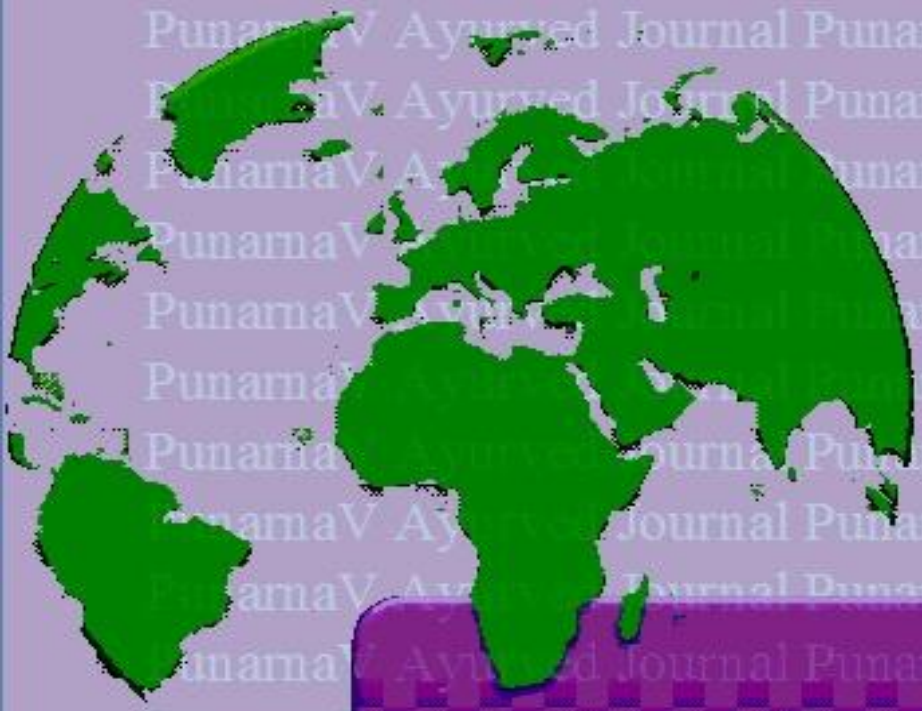
MONTH: FEB-MAR: 2015

VOL 2: ISSUE: 5

ISSN: 2348-1846



PunarnaV

AN INTERNATIONAL PEER REVIEWED AYURVED JOURNAL

ON LINE BI-MONTHLY AYURVED JOURNAL

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EVIDENCE BASED PHARMACO- CLINICAL STUDIES ON ASHWAGANDHA (*WITHANIA SOMNIFERA* L DUNAL)

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ABSTRACT:

Plants are one of the most important sources of medicines in world. Clinical experiences built over many centuries provide a substantial basis for the development of safe and effective use of herbal medicines in the current day healthcare system. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety profiles besides being economical, effective and their easy availability. At present, very few medicinal herbs are evaluated for their clinical efficacy along with safety and quality profile. Assurances of these have become a key issue in industrialized and developing countries. Withania somnifera L Dunal (Ashwagandha) Indian ginseng is an important herb in the Ayurvedic and indigenous medical systems for over 3000 years has commanded great respect in Ayurvedic practice. Present study compiles literature from classical ayurvedic texts, lexicons scientific literature, pharmacopeia of India, various journals and monographs .Historically, the plant has been used as a Vrushya (Aphrodisiac), Balya (Strength), and Rasayana (Rejuvenator). Clinical trials and experimental research support the use of Ashwagandha for anxiety, cognitive and neurological disorders, inflammation, bronchitis, asthma, ulcers, emaciation, insomnia, Parkinson's disease and as a potentially useful adjunct for patients undergoing radiation and chemotherapy. Thus, it is bestowed with properties like adaptogen, antioxidant, anti-inflammatory, chemopreotective, antitussive, immonomodulator etc.

Key words: *Ashwagandha, Clinical trials, experimental research*

INTRODUCTION

Currently, Ayurveda is becoming popular globally. According to a survey (1993) of World Health Organization (WHO), the practitioners of traditional system of medicine treat about 80% of patients in India, 85% in Burma and 90% in Bangladesh. At present, many people in developing countries have begun to turn to

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alternative system of medicine including usage of medicinal herbs.

