सत्यमेव जयते

Ministry of Ayush

Government of India

Ashwagandha

(Withania somnifera)

Safety Dossier 2.0

Ashwagandha (Withania somnifera) is a herb that has been used since times immemorial for its health benefits. This dossier is a comprehensive review of literature related to Ashwagandha and its safety.

Ashwagandha

(Withania somnifera)

Safety Dossier 2.0

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Background

Ashwagandha (*Withania somnifera*) is a herb that has been used since times immemorial for its health benefits. During the COVID-19 pandemic, its use surged as a herbal supplement, particularly valued for its adaptogenic and immune-boosting properties. *Withania somnifera*) is the most widespread species in the genus and it occurs naturally in semi-arid and drier regions stretching from the Mediterranean across tropical Africa, South Africa, and the Canary and Cape Verde Islands, as well as Afghanistan, Baluchistan, Pakistan, Sri Lanka, China, Nepal and India. It is also grown in gardens in warmer parts of Europe and has emerged as a natural weed in South Australia and New South Wales (Paul et al 2021). Ashwagandha has been trusted for its preventive, promotive, and therapeutic applications. In recent years, modern research has further validated these traditional claims. In 2023, the Ministry of Ayush released the first version of this dossier. This updated dossier embraces all relevant studies published to date, focusing specifically on the safety aspect Ashwagandha.

The primary goal of this safety dossier is to consolidate current evidence-based knowledge about Ashwagandha root, making it accessible to academicians, researchers, practitioners of both conventional and traditional medicine, policymakers, and the general public. Unless specifically indicated, the dossier describes the Ashwagandha root alone. The need for this dossier partly arises from concerns certain bodies regulatory bodies regarding the potential adverse effects of Ashwagandha on human health. Herbal and natural products often face scrutiny from conventional medical practitioners, driven by rigorous scientific inquiry or a cautious attitude toward the unfamiliar.

An important aspect to consider is the part of the Ashwagandha plant used. Traditionally, the root is the recommended part for human use. However, other parts, such as the leaves, have been used with less favorable outcomes. This dossier focuses on root preparations, excluding multi-herbal or multi-part preparations of Ashwagandha that include other plant components. References to poly-herbal preparations containing Ashwagandha are limited due to the difficulty in ascribing the efficacy and safety of individual herbs.

In preparing this dossier, the expert committee has relied primarily on original research published till May 2024 in indexed journals. The committee has strived to include the most reliable and credible scientific information to make this document a comprehensive account of the topic, without compromising its scientific integrity.

Introduction

Ashwagandha is one of the most widely used herbs in Indian traditional systems of medicine including Ayurveda, Siddha, Sowa Rigpa, Unani, and Homeopathy (ASU&H) with a variety of medicinal effects attributed to its multi-dimensional uses. The plant botanically identified as *Withania somnifera* (L.) Dunal (Family- Solanaceae) is a small perennial herb with white flowers and orange-red berries commonly found in warmer regions of India. The plant is also known as "Indian winter cherry" and "Indian ginseng".

Ashwagandha root has been documented to be used in Indian traditional medicine since 1000-1500 BC and is recognized for its diverse pharmacological profile encompassing adaptogenic, immunomodulatory, rejuvenative, and aphrodisiac properties. It is extensively documented in Ayurvedic texts as *Rasayana,* which means beneficial for rejuvenation, immunomodulation, and longevity, and also for treating several health conditions including but not limited to musculoskeletal, neurological, dermatological, respiratory and reproductive system disorders (**Balasubramani et al 2011**).

Pharmacologically, Ashwagandha is characterized by a rich content of *withanolides* glycosides, *withanolide aglycones*, and alkaloids, contributing to its wide-ranging bioactivities including antioxidant, adaptogenic, immunomodulatory, anti-arthritic, anti-osteoporotic, hepatoprotective, nephroprotective, and antidiabetic effects (**Dar et al 2015**). The therapeutic versatility of Ashwagandha is further evidenced by its incorporation into numerous dosage forms - powders, tablets, capsules, liquids, and topical through various routes of administration.

