While in alcohol extract from defatted seeds, LD50 in albino mice was recorded 1750 +/- 41 mg (p.o). [75]

Clinical Studies

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. [77]

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. [78]

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.[79]

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 standardized 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 standardised aqueous extract of *Withania somnifera* produced significant increase in Pain Threshold time compared baseline and placebo. [80]

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.[81]

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.[82]

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. [83]

Adjuvant to chemotherapy

Fifty patients were recruited to each group, with a median age of 51 years (range 36–70 years) in the *W. 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 *W. 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 *W. somnifera* root extract plus chemotherapy. Addition of *W. 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.[84]

Cardio vascular protection

Forty normal healthy subjects (either sex, mean age 20.6 ± 2.5yrs and mean Body Mass Index 21.9 ± 2.2) of which 10 received standardized root extracts of *Withania somnifera*, 10 received standardized bark extract of *Terminalia arjuna* and the rest of the 10 received standardized root extract of *Withania somnifera* in addition to bark extract of *Terminalia arjuna*. Both the drugs were given in the form of capsules (dosage 500mg/day for both the drugs). Ten participants received placebo (capsules filled with flour). All the subjects continued the regimen for 8 weeks. All variables were assessed before and after the course of drug administration. *Withania somnifera* increased velocity, power and VO2 max whereas *Terminalia arjuna* increased VO2 max and lowered resting systolic blood pressure. When given in combination, the improvement was seen in all parameters except balance and diastolic blood pressure. *Withania somnifera* may therefore be useful for generalized weakness and to improve speed and lower limb muscular strength and neuro-muscular co-ordination. *Terminalia arjuna* may prove useful to improve cardio-vascular endurance and lowering systolic blood pressure. Both drugs appear to be safe for young adults when given for mentioned dosage and duration. [85]

Hypoglycemic and hypocholesterolemic effect

Hypoglycemic, diuretic, and hypocholesterolemic effects of Ashwagandha root were assessed in human subjects, in which six type 2 diabetes mellitus subjects and six mildly hyper-cholesterolemic subjects were treated with a powder extract for 30 days. A decrease in blood glucose comparable to that of an oral hypoglycaemic drug was observed. Significant increases in urine sodium, urine volume, and decreases in serum cholesterol, triglycerides, and low-density lipoproteins were also seen. [86]

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. [87]

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 (Erythrocite sedimentations) rate were noted.[88]

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.[89]

Drug Interactions:

W. 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 *W. 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. [90]

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. [91]

Caution: There are ethanomedicinal reports that Ashwagandha may potentiate the effects of barbiturates; therefore, caution should be used if taking this combination.[92] Consumption with alcohol, other drugs or natural health products with sedative properties is not recommended. [93] Consult a healthcare practitioner prior to use in pregnant or breastfeeding mother. (Upton 2000)

CONCLUSION

In Ayurvedic classics Ashwaganhda is reported having Shothahara, Vedanasthapana, Mastishkashamaka, Deepana, Anulomana, Shoolaprashmana, Krimighna, Raktashodhaka, Kaphaghna, Shwasahara, Vajikarana, Garbhashayashothahara, Yonishoolahara, Mootrala, Kushthaghna, Balya, Brinhana, Rasayana activities. Several experimental studies are conducted on Ashwagandha and its constituents providing the scientific bases for the activities reported in Ayurveda. Significant amount of investigations have been carried out on anticancer and chemoprotective activities of Ashwagandha indicate the drug is a potentially useful adjunct for patients undergoing radiation and chemotherapy The Ashwagandha was evaluated in various experimental models for assessment of activities of Ashwagandha. Clinical trials carried out for Anti-inflammatory, sedative, , as adjuvant to chemotherapy, rejuvenating effect, hypoglycemic and hypocholesterolemic, Cardioprotective, *Rasayan,* growth-promoting effect of Ashwagandha support and provid scientific validations. The drug found safe in long term usage and also in higher amount and can be supportive with some modern medicine as its proven significant antimicrobial activities with amikacin and immunopotentiation with DPT vaccine, increasing their therapeutic effects. In nut shell, the drug can be a broad spectrum medicine for the treatment of various disorders and also can

be used by healthy individual for maintainance of positive health.