Ashwagandha is one of the prime drugs of Ayurvedic materia medica botanically identified as *Withania somnifera L Dunal* (*WS*) belonging to Solanaceae family. It is a small evergreen woody shrub that gro*WS* 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. This plant is used in more than 200 formulations in Ayurveda, Unani and Siddha. *Acharya Charaka* included it in *Balya* and *Brimhana-gana* and attributed *Balya, Vrishya* and *Rasayana* properties to it. *Bhavmishra* suggested as substitute of *Kakoli* and *Kshirakakoli*. Earliest references of use of plants as medicine appear in *Rigveda* (3500–1600 B.C.).It is indicated in the management of various disease conditions like bronchial asthma, chronic fever, cold, cough, malaria, dysentery, convulsions, diabetes, diarrhoea, arthritis, emetic syndrome, skin diseases, insect bite, gastric ulcer, hepatic, cardiovascular and immunological disorders. The plant is claimed to have potent aphrodisiac, rejuvenator and life prolonging properties.

METHODS AND MATERIALS

The objective of this paper is to review the literature regarding *Ashwagandha* a commonly used herb in Ayurvedic medicine. Specifically, the literature was reviewed from classical ayurvedic texts, lexicons scientific literature, pharmacopeia's of India, various journals and monographs pertaining to chemical properties, therapeutic benefits, research activities and toxicity studies reported about *WS (Ashwagandha)*

ACTIVE CONSTITUENTS[1]

The major biochemical constituents of *Ashwagandha* root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides. More than 45 withanolides have been isolated from the leaves, fruits and roots of *Withania somnifera*.At present, 12 alkaloids, 35 withanolides, and several sitoindosides from this plant have been isolated and studied. The Indian chemotype has a withnolide content of 2-4% (dry roots), in which withaferin –A, withanolide A and withanone appear to be the major compounds amongst the non-glycosidal Withanolides. Much of *Ashwagandha*'s pharmacological activity has been attributed to two main Withanolides, withaferin A and Withanolides D. Specially mentioned compounds are withanoside IV,VI, sitoindoside –IX, X, coagulin-Q, viscosalactone-B, glycosides because of their biological activities.

PHARMACODYNAMIC PRINCIPLES AND INDICATIONS OF *ASHWAGANDHA* DESCRIBED IN AYURVEDIC CLASSICS

***Rasa* (taste)**	*Tikta-Katu-Madhura (Bitter,pungent-sweet)*
***Veerya* (Potency)**	*Ushna (Hot)*
***Vipaka* (Post digestive effect)**	*Madhura (Sweet)*
***Guna* (Quality)**	*Laghu, Snighdha (Light and unctuous)*
Synonyms	*Vajigandha, Hayamarak, Varahakarni, Varada, Kushthagandhini*
Indications	*Vatavyadhi , Shwitra, Shotha, Kshaya*
Action	*-Balya, Rasayana, Shukrala*

MECHANISMS OF ACTION AYURVEDIC

Madhur Rasa ,Vipaka* and *Ushna veerya	pacifies *Vata*
Tikta Kashaya Rasa* and *Ushna Veerya	pacifies *Kapha*
Madhur Vipaka	increases *Rasa* and specificaly *Mamsa Shukra*
Madhura Rasa* and *Vipaka	*Shukrajanana* effect
Ushna Veerya	*Shukrapravartana*

Thus for *Vajeekaran* (Spermatopoiesis)purpose drug has got prime importance and also the drug is most useful in *Vandhyatwa* (infertility)and *Dhatukshayaj vatavyadhi*(degenerative diseases).

RESEARCH

The Withanolides serve as important hormone precursors that can convert into human physiologic hormones as needed. *Ashwagandha* is thought to be amphoteric i.e., it can help to regulate important physiologic processes. The theory is that when there is an excess of a certain hormone, the plant-based hormone precursor occupies cell membrane receptor sites so the actual hormone cannot attach and exert its effect. If the hormone level is low, the plant-based hormone exerts a minimal effect.

EXPERIMENTAL PHARMACOLOGY

Table 1- In vitro studies on *Ashwagandha*

Activity	Study type details	Findings
Antioxidant[2]	*WS* glycowithanolides, orally 1 hr prior to the stress procedure (chronic footshock stress induced changes in rat brain frontal cortex and striatum) for 21 days, in the doses of 10, 20 and 50 mg/kg	Dose-related reversal of the stress effects was observed. Thus,*WS*G tended to normalise the augmented SOD and LPO activities and enhanced the activities of CAT and GPX indicating its antistress adaptogen effect.
Anti-tumor[3]	Withaferin A radiosensitizer ratio of 1:5 for *in vitro* cell killing of V79 Chinese hamster cell at a non-toxic concentration of about 2 mM/L.	Result suggestive of its antitumor activity as well as enhancement of the effects of radiation by *WS*.