Ashwagandha root is recognized for its broad spectrum of pharmacological properties that are well-supported not only by traditional medicine text but also by modern scientific research. Its adaptogenic qualities make it particularly effective in stress management, improving mental clarity, and reducing anxiety. As a potent antioxidant, it helps combat oxidative stress and mitigate cellular damage linked to aging and diseases. Significant improvements in cognitive function have been observed as a result of the inhibition of amyloid β-42, and a reduction in pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and MCP-1, nitric oxide, and lipid peroxidation (**Pandey et. al. 2018**). The anti-inflammatory effects of Ashwagandha make it beneficial for conditions such as arthritis, while its anxiolytic and antidepressant properties aid in managing anxiety and depression by modulating the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, Ashwagandha favorably modulates immune function by modulating immune pathways and white blood cell production. Neuroprotective effects suggest its utility in combating neurodegenerative diseases by promoting nerve cell growth and cognitive function. The root extract of Ashwagandha led to increased VO2 max, enhanced cardiorespiratory endurance, and improved QOL in healthy athletic adults. (**Choudhary et al 2015**). This herb also exhibits significant potential in improving cardiovascular (**Choudhary et al 2015; Shenoy et al 2012**), metabolic (**Andallu and**

Radhika, 2000), and endocrine health (**Ambiye et al 2013; Gupta et al 2013; Mahdi et al 2009**), demonstrating cardioprotective (**Mohanty et al 2004**), anti-diabetic (**Nayak et al 2015**), and thyroid-regulating effects (**Sharma et al 2018**) respectively. These diverse benefits highlight Ashwagandha's role as a valuable natural remedy, adaptable to a variety of therapeutic applications.

Clinical trials focusing on conditions such as stress and anxiety (**Choudhary et al 2017b**), sleep disturbances (**Langade et al 2019**), cognitive functions (**Choudhary et al 2017a**), rheumatoid arthritis (**Khan et al 2015**), osteoarthritis, hypercholesterolemia (**Andallu and Radhika, 2000**), muscle strength (**Choudhary et al 2015**; **Wankhede et al 2015**) and menopausal symptoms (**Gopal et al 2021**) emphasize its value in both traditional and contemporary medicinal practices. During the recent pandemic of COVID-19, Ashwagandha roots were evaluated for the management and prophylaxis of COVID-19, which further proposes a hypothesis of adaptogenic and immunomodulatory properties of the herb (**Saggam et al 2021**). Ashwagandha is not only effective but also considered safe for various health applications, supported by its long-standing use in traditional medicine and modern scientific validation.

Technical Specifications

General Information

Scientific name:	*Withania somnifera* (L.) Dunal
Family:	Solanaceae
Part used:	Root of *Withania somnifera* (L.) Dunal plant (API, vol. III)
Distribution and Habitat:	*Withania somnifera* is the most widespread species in the genus and it occurs naturally in semi-arid and drier regions

Names in AYUSH Systems of Medicine

Ayurveda*:*	*Ashwagandha*
Unani*:*	*Asgand*
Siddha*:*	*Amukkarā*
Homeopathy:	*Withania somnifera*
Sowa-Rigpa:	*Ba-dzi-gandha*
Dose:	
Ayurveda:	3-6 g powder (API Part I, vol. VIII)
Siddha:	3-6 g powder (SPI Part I, vol. I)
Unani:	5-10 g powder (UPI Part I, vol. I)
Homeopathy:	Mother Tincture Ø Drug strength 1/10, Homoeopathic Pharmacopoeia of India. vol. x)

Chemical Composition:

Various preliminary phytochemical screenings revealed the presence of several compounds including steroidal lactones, alkaloids, saponins, flavonoids, tannins, starch, phenolic compounds, carbohydrates, withanolides, sitoindosides, anaferine, anahygrine, ß-sitosterol, chlorogenic acid, cysteine, cuscohygrine, pseudotropine, withanine, scopoletin, withananine, somniferinine, somniferiene, tropanol, 14-α-hydroxywithanone, and 6,7β-Epoxywithanon (**Saleem et al., 2020**).