REFERENCE

1. Ven Murthy MR, Ranjekar PK, Ramassamy C, Deshpande M.; (2010)Scientific basis for the use of Indian Ayurvedic medicinal plants in the treatment of neurodegenerative disorders: Ashwagandha. Cent Nerv Syst Agents Med Chem. Sep 1;10 (3):238 - 246.
2. Sangwan RS, (2004)*et al* Phytochemical variability in commericial herbal products and preparations of Withania somnifera (Ashwagandha). Curr. Sci. 86:461–465.
3. Proff.K. Nishteswar, K.Hemadri, Dravyaguna Vijnana, Chaukhambha Samskrit Pratishthana, First edition , P-121.
4. Bone K. *et al*; Clinical applications of Ayurvedic and Chinese herbs-Monographs for the Western Herbal Practitioner. Australia: Phytotherapy Press; 1996:137-141.
5. Anonymous, The Ayurvedic Pharmacopeia of India, part I and I vol I, Dept. of Ayush, Ministry of health & family welfare, New Delhi., 200.
6. Anonymous, The Ayurvedic formulary of India, Part 1, Dept. of Ayush, Ministry of health & family welfare, New Delhi., 2004.
7. Anonymous, Database on Indian medicinal plants CCRAS, New Delhi vol-3, P- 88.
8. Ibidem (11) and (12) The API and The AFI, 2003.
9. 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.
10. C. P. Khare, Indian Medicinal Plants - An Illustrated Dictionary. ISBN: 978-0-387-70637-5 Springers edition. 2007-p.-717.
11. Anonymous, Database on medicinal plants used in Ayurveda. CCRAS, New Delhi vol-3, 2001 P- 88.
12. Santvani khyati *et al* - A preliminalry physicochemical assay of Ashwagandha granules–Apilot study. WWW.IJRAP.net, IJRAP-2011, 2(4) 1026-1032.
13. 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. Journal of Ethanopharmacology. Volume 74, Issue 1, January 2001, Pages 1–6.
14. Russo. A.,Lzzo A. A. Cardile, V., Borrelli, G., Vanella, A., 2001. Indian medicinal plants as antiradicals and DNA cleavage protectors.Phytomedicine.2001Mar;8(2):125-32.
15. Bahr V. and Hansel R, Immunomodulating Properties of 5,20α(R) - Dihydroxy - 6α, 7α -epoxy-1-oxo-(5α)- with α- 2,24-dienolide and Solasodine. J. Meal. Plant Res. 1982; 44, 32-33.
16. Immune response modulation to DPT vaccine by aqueous extract of *Withania somnifera* in experimental system. International Immunopharmacology June 2004,4(6), 841–849.
17. Bahr V. and Hansel R, Immunomodulating Properties of 5,20α(R) - Dihydroxy - 6α, 7α -epoxy-1-oxo-(5α)- with α- 2,24-dienolide and Solasodine. J. Meal. Plant Res. 1982; 44, 32-33.
18. Davis L, Kuttan G. *et al* Immunomodulatory activity of Withania *somnifera*.J Ethnopharmacol 2000*; 71:193-200*.
19. Anonymous. The Wealth of India. Vol. X (Sp-W), Publications and Information Directorate, Council of Scientific and Industrial Research (CSIR), New Delhi, 1982; 580-585.
20. venil n sumantran *et al*, Chondroprotective potential of root extracts of *Withania somnifera* in osteoarthritis. *J. Biosci.* 32(2), March 2007, 299–307.
21. Somasundaram S, Sadique J, Subramoniam A. Influenceofextra-intestinal inflammation on the in vitro absorption of 14C-glucose and the effects of anti-inflammatory drugs in the jejunum of rats. *Clin Exp Pharmacol Physiol* 1983; 10:147-152.
22. Rastogi RP and 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) Vol. 6: 148.