TABLE 2: Activities evaluated on *Ashwagandha in vivo* models

No.	Activity	Study details	Result & discussion
1.	Adaptogen[4]	50% methanolic extract and Sitoindosides – VII and VIII(root) given an hour before experiment for a period of 21 days in the animals receiving a mild electric shock to their feet.	Resulting stress on the animals produced hyperglycemia, glucose intolerance, increase in plasma corticosterone levels, gastric ulcer, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression.*WS* significantly reduced level of stress.
2.	anti-arthritic and anti-inflammatory[5,6]	Powdered root of *WS* (1 g/kg suspended in 2% gum acacia, 50 mg/mL) was given orally one hour before the induction of inflammation by injection of Freund's complete adjuvant in rats and continued daily for three days; phenylbutazone (100mg/kg) was given as a positive control.	*WS* was found to cause considerable reduction in inflammation. Acute phase reactants of the blood monitored by crossed immunoelectrophoresis showed changes in the concentration of many serum proteins (α2-glycoprotein, major acute phase α1-protein, and pre-albumin) in the *WS* group. The α2-glycoprotein found only in inflamed rat serum was decreased to undetectable levels in the *WS* group.
		The doses of *WS* root powder were 500,	Maximum effect (about 75%) was seen at

		1000, 1500, or 1200 mg/kg given as suspension orally 3-4 hours prior to induction of inflammation.(by sub-plantar injection of carrageenan suspension)	1000 mg/kg. *WS* caused dose-dependent suppression of α2-macroglobulin (an indicator for anti-inflammatory drugs) in the serum of inflamed rats. .
3.	Anti-asthma[7]	Study carried out in 6 groups a)Control mice b) Asthmatic mice c) Mice exposed to physiologically comparable levels of *W. somnifera* (45µl/kg of body mass) d) Mice exposed to anti-oxidant (Selenium) (0.02µg/100µl) e)Mice exposed to combination *W. somnifera* and anti-oxidant (45 µl + 100µl) f)Mice exposed to low dose hydrocortisone (100mg/kg)	*WS* and *WS* combined with selenium significantly decreased the white blood cells in both bronchial lavage as well as blood smears, suggesting that drug has an anti-inflammatory potential and it, in combination with an anti-oxidant like selenium, might successfully be used in the treatment of asthma.
4.	Antidiabetic	200-400mg/kg of the aqueous root extract of *W.coagulans* (3.9% withaolides) given in streptozotocin induced diabetic rats rats after five weeks by 76-89%.	Normalize blood glucose by 76-89%, which correlated with improvements in oxidative biomarkers and pancreatic β-cell structure.[8a]
		WS(100-200mg/kg) root and leaf extract in alloxan induced diabetic rats oral after ingestion.	-Reduce adverse changes to glucose metabolism. -The higher dose of 200mg/kg was as effective as 0.6mg/kg glibenclamide (anti-diabetic drug) at reducing blood glucose and HbA1c (to near control levels, although not completely) and increasing hepatic liver glycogen and hemoglobin levels. A decrease in glucose-6-phosphatase activity is also seen in the livers of diabetic animals treated with *WS*, to a similar potency as glibenclamide.[8b]
		1000mg/kg of the dried fruits of *W.coagulans* (60% ethyl acetate extract)	is also effective in reducing blood glucose in streptozotocin induced diabetic mice with a potency comparable with 1mg/kg glipizide over four weeks.[8c]
5.	Anthelminthic	The hydroalcoholic extracts of *WS* and *Ocimum sanctum* at a dose of 40 mg/ml given to adult earthworm. Piperazine citrate (10 mg/ml) was used as a reference standard.	The time of paralysis was 2.5±0.6 and 2.8±0.8 whereas the time of death was 6.5±0.7and 7.1±0.9 in the case of Os and *WS* respectively. *WS* has anthelminthic activity as comparable with OS.[9]
6.	Antioxidant	Active glycowithanolides of *WS* (10 or 20 mg/kg intraperitoneally) were given once daily for 21 days to groups of six rats.	Dose-related increases in all enzymes like free-radical scavenging enzymes, superoxide dismutase(SOD), catalase (CAT), and glutathione peroxidase(GPX) levels in the rat brain frontal cortex and striatum were observed; the increases comparable to those seen with deprenyl (a known antioxidant) administration (2 g/kg/ day intraperitoneally). This implies that *WS* does have an antioxidant effect.[10]
7.	Antiparkinson's	*WS* at 100mg/kg was given alongside the paraquat for nine weeks in paraquat induced rat model of Parkinson	Appears to partially attenuate the alterations in motor performance and neurological inflammatory biomarkers relative to control in a time-dependent manner.[11a]
		Rats pretreated with 100-300mg/kg *WS* root for 21 days.	Subsequent changes in motor performance.[11a]