Regulatory Requirements

Ashwagandha, known for its adaptogenic and therapeutic properties, must comply with specific regulatory standards for contaminants to ensure product safety and quality. Various countries have established permissible limits for heavy metals, aflatoxins, and microbial contaminants. These standards are designed to minimize health risks and ensure the consistency and reliability of herbal supplements. The permissible limits are defined by the U.S. Pharmacopeia (USP), the European Union (EU), and Indian regulations for heavy metals, aflatoxins, and microbial contaminants in dietary supplements **(Annexure 1)**.

Safety Profile of Ashwagandha

Thousands of years of use in traditional medicine and available scientific evidence demonstrate that Ashwagandha is well-tolerated, safe, and clinically effective. The data obtained from various studies did not demonstrate any serious adverse events.

Despite of its extensive usage and clinical evidence, safety concerns have been noticed in recent times from a few quarters. The evidence for the safety of Ashwagandha is further evaluated through the various studies published recently (more than 500 PubMed-indexed citations). In the succeeding sections of this dossier, the safety concerns on the liver, thyroid, sex hormones, immunomodulatory, central nervous system, and abortifacient activities have been addressed based on available studies.

Summary of pre-clinical studies of Ashwagandha

There are numerous studies conducted to evaluate the safety of Ashwagandha root extract. These studies cover various toxicological evaluations, including acute, sub-acute, 90-day repeated dose toxicity, mutagenicity/genotoxicity, and prenatal developmental toxicity assessments. The findings consistently indicate that Ashwagandha root extracts, administered in various dosages up to 2000 mg/kg, exhibited no evidence of morbidity, mortality, or toxicologically relevant clinical signs in animal models. Thus, the root extract has proven to be safe and well-tolerated. The table below summarizes these comprehensive pre-clinical studies.

S.no	Reference	Experimental Model	Ashwagandha formulation	Conclusion
Acute Toxicity studies (Single dose studies)				
1.	Khojah EY et al., 2020	Male albino mice	Root extract	No toxicity was observed even at 2000 mg/kg.
	Patel SB et al., 2016	Wistar rats	Root extract	No toxicologically significant changes were observed. NOAEL was determined to be 2000 mg/kg.
	Prabu PC et al., 2013	Wistar rats	Hydroalcoholic root extract	No toxicity was observed even at 2000 mg/kg.
	Jain H et al., 2010	Mice	Hydroalcoholic extract of roots	2000 mg/kg dose is considered safe. No mortality or gross behavioral changes were observed
Sub-acute toxicity studies (Repeated dosing for 14 to 28 days)				
2.	Kalaivani et al., 2024	Nulliparous and non-pregnant Wistar Albino rats	Standardized aqueous root extract	No mortality, morbidity, or toxicity. No effects on body weight, feed consumption, organ weights, or gross pathology. The extract was well tolerated up to 2000 mg/kg for 14 days
	Langade et al., 2023	Wistar rats	Standardized aqueous root extract	No signs of intoxication. Vital liver parameters remained stable, and no abnormalities in general parameters. All hematological and biochemical parameters were within normal range, indicating safety in 28 days study
	Khojah EY et al., 2020	Male albino mice	Root extract	No toxicity was observed even at 2000 mg/kg in 28 days study
	Prabu PC et al., 2013	Wistar rats	Hydroalcoholic extract of roots	No toxic signs or mortality. No significant changes in body weights, organ weights, or haemato-biochemical parameters. NOAEL was determined to be 2000 mg/kg in 28 days study