23. SK Bhattacharya et al Anti-stress activity of sitoindosides VII and VIII, new acylsteryl glucosides from *Withania somnifera*Phytother Res.; 1987 1(1) 32–37.
24. B.Singh, B.Chauhan, D.K. Gupta Adaptogenic activity of a novel withanolide-free aqueous fraction from the roots of Withania somnifera Dun. Phytother Res.2003; 17(5):531-6.
25. S.K.Bhattacharya, A.Bhattacharya, K.Sairam, S.Ghosal, Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: an experimental study. Phytomedicine, 2000: 7:463.
26. S. Sharma, S.Dahanukar, S.M. Karandikar, Indian drugs, 23, 133 (1985) .
27. Mohsen Khalili *et al* The effect of oral administration of *Withania somnifera* root on formalin-induced pain in diabetic rats. Basic and clinical neuro science, 2009 : 1(1) .
28. S. Sivamani *et al.*, Anti-inflammatory activity of *Withania somnifera* leaf extract in stainless steel implant induced inflammation in adult zebrafish. Journal of Genetic Eng. and Biotech. 2014. http://dx.doi.org/10.1016/j.jgeb.2014.01.002.
29. Anbalagan K, Sadique J. *et al* Influence of an Indian medicine *(*Ashwagandha*)* on acute-phase reactants in inflammation. Indian J Exp Biol. 1981 Mar; 19(3):245-9.
30. Santhi N, Identification of potential anti-inflammatory bioactive compounds from *Withania somnifera* (L.) Dunal: Molecular docking studies using Glide. http://cs.nyu.edu/parida/APBC2010/poster_abstracts/85.pdf.
31. Begum VH, Sadique J. Effect of *Withania somnifera* on glycosaminoglycan synthesis in carrageenin-induced air pouch granuloma. *Biochem Med Metab Biol* 1987; 38:272-277.
32. al Hindawi MK, al Khafaji SH, Abdul-Nabi MH; Anti-granuloma activity of Iraqi *Withania somnifera*. *J Ethnopharmacol* 1992; 37:113- 116.
33. Agarwal R, Diwanay S, Patki P, Patwardhan B. 1999. Studies on immunomodulatory activity of *Withania somnifera* (ashwagandha) extracts in experimental immune inflammation. *J Ethnopharmacol* 67:27-35.
34. Jayanthi M.K, prathima C, huralikuppi J. C., Suresha R.N and Muralidhar. Anti-depressant effects of *withania somnifera* fat (Ashwagandha ghrutha) extract in experimental mice. IJPBS, 2012: 3(1): 33-42.
35. 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):1-6.
36. Nabeel Al Ani, Sabreen A.Hadi, Rawaa Nazar. Antimicrobial activities of Withania Somnifera Crude extract Scientia Agriculturae2013: 4 (3) ;74-76.
37. Alam *et al* Methanolic extracts of *Withania somnifera* leaves, fruits and roots possess antioxidant properties and antibacterial activities. BMC Complementary and Alternative Medicine 2012, 12(175) 7-8 http://www.biomedcentral.com/1472-6882/12/175.
38. Mohamed El-Sayed El-Boshy Effect of *Withania somnifera* Extracts on Some Selective Biochemical, Hematological, and Immunological Parameters in Guinea Pigs Experimental Infected with *E. Coli*. ISRN Veterinary Science Volume 2013.
39. Rajasankar S *et al* Withania somnifera root extractimproves catecholamines and physiological abnormalities seen in a Parkinsons disease model mouse. *Ethnopharmacol.2009;* 125: 369-373.
40. Dhuley JN. *Adaptogenic and cardioprotective action of ashwagandha in rats and frogs*. J Ethnopharmacol. 2000; 70:57-63.
41. I.Mohanty *et al* Mechanism of cardioprotective effect of *Withania somnifera* in experimentally induced myocardial infraction. Basic.clinic. pharmacology. toxiclogy; April 2004;94(4):184-90.
42. Grandhi A, Mujumdar A.M, Patwardhan B. A comparative pharmacological investigation of Ashwagandha and Ginseng. *J Ethnopharmacol* 1994;44:131-135.