		At a dose of 200mg/kg and 300mg/kg	Performing equally and to about half preservation.[11a]
		100mg/kg for 7-28 days against MPTP toxicity in mice.	There was a slight preservation in dopamine concentrations in the mouse striatum after a week which did not increase in potency after a month; DOPAC and homovanillic acid were unaffected, and this minor buffering effect correlated with the preservation in glutathione concentrations.[11b]
8.	Antistress activity	Alcohol extract from defatted seeds of *WS* dissolved in normal saline was given (100 mg/kg intraperitoneally as a single dose) to 20-25g mice in a swimming performance test in water at 28º-30ºC. Controls were given saline	The extracts approximately doubled the swimming time when compared to controls.[12]
		The alcohol extract of *WS* (100 mg/ kg, twice daily orally on day 1, 4 or 7)	Reduced stress-induced increases in blood urea nitrogen levels, blood lactic acid, and adrenal hypertrophy, but did not affect changes in thymus weight and hyperglycemia in rats.[13]
		WS root powder (100 mg/kg orally as an aqueous suspension daily for seven days) given before the swimming test in water at 10ºC	Increased total swimming time, indicating better stress tolerance in rats. These results indicated a significant increase in plasma corticosterone level, phagocyte index, and avidity index in control rats, whereas these levels were near normal in *WS* rats subjected to the same test.[14]
9.	Anti-tumor	*WS* (ethanol extract of whole plant, 200 mg/kg daily orally for seven months) and urethane (125 mg/kg without food biweekly for 7 months) in urethane-induced lung adenomas in adult male albino mice.	Reduction in tumor incidence significantly (tumor incidence: untreated control- 0/25; urethane treated- 19/19; *WS* treated-0/26, and *WS* plus urethane treated, 6/24($p<0.05$). -In addition to providing protection from carcinogenic effects, *WS* treatment also reversed the adverse effects of urethane on total leukocyte count, lymphocyte count, body weight, and mortality.[15]
		Ethanol extract of *WS* root (400 mg/kg and up, daily for 15 days) after intra-dermal inoculation of 5x105 cells of S-180 in BALB/c mice	Complete regression of tumor after the initial growth. A 55-percent complete regression was obtained at 1000mg/kg; however, it was a lethal dose in some cases.[16]
10	Antitussive	The polysaccharide component of *WS* fed to guinea pigs at 50mg/kg and measured 30-300 minutes after oral intake	More effective than 10mg/kg codeine phosphate, but less effective than *glycyrrhiza glabra* Linn polysaccharide.[17]
11	Hutingtons disease	In a mouse model of Huntington's Disease induced by 3-nitropropionic acid, *WS* at 100-200mg/kg for two weeks alongside the 3-NP toxin was able to dose-dependently.	Attenuate alterations in motor function and body weight seen with 3-NP control, this was associated with reductions in lipid peroxidation and (at the higher dose) mild preservation of mitochondrial function.[18]
12	Nervous system effect	Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of cultivated variety of *WS* were studied on brain cholinergic, glutamatergic and GABAergic receptors in male wistar rats.	The compounds slightly enhanced acetylcholinesterase (AChE) activity in the lateral septum and globus pallidus, and decreased AChE activity in the vertical diagonal band.[19]
13	Thyrotropic effect.	Mice were given *WS* root extract (1.4 g/kg by gavage, daily for 20 days)	The treatment significantly increased the serum levels of triiodothyronine (T3) and tetraiodothyronine (T4).[20]