S.no	Reference	Experimental Model	Ashwagandha formulation	Conclusion
	Patel SB et al., 2016	Wistar rats	Root extract	No toxicologically significant changes were observed. NOAEL was determined to be 2000 mg/kg. The extract showed no adverse effects even after a 14-day recovery period following 28 days of administration.
90-day Repeated Dose Toxicity studies				
3.	Kalaivani et al., 2023	Nulliparous and non-pregnant Wistar Albino rats	Root extract	No morbidity, mortality, or clinical toxicity. No adverse effects on body weight, food consumption, blood indices, or liver histopathology. NOAEL was determined to be 2000 mg/kg.
Mutagenicity/Genotoxicity Test				
4.	Kalaivani et al., 2023	Swiss Albino mice & Various in vitro genotoxicity models	Root extract	The results demonstrated Ashwagandha root extract failed to show any mutagenic effects up to a dose of 5 mg/plate in the Bacterial reverse mutation test, and did not show any clastogenic activity in doses up to 2 mg/ml in chromosome aberration (CA) test with and without metabolic activation. Also, in the In vivo micronucleus test Ashwagandha root extract at doses up to 2000 mg/kg body weight showed no evidence of clastogenic activity or cytogenetic damage in the bone marrow erythrocytes of Swiss albino mice
Prenatal and Developmental Toxicity Study				
5.	Prabu PC et al., 2015	Wistar rats	Root extract	No maternal or fetal toxicity was observed. The extract did not affect body weight, number of viable fetuses, or cause malformations. NOAEL was determined to be 2000 mg/kg.

Effect of Ashwagandha on pregnancy, fetal development, and female sexual health

The safety of Ashwagandha during pregnancy and fetal development has been evaluated in the following studies:

Reference	Description of the study	Study type	Nature of Evidence	Conclusions
Kalaivani et al 2023	90-days toxicity Wistar Albino rats, Root extract 2000 mg/kg/day	Controlled Pre-Clinical	90-days toxicity study	Histopathology of ovaries and uterus with cervix and vaginal cytology was observed in female animals of all the groups on day 91 and in the recovery group on day 105 in the control and high dose (2000 mg/kg/day) groups. The microscopic examination did not reveal any test item related histopathological finding in any of the animals when compared with animals of the control group.
Prabu et al 2015	Pregnant rats Root extract Up to 2000 mg/kg/day	Pre-clinical	Maternal & fetal toxicity	No evidence of maternal or fetal toxicity was observed. Root extract caused no changes in the body weight of parental females, number of corpora lutea, implantations, viable fetuses, external, skeletal, and visceral malformations.
Smith et al 2023	Root extract, 400 mg/day,	Randomized, double-blind, placebo-controlled Clinical trial	Safety and Efficacy	Reported a slight increase in serum estradiol level, however, the estradiol remained within the normal range.
Gopal et al 2021	300mg Root Extract in perimenopausal women for 8 weeks	Randomized, double-blind, placebo-controlled Clinical trial	Safety and Efficacy	There was a reduction in MENQoL score, hot flash score, serum FSH, and serum LH and an increase in serum estradiol level.
Ajgaonkar et al 2022	300mg Root Extract in women with Hypoactive sexual desire disorder (HSDD)	Prospective, Randomized, Placebo-controlled Clinical Study	Safety and Efficacy	Reported improvement in sexual functions.

However, the World Health Organization (2009) in its monograph on Ashwagandha mentioned that there is a lack of safety data and cautioned its use during pregnancy or breastfeeding as cited from the American Herbal Pharmacopoeia Ashwagandha Root Monograph and Therapeutic Compendium (2000).

Further, Roy Upton, President of American Herbal Pharmacopoeia, recently stated that 'earlier cautions regarding the use of Ashwagandha in pregnancy and its claimed use as an abortifacient were based on anecdotal reports from the ethnobotanical literature that provided no indication that such an effect was evident. The misrepresentation of the AHP monograph has been repeated uncritically resulting in the misconception that Ashwagandha root is potentially unsafe.' On the contrary, he quoted that 'based on a critical and comprehensive review of the traditional and modern literature, as well as the opinion of the majority of experts, there is no evidence of an abortifacient effect of Ashwagandha root.' Adequate caution is warranted when using any substance during pregnancy, there is no experimental or clinical study that has reported such an effect **(Annexure 2)**.

The American Herbal Products Association's Botanical Safety Handbook (BSH) reclassified its safety Class from 2d to 1 based on new studies and affirmed the reproductive safety of Ashwagandha in 2022. BSH Class 1 signifies that a plant is considered safe when used appropriately.

Published preclinical and clinical studies have reported no adverse effects on female sex organs, pregnancy or fetal development in the recommended doses.