43. Rastogi RP and 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) Vol. 1: 434-436; 766.
44. M. Suresh Gupta *et al* Immunomodulatory Activity of the Ayurvedic Formulation "Ashwagandha Churna" Pharmaceutical biology, 2006, Vol. 44, No. 4 , Pages 263-265.
45. Mohammed Ziauddin *et al* Studies on the immunomodulatory effects of Ashwagandha. Journal of ethnopharmacology. 1996; 50(2): 69-76.
46. Sadhana Sharma *et al* therapeutic potential of hydromethanolic root extract of *withania somnifera* on neurological parameters in swiss albino mice subjected to lead nitrate. International journal of current pharmaceutical research issn-0975-7066 vol 3, issue 2, 2011.
47. Jain S, Shukla SD, Sharma K, Bhatnagar M. Neuroprotective Effects of *Withania somnifera* in Hippocampal Sub-regions of Female Albino Rat. Phytother Res. 2001;15(6):544-8.
48. Mahdeep Bhatnagar, Durgesh Sharma, Mahendra Salvi, Neuroprotective effects of Withania somnifera Dunala: A possible mechanism. Neurochem Res -2009; 43: 1975-1983.
49. Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Anxiolytic-antidepressant activity of *Withania somnifera* glycowithanolides: an experimental study. Phytomedicine. 2000 Dec; 7(6):463-9.
50. Andallu B, Radhika B. Hypoglycemic, diuretic and hypocholesterolemic effect of winter cherry (*Withania somnifera*) root. Indian J Exp Biol 2000; 38:607-609.
51. Panda S, Kar A. *Withania somnifera* and *Bauhinia pupurea* in the regulation of circulating thyroid hormone concentrations in female mice. J Ethnopharmacol 1999; 67:233-239.
52. Hoda Q *et al* Hum. Exp. Toxicol. 2010 29: 653-65.
53. Dikasso D, et *al* Ethiop. Med. J. 2006 44: 279-285.
54. Jeyanthi T, Subramanian P. Ren. Fai *l*200931: 814 - 821.
55. Akbarsha MA *et. al*. Curative property of *Withania somnifera* root in the context of carbendazim-induced histopathological changes in the liver and kidney of rat. Phytomedicine. 2000 Dec;7(6):499-507.
56. Prakash J, Gupta SK, Kochupill ai V, Singh N, Gupta YK, Joshi S. Chemopreventive activity of *Withania somnifera* in experimentally induced fibrosarcoma tumours in Swiss albino mice. Phytother Res. 2001; 15(3):240-244.
57. properties of highly purified L-asparaginase from *Withania somnifera* against acute lymphoblastic leukemia. Appl Biochem Biotechnol. 2010; 160(6):1833-1840.
58. Muralikrishnan G, Amanullah S, Basha MI, Dinda AK, Shakeel F. Modulating effect of *Withania somnifera* on TCA cycle enzymes and electron transport chain in azoxymethane-inducedcolon cancer inmice.ImmunopharmacolImmunotoxicol. 2010; 32(3):523-527.
59. Koduru S, Kumar R, Srinivasan S, Evers MB, Damodaran C. Notch-1 inhibition by Withaferin-A: a therapeutic target against colon carcinogenesis. Mol Cancer Ther. 2010 Jan; 9(1):202-10.
60. Jayaprakasam B, Zhang Y, Seeram NP, Nair MG. Growth inhibition of human tumor cell lines by withanolides from *Withania somnifera* leaves. Life Sci. 2003; 74(1):125-32.
61. Thaiparambil JT, Bender L, Ganesh T, Kline E, Patel P, Liu Y, Tighiouart M, Vertino PM, Harvey RD, Garcia A, Marcus AI. Withaferin A inhibits breast cancer invasion and metastasis at subcytotoxic doses by inducing vimentin disassembly and serine56 phosphorylation. Int J Cancer 2011.
62. Jayaprakasam B, Zhang Y, Seeram NP, Nair MG. Growth inhibition of human tumor cell lines by withanolides from *Withania somnifera* leaves. Life Sci. 2003; 74(1):125-32.
63. Senthilnathan P, Padmavathi R, Banu SM, Sakthisekaran D. Enhancement of antitumor effect of paclitaxel in combination with immunomodulatory *Withania somnifera* on benzo(a)pyrene induced experimental lung cancer. Chem Biol Interact. 2006; 159(3):180- 185.