14	*Hepato-protective*	Withaferin A at 10mg/kg dose against CCl4-induced hepatotoxicity in rats.	*WS* significantly reduced hepatic lipid peroxidation and increased the activity of superoxide dismutase and catalase suggesting stimulant activity on thyroid and hepatic antioxidant. Significantly protective effect as effective as hydrocortisone of same dose.[21]
15	Immunomodulatory	Root extract 20mg/kg/animal i.p. 5 doses in babl/c mice	-Increase in WBC count on 10^{th} day 17125 cell/$mm^{3.}$ -Significant increased in bone marrow cellularity($27*10^6$ as well as alpha esterase cell no.(P less than 0.0001) -Enhancement in circulating antibody titre & number of plaque forming cells in spleen. -maximum plaque forming cells $985/10^6$ on 4^{th} day -Increase in phagocytic acticity in peritoneal macrophage(76.5 pigment cells/200) when compare to controle(31.5pigment/200).[22]
16	Anti-malarial	*WS* extracts were administered by intra gastric tube daily for four days starting from the day of Plasmodium berghei, 0.2 ml of x l0 (7) parasites inoculation with positive controls were given chloroquine	-Parasitemia percent inhibition of W. somnifera roots and root barks were 50.43% and 29.13% respectively, with 600 mg/kg dose. -Extracts of the leaves and root barks of W. somnifera showed parasite suppressive effect and a protective effect on PCV drop.[23]
17	Decreases libido	moderate dose in mice (25-50mg/kg bodyweight for 21 days)	Reductions in stress and decreases in the reductions in sexual activity induced by chronic stress; in a relatively dose-dependent manner.[24]
		3g/kg in mice daily	did note reductions in libido and larger dose has to used

TABLE 3: Clinical studies on *Ashwagandha*

No	Activity	Study details	Result
1	Anti-ageing	In a double-blind clinical trial,*WS* 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 Hb, RBC count, hair melanin, and seated stature was observed. Serum cholesterol decreased. ESR rate decreased significantly and 71.4 % reported improvement in sexual performance.[25]
2	Chondro-protective	Aqueous extract *WS* root powders (A and B at 0.05 mg/ml)	statistically significant, short-term chondro- protective activity in 50% of OA cases tested in an explants model of human OA cartilage damage.[26]
3	Chronic stress	*WS* extract of leaf & root in a dose of 125mg OD, 125 mg BD & 250 BD to randomizely assigned participant and placebo group. Stress level was assessed at 0,30 & 60^{th} day using modifies Hamilton scale	Between 0 & 60 the *WS*E 125mg OD group decreased significantly more than placebo for mean Hamilton score, serum cortisone, CRP, pulse rate blood pressure and increase significantly mean DHEAS and Hb. -Significant response in fasting blood sugar ,serum lipid profile and cardiac risk ratio.[27]
4	Hypotensive	51 stress-oriented hypertensive subjects in the age group of 40 to 70 years, selected by purposive sampling. Group I - 2gm of *WS* root powder. Group II- of 2gm of *WS* root powder with milk and water respectively in morning. Blood pressure was also	Overall decrease in systolic blood pressure was found though it was non- significant. Further, decrease in systolic blood pressure was significant in group I, whereas decrease in diastolic blood pressure was significant in both the groups. Hence, supplementation of *Ashwagandha* with

		recorded over a period of 3 months.	milk is recommended in treatment of stress- oriented hypertension.[28]
5	Anti-inflammatory	In a double-blind, placebo-controlled cross-over study, 42 patients with osteoarthritis were randomized to receive a formula containing *Ashwagandha*, turmeric, Boswellia and zinc complex or placebo for 3 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 (ESR) were noted.[29]
6	Spermatogenic	In a randomized clinical trial on 68 male patients having sperm count below 20 millions/ml were given root extract of 225mg of Ashwagandha thrice a day after meal for ninety days.	There was steady statistical significant improvement in sperm concentration (25.61 8.6 ± * 10^6 /ml), sperm volume (2.76 ±0.6 ml) and sperm motility (29.19 ± 6.31%) as compared to baseline values at zero day. Serum testosterone(5.72 ± 1.39 ng/ml, $p < 0.0001$)and serum LH level(5.31±1.33 mIU/ml, $p < 0.001$)were found significantly increased following the root extract treatment.[30]
7	Memory enhancer	Oral administration of root extract (50,100 & 200mg/kg)	Increase memory acquisition and retention in experimental mice.
8	Anti-anxiety	Root powder in dose of 3gm orally BD on 180 patients for 1 weeks	Effective results in generalized anxiety disorder in age group of 18-45years of either sex in comparison with placebo and jacobsons relaxation exercise.[31]
9	Prevention against lead toxicity	*WS* root extract	Capable in treating/preventing lead toxicity to certain extent. Thus, it appears likely that these dietary supplements could be beneficial for population in endemic areas against lead toxicity.[32]