Effect of Ashwagandha on male reproductive system

There are multiple reports, exploring the therapeutic potential of Ashwagandha roots for reproductive system disorders e.g. infertility, problems with ejaculation, testicular failure, and abnormal volume and/or quality of semen. Some of the published studies are reported below. It would be pertinent to mention that the results of the recommended part of the herb i.e. roots are different from other plant parts and hence one should be careful in interpreting the results of other plant parts and assuming the same results for the root.

Pre-clinical studies (on Root):

S.No	Reference	Ashwagandha Formulation with Dose	Experimental Model	Conclusions
1	Yadav A et al 2024	Purified root powder, 150 and 300 mg/kg/ day for 30 days	Stressed and sexually sluggish male rats	Improvements in sexual activities, increased frequencies of erections, mounts, intromissions, and ejaculations, and positive influence on neurotransmitter and hormone levels linked to sexual desire and stress management. A dose-dependent increase in serum LH, FSH, and testosterone levels.
2	Sahin et al 2016	Root extract, 300 mg/ kg/day for 8 weeks	Sprague-Dawley male rats	No effect on the weight of testes, epididymis, vas deferens, ventral prostate; Increased mounting & intromission frequency, sperm count & motility, serum testosterone; activated Nrf2/ HO-1 pathway while inhibiting NF-κB levels. No effect on testes histopathology & sperm morphology
3	Rahmati et al 2016	Root powder mixed pelleted food, 6.25% w/w (equivalent to 300 mg/kg/day) for 21 days	Morphine-addicted male rats	Morphine addiction reduces the level of testosterone, LH, and estrogen without any effect on FSH and progesterone. Ashwagandha restored testosterone, LH, and estrogen levels to normal levels
4	Kumar A et al 2015	Root extract, 100 mg/ kg body weight; for 30 days	Arsenic-induced testicular toxicity in Male Charles Foster rats	Significant ameliorative effects; improved sperm counts, sperm motility, hormonal balance, and reduced lipid peroxidation; restored testicular histology.
5	Ganu et al 2010	Root powder; up to 400 mg/kg/day for 4 weeks	Male Wistar rats	Sperm cells improved; mating behavior improved; Testes & prostate weight increased
6	Kiasalari et al2009	Root powder Mixed pelleted food, 6.25% for 4 weeks	Streptozotocin induced diabetic male Wistar rats	WS was effective in lowering FSH serum levels in both diabetic and non-diabetic groups while increasing progesterone, testosterone, and LH levels in non-diabetic treated animals. Ashwagandha also reversed the reductive effect of diabetes on progesterone.