64. Mondal S, Mandal C, Sangwan R, Chandra S, Mandal C. Withanolide D induces apoptosis in leukemia by targeting the activation of neutral sphingomyelinase-ceramide cascade mediated by synergistic activation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase. Mol Cancer. 2010; 9:239.
65. Padmavathi B, Rath PC, Rao AR, Singh RP. Roots of *Withania somnifera* Inhibit Forestomach and Skin Carcinogenesis in Mice. Evid Based Complement Alternat Med. 2005; 2(1):99-105.
66. Chandra R. The treatment of skin carcinoma, induced by UV B radiation, using 1-oxo-5beta, 6beta-epoxy-witha-2-enolide, isolated from the roots of *Withania somnifera*, in a rat model. Phytomedicine. 2004; 11(5):452-460.
67. Prakash J, Gupta SK, Dinda AK. *Withania somnifera* root extract prevents DMBA-induced squamous cell carcinoma of skin in *Swiss albino* mice. Nutr Cancer. 2002; 42(1):91-7.
68. Yadav B, Bajaj A, Saxena M, Saxena AK. *In Vitro* Anticancer Activity of the root, stem and leaves of *Withania Somnifera* against Various Human Cancer Cell Lines. Indian J Pharm Sci. 2010; 72(5): 659-663.
69. Davis L, Kuttan G. Effect of *Withania somnifera* on 20- methylcholanthrene induced fibrosarcoma. J Exp Clin Cancer Res. 2000 Jun; 19(2):165-167.
70. Yu Y, Hamza A, Zhang T, Gu M, Zou P, Newman B, Li Y, Gunatilaka AA, Zhan CG, Sun D. Withaferin A targets heat shock protein 90 in pancreatic cancer cells. Biochem Pharmacol. 2010;79(4):542-551.
71. Singh N, Nath R, Lata A, Singh SP, Kohli RP, Bhargava KP. 1982. *Withania somnifera* (ashwaganda), a rejuvenating herbal drug which enhances survival during stress (an adaptogen). *Int J Crude Drug Res* 20(1):29-35.
72. Ghosal S, Lal J, Srivastava R, Bhattacharya SK, Sachidananda U, Jaiswal A, Chattopadhyay U. 1989. Immunomodulatory and CNS effects of sitoindosides IX and X, two new glycowithanolides from *Withania somnifera*. *Phytother Res* 3(5):201-6.
73. H.Jain *et al*, Extraction of Ashwagandha by conventional extraction and evaluation of its anti stress activity. International journal of green pharmacy, July-Sept-2010.
74. Singh N, Nath R, Lata A; *Withania somnifera* (ashwagandha), a rejuvenating herbal drug which enhances survival during stress (an adaptogen). *Int J Crude Drug Res* 1982; 20:29-35.
75. Grandhi A, Mujumdar AM, Patwardhan B. A comparative pharmacological investigation of Ashwagandha and Ginseng. *J Ethnopharmacol* 1994;44:131-135.
76. Sukha Dev, A Selection of Prime Ayurvedic Plant Drugs Ancient-Modern Concordance. Anamaya Publishers, New Delhi 2006.P.448.
77. Sukha Dev, A Selection of Prime Ayurvedic Plant Drugs Ancient-Modern Concordance. Anamaya Publishers, New Delhi 2006. P. 448.
78. Bone K. Clinical Applications of Ayurvedic and Chinese Herbs. Monographs for the Western Herbal Practitioner. Australia: Phytotherapy Press; 1996:137-141.
79. 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.
80. 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), Vol. 01, Issue 02, pp.1-6 ISSN 2052-5176.
81. 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.
82. A standardized WS extract significantly reduces stress related parameters in chronically stressed humans: A double blind, Randomized, Placebo-controlled study. JANA, Vol-2 No-8, 2008.
83. Chittaranjan Andrade, Anitha Aswath, S.K. Chaturvedi, M. Srinivasa & R.

Raguram: A double-blind, placebo-
84. efficacy of an ethanolic extract of *withania somnifera* Indian Journal of Psychiatry, 2000, 42 (3), 295-301.
85. 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.
86. Jaspal Singh Sandhu, *et al* Effects of *Withania somnifera* (Ashwagandha) and *Terminalia arjuna* (Arjuna) on physical performance and cardiorespiratory endurance in healthy young adults. Int J Ayurveda Res. 2010; 1(3): 144–149.
87. Ibidem –(51)Andallu B, Radhika B. *Indian J Exp Biol* 2000;38:607-609.
88. 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.
89. 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.
controlled evaluation Of the anxiolytic
90. 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.
91. 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.
92. 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.
93. *Withania somnifera* Monograph Alternative Medicine Review. Thorne Research, 2004; 9(2): 212.
94. Berardi RR *et al* editors. Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care. Washington (DC): American Pharmaceutical Association; 17th edition 2002, p-193.