Studies of Ashwagandha (*Withania somnifera* Dunal)

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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, cardoprotective, 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].
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 pharmacognostic 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), Shosha (cachexia), Unmada (mania/psychosis), for Murchha (syncope), Apasmara (epilepsy), In Ayurvedic classics, Ashwagandha is indicated. Acquired were presented in concise form. Medicinal plants were reviewed critically and data databases, texts and research journals on Ayurvedic classical texts, compendia, lexicons, Ayurvedic, experimental and clinical aspects. Have been made to review Ashwagandha with pharmcognostic and pharmacological (in vitro) profiles. Keep this in view, attempt has been made to review Ashwagandha with Ashwagandha with in vitro pharmacological and in vivo pharmacological activity. In Vivo models have been conducted to evaluate it efficacy on different biological systems. Activities screened are presented in bellow tables.

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. 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.

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.

| Major Chemical Constituents |
| Phytochemical contents |

<p>| Table 1: Activities screened on In vitro models |</p>
<table>
<thead>
<tr>
<th>Effects/activity</th>
<th>Active constituents</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>Withaferin –A</td>
<td>A. Bhattacharya et al[13]</td>
</tr>
<tr>
<td></td>
<td>Methanolic extract</td>
<td>A. russo et al[14]</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Withanolides</td>
<td>V. Bahr, R. Hansel et al[15]</td>
</tr>
<tr>
<td></td>
<td>Aqueous extract</td>
<td>M. Gautam et al[16]</td>
</tr>
<tr>
<td></td>
<td>Glycowithanolides</td>
<td>V. Bahr, R. Hansel et al[17]</td>
</tr>
<tr>
<td></td>
<td>70% ethanolic extract</td>
<td>L. Davis, G. Kuttan et al[18]</td>
</tr>
<tr>
<td>Relaxant and antispasmodic effects and direct musculotropic action</td>
<td>The total alkaloids of Ashwagandha</td>
<td>The WO1-1982[19]</td>
</tr>
<tr>
<td>Chondroprotective</td>
<td>aqueous extracts of Withania somnifera root powder</td>
<td>Venil N Sumantran. [20]</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Somasundaram S[21]</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Table 2: Activities evaluated on In Vivo models |</p>
<table>
<thead>
<tr>
<th>S. No</th>
<th>Effects/activity</th>
<th>Part used</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Depressant effect (tranquillizer-sedative type)</td>
<td>Total alkaloids</td>
<td>Rastogi RP[22]</td>
</tr>
<tr>
<td>2</td>
<td>Adaptogenic</td>
<td>50% methanolic extract and Sitoindosides – VII and VIII(root)</td>
<td>S.K.Bhattacharya et al[23]</td>
</tr>
</tbody>
</table>
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. LD50s 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 up to 200 mg/kg body weight. [73]

LD50 was recorded in rats - 465 mg/kg (332-651 mg/kg) and in mice - 432 mg/kg (299-626 mg/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 2 months 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 compared 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 0 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 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 extract 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 hypcholesterolemic effect
Hypoglycemic, diuretic, and hypcholesterolemic effects of Ashwagandha root were assessed in human subjects, in which six type 2 diabetes mellitus subjects and six mildly hypercholesterolemic 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 and 3 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 (*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 (Erythrocyte 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 ethnomedicinal 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 Ashwagandha is reported having Shothahara, Vedanasthapana, Mastishkashamaka, Deepana, Anulomana, Shoolaprashtmana, Krimighna, Raktashodhaka, Kaphaghna, Shwasahara, Vajikarana, Garbashayashothahara, 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 maintenance of positive health.

REFERENCE