Clinical Studies

Several clinical studies have supported the per-clinical finding Regarding the safety of Ashwagandha on the male reproductive system. A summary of few such studies is recapitulate below.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events	Summary of results
Male Sexual Function and Fertility, Ambiye et al., 2013 (India)	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Infertile men / aged between 22 and 40 years Ashwagandha (n=21, 21), Placebo (n=25, 25)	225mg - Standardized Aqueous Ashwagandha Root Extract Thrice daily	Semen Parameters, Serum Testosterone, Serum Luteinizing Hormone	Ashwagandha (0) Placebo (0) The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.	Ashwagandha is associated with significant increase in sperm concentration, semen volume, sperm motility, serum testosterone, and LH. No changes occurred in the placebo group
Male Sexual Function, Chauhan et al 2022 (India)	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Males aged between 21 and 45 years with low sexual desire Ashwagandha (n=25, 25), Placebo (n=25, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	DISF-M, Serum Testosterone, PRL, SF-36	Ashwagandha (4 - Sleepiness, Mild Abdominal Pain, Low-Grade Joint Pain) Placebo (3 - Abdominal Pain, Mild Diarrhea)	Compared to the placebo, Ashwagandha was associated with significantly greater increase in Total DISF-M scores and serum testosterone levels. The reported adverse events were of mild severity and no intervention was required.
Idiopathic Male infertility Azgomi et al 2018a (Iran)	Triple-blind, Randomised, Parallel Group, Two Arm, clinical trial. 12 Weeks	Married infertile male patients aged between 18 and 45 years Ashwagandha (n=50, 46) Pentoxifyline (n=50, 45)	6 capsules containing 5 g Hydroalcoholi-cAshwagandha root extract once daily 6 capsules con-taining 800 mg Pentoxifylline once daily	Sperm parameters	Ashwagandha (1 - nausea and epigastric pain) Pentoxifyline (3 - nausea and epigastric pain) These events were resolved without any intervention and participants continued the study treatments till the end of the study.	Within group Ashwagandha markedly in-creased mean sperm count, progressive motil-ity, and improved sperm morphol-ogy. However, the impacts of the two medications were not significantly different.
Seminal plasma metabolites of infertile males Gupta et al 2013 (India)	Clinical Study 12 Weeks	Infertile males aged 22–45 years Ashwagandha (n=180) Control (n=50)	Withania somnifera root powder (WSR) 5 g/day	Semen Profile, Testosterone, LH, FSH, PRL, IDH, LDH, ALT, AST	Ashwagandha (0) Control(0) The safety of Ashwagandha was confirmed as there were no adverse events reported and Ashwagandha was well tolerated by all the participants.	Compared to the baseline, WSR repairs the disturbed concentrations of lactate, alanine, citrate, GPC, histidine, and phenylalanine in seminal plasma and recovers the quality of semen. Serum biochemistry was also improved over post therapy.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events	Summary of results
Psychogenic erectile dysfunction Mamidi et al 2011 (India)	Randomized, Single-blind, Placebo-controlled, parallel-group study. 8 Weeks	Patients with psychogenic erectile dysfunction aged between 18 - 60 years Ashwagandha (n=46, 41) Placebo (n=49, 45)	4 tablets 500mg Ashwagandha root powder - thrice daily	Semen analysis, Routine Hematological tests, Biochemical Investigations, Serum Testosterone	Ashwagandha (0) Placebo (0) Ashwagandha was well tolerated by all the participants.	Compared to the baseline there was significant improvement in IIEF items, but the result was insignificant when compared to placebo.
Stress and Fatigue Smith et al 2023 (Australia)	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Healthy Adults aged between 40 and 75 years Ashwagandha (n=60, 55), Placebo (n=60, 56)	200 mg - HydroalcoholicAshwagandha root extract - twice daily	PSS, CFS PROMIS-29, Sex hormone concentrations, MDA, FG, HbA1c, TSH, HRV, Grip strength, Anthropometric measures, LFT, RFT, FBC	Ashwagandha (13 - Digestive disturbances, Mood disturbances/ changes, Headaches/ migraines, Increased appetite, Increased tiredness) Placebo (15 - Digestive disturbances, Mood disturbances/ changes, Headaches/ migraines, Increased appetite, Itchy Skin, Increased tiredness) The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.	In the Ashwagandha group, there was a significant increase in the blood concentrations of free testosterone and luteinizing hormone compared to the placebo group. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study.
Muscle Strength and Recovery Wankhede et al 2015	Randomized, double-blind, placebo-controlled clinical study 8-week	Healthy males aged between 18 and 50 years Ashwagandha (n=29), Placebo (n=28)	Standardized Aqueous Ashwagandha Root Extract 300mg twice daily	Serum Testosterone	Ashwagandha (0) Placebo (0)	The serum testosterone level was significantly increased in the Ashwagandha group as compared to placebo control.
Semen Quality, and Reproductive hormone levels Ahmad et al 2010	Prospective Clinical Study 3 Months	infertile males and matched healthy controls aged 25–40 years Ashwagandha (n=75) Control (n=75)	Withaniasomnifera root powder (5 g/day)	Semen profile, Oxidative biomarkers, Reproductive hormone levels	Ashwagandha (0) Control (0) The safety of Ashwagandha was confirmed and Ashwagandha was well tolerated by all the participants.	The treatment with Ashwagandha significantly increased serum testosterone and LH and reduced the levels of FSH and PRL

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events	Summary of results
Semen Quality in Stress-Related Male Fertility Mahdi et al 2011	Clinical study	Normozoospermic but infertile individuals (n=60) and Normozoospermic fertile men (n=60) as controls	Root powder of W. somnifera 5 g/day for 3 months	Biochemical and stress parameters including Serum testosterone (T), LH, FSH and PRL	Not Reported	Treatment resulted in a decrease in stress, improved the level of anti-oxidants and improved overall semen quality in a significant number of individuals. The treatment resulted in pregnancy in the partners of 14% of the patients.