PRECLINICAL SAFETY DATA[33]

The acute toxicity study showed that all the extracts of *WS* were safe upto 200 mg/kg body weight.[33a]

ACUTE TOXICITY

Root: [33b] Two-percent suspension of ashwagandholine (total alkaloids from the roots of *WS*) prepared in 10% propylene glycol using 2% gum acacia as suspending agent.

LD50: in rats - 465 mg/kg (332-651 mg/kg

in mice - 432 mg/kg (299-626mg/kg)

Seeds[33c]**:** an alcohol extract of defatted seeds of *WS* dissolved in normal saline. LD50: in albino mice 1750 +/- 41 mg (p.o).

CHRONIC TOXICITY STUDY

WS root decoction upto dose of 100mg/kg for 4 months

WS root decoction upto dose of 200mg/kg for 4 months found to be safe.[34d]

The activity of the *WS* extract was approximately equal to the *Panax ginseng* extract in a rat model of chronic stress without any side effects.[33e] No adverse events were reported with the use of up to 3g of *WS* extract tablets for a period of one year in human beings.[33f]

PHARMACOKINETIC PROPERTIES[34]

Administration of *WS* 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.

POSOLOGY

-A typical dose of *Ashwagandha* is 3-6 grams daily of the dried root.[35a]

- 1.5 % withanolides: 450-1350 mg per day

-8% withanolides: 200-250 mg per day.[35b]

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

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. [36]

CONTRAINDICATIONS

Patients with known allergies/hypersensitivities to *WS*, or to members of the Solanaceae. Large doses of *WS* may possess abortifacient properties; therefore, it should not be taken during pregnancy. Since *WS* acts as a mild central nervous system depressant, patients should avoid alcohol, sedatives, and other anxiolytic drugs while taking *WS*. [37]

CAUTION

Monitor patients with diabetes, or those using hypoglycaemic agents,*WS* is associated with glucose lowering effects as there is limited clinical data available about this aspect. [38]

DISCUSSION

In Ayurvedic classics, *Ashwagandha* is attributed with *Balya*, *Bruhana* and *Shukrala* activities. The drug has broad spectrum activities and proven its efficiency from pediatric to geriatric disorders. Its considered as a safe remedy and as a tonic in geriatrics. The classics have described drugs mostly in the management of *Vatavyadhi*, *Vandhyatwa* and as a *Balya* but the analysis of various pharmacological and clinical data indicates that *WS* root is reported to possess activities like Immunomodulation, antioxidant, health tonic, adaptogenic, chemoprotective ,hepatoprotective, anticancer activities.*WS* sho*WS* a great potential as a safe and effective in immunomodulation, hematopoietic and hormonal changes. Its activities on male and female infertility, anti-inflammatory, analgesic, cardiovascular protectant, CNS protectant, mental functions enhancer, adaptogenic and immunomodulatory are proven both by experimentally as well as clinically.

The drug plays a key role in the management of lifestyle diseases like hypothyroidism, depression, insomnia, Ulcers, asthma etc. Experimentally, it has also been proven safe against occupational disease like lead toxicity; still a large scale clinical trial on industrialized area workers is a needed to support the data. More clinical researches are needed to determine that *WS* can duplicate the chemoprotective, hepatoprotective and hormonal activities in humans with specified biological markers and to decide an optimal dosage range for achieving these effects. In Parkinson's disease, the drug has good response in clinical signs like tremors, stiffness, bradycardia etc.

As the drug has proven preventive effect against lead toxicity, it can be thought of giving as an *Anupana* of *Rasakalapa* containing lead when long term administration is advised.

CONCLUSION

From the studies reported, it can be concluded that drug decreases biomarkers like total cholesterol, triglycerides, LDL, BSL, Serum cortisone, CRP and increases Hb, RBC, LH, Testosterone, seminal motility, serum DHEA, natural killer cells, HDL etc. The potential beneficial effects

of *WS* in anxiety, cognitive and neurological disorders, inflammation and Parkinson's disease should be assessed on larger patient population through randomized control clinical trials.

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