The above studies convincingly conclude the clinical safety and positive effects of Ashwagandha roots on male reproductive system.

Effect of Ashwagandha on Thyroid Gland

Ashwagandha is reported in several studies to restore thyroid hormone levels to near normal in experimental models of hypothyroidism. Summary of few such studies is recapitulated below:

S.No	Reference	Ashwagandha Formulation with Dose	Experimental Model	Conclusions
1	Hosny et al 2021	Ashwagandha root extract (AE), 500 mg/kg	Propylthiouracil-induced thyroid dysfunction in male Wistar Albino rats	Restored T3 and T4 levels, improved oxidative stress markers, reduced hippocampal TNF-α levels, and reduced nervous system complications.
2	Abdel-Wahhab et al 2019	Ashwagandha methanolic extract (AME), 500 mg/kg/day	Male albino rats with hypothyroidism induced by propylthiouracil	Improved thyroid hormones to near-normal levels, reduced oxidative stress markers, and ameliorated histopathological changes in the thyroid gland.
3	Panda and Kar, 1998	Ashwagandha root extract, 1.4g/kg/day, for 20 days	20 adult healthy Swiss albino male mice	Increased levels of T4 and T3 and antioxidant enzymes in the liver. Reduced hepatic lipid peroxidation.
4	Panda and Kar, 1999	Ashwagandha root extract (1.4 g/kg body weight)	28 adult healthy Swiss albino female mice	Increased T4 but not T3 level. Decreased lipid peroxidation and increased levels of antioxidant enzymes.

In a recently published study, **Kalaivani et al 2023**, evaluated Ashwagandha root extract, up to 2000 mg/kg/day p.o.) in a 90-day toxicity study in 100 non-pregnant Wistar Albino rats. There was no effect on thyroid hormones including TSH, T3, and T4. Notably, no abnormalities were detected in the histopathology examination of several tissues.

This study thus adds important information to the studies by **Abdel-Wahhab et al 2019, Panda and Kar (1998 and 1999)** that are listed in above Table. Ashwagandha root extract improved thyroid hormone levels, but none of these studies reported levels exceeding the normal physiological range.

These studies suggest that though Ashwagandha has the potential to increase thyroid hormone levels, one may, however, doubt whether the findings by Panda and Kar and the observation that Ashwagandha counteracts propylthiouracil-induced thyroid dysfunction signal an increased risk of inducing hyperthyroidism. All changes in thyroid hormone levels were within the physiological range and there was no abnormality in thyroid gland histopathology findings.

Vaidya VG et al 2024, undertook a non-randomized, open-label, single-treatment clinical study conducted over 4 weeks to evaluate the safety of hydroalcoholic Ashwagandha root extract

with 18 healthy male participants. Ashwagandha was administered at a dosage of 500 mg twice daily (1000mg/day). The serum thyroid hormones TSH, T3, and T4 levels after 30 days of treatment remained within normal values, leading authors to conclude that Ashwagandha root extract is safe and well-tolerated by healthy human subjects.

In another randomized, double-blind, placebo-controlled, and parallel-group clinical study by **Verma et al 2021,** conducted on 80 healthy individuals, Ashwagandha 600 mg/day supplementation for 8 weeks, showed no statistically significant change or abnormality observed in serum thyroid hormones.

In a clinical trial of 50 subjects **(Sharma et al 2018)** with hypothyroidism, Ashwagandha root extract 600 mg/day for 8 weeks improved the serum levels of thyroid hormones (TSH, T3, and T4) near to normal levels.

None of the subjects in these clinical studies reported that thyroid hormones increased beyond normal levels.

Two experimental papers by **Panda & Kar (1998 and 1999),** showed that aqueous root extract increased the T4 (in males and females) and T3 (in females) in mice fed Ashwagandha 1.4 g/kg/day for 20 days. In another study by **Abdel-Wahhab et al 2019** where root extract normalized T3, T4, and TSH values in chemically-induced hypothyroidism in rats, the concern was that in normal rats, root extract increased the level of serum free T3. However, it must be noted that all the changes seen in free T3/T4 levels were within normal limits and there was no sign of hyperthyroidism.

Further, a case report by **van der Hooft 2005** reported thyrotoxicosis with low TSH and increased T4 level in a 32-year-old healthy female taking Ashwagandha for fatigue. In a clinical trial of 50 subjects **(Sharma et al 2018)** with hypothyroidism, where Ashwagandha root extract 600 mg daily was administered for 8 weeks, improved the serum levels of thyroid hormones (TSH, T3, and T4) near to normal levels. In none of the subjects, the thyroid hormones increased beyond normal levels. Recently, a couple of case reports have described thyroid hormone imbalance, probably linked to Ashwagandha. **Hayashi et al 2024** from Japan reported that in a 47-year-old bodybuilder, thyrotoxicosis developed after 2 months of Ashwagandha which was reversed on discontinuation of the herb. In another case report from **Kamal et al 2022**, From the USA, a 73-year-old female taking Ashwagandha for hyperthyroidism for 2 years, developed low TSH levels but a normal range of serum T3 and T4 levels and increased Thyroid microsomal antibody representing Hashimoto thyroiditis.

Such rare instances reported in case reports do not mention co-morbidity, concomitant medications, and other confounders, hence the findings may be attributed to dosing rationale and individual idiosyncrasies.

Can Ashwagandha be linked to hyperthyroidism as claimed in a few reports?

The central question is if Ashwagandha has any direct or indirect effect on the thyroid gland or thyroid hormone release and can cause thyrotoxicosis as a side effect?

The 90-day repeated dose toxicity at a high dose level of 2000 mg/kg/day did not show any changes in serum thyroid hormone levels in normal healthy rats and the histopathology findings were normal **(Kalaivani et al 2023).** This and other safety studies exclude an intrinsic effect of Ashwagandha on thyroid gland morphology or thyroid hormone release. In other studies, undertaken in chemically induced hypothyroid rats, Ashwagandha improved the thyroid hormone levels near to normal. None of these studies reported serum thyroid hormone levels beyond the normal range. It is well-reported that high-grade inflammation and oxidative stress are responsible for chemically induced hypothyroidism.

In a case reported by **van der Hooft 2005,** post-partum thyroiditis is not completely ruled out and the author himself reported that the relationship between the use of Ashwagandha and the change in serum thyroid hormone levels can only be considered suggestive, but does not prove a causal relationship.

Kamal et al 2022, from the USA, reported a 73-year-old female taking Ashwagandha for hyperthyroidism for 2 years. However, they failed to confirm the chemical analysis of the content of the capsule. It is important to mention that **Kang et al 2013** reported that nine out of ten commercially available supplements recommended for hypothyroidism including Ashwagandha, contain amounts of T3 and T4 that exceed the doses required to treat hypothyroidism.

Thus, Ashwagandha has not been proven to influence thyroid function in healthy animals or humans. In experimental hypothyroidism induced by propylthiouracil and in humans with hypothyroidism, some increase in thyroid hormone levels has been observed though changes are within normal limits. Placed in a context one should note that many plant antioxidants have been shown to either lower or raise thyroid hormones within the normal ranges. e.g. flavonoids lower thyroid hormone levels **(Paunkov et al 2019 and Wu et al 2024).** On the other side an extract of herb *Bacopa monnieri,* increased the thyroid levels in propylthiouracil-induced hypothyroidism in rats **(Vigneshwar et al 2021).** Even dietary habits as the degree of adherence to a healthy Mediterranean diet have been shown to influence the levels **(Juresko et al 2024)**. The observation that Ashwagandha decreases hepatic lipid peroxidation simultaneously with the increasing effect on thyroid hormone levels should be placed in this context.

Interpreting discrete effects that do not involve lowered TSH or free T3 levels is thus complex. Thyroid hormone levels are not only influenced by the crucial feedback regulation via the TRH-TSH axis, but T4 and T3 levels are also influenced by peripheral metabolism via deiodination- and other reactions **(Kelly, 2000)**, and expression of receptors and levels of transport proteins will influence the effects. The regulation is controlled to the extent that levothyroxine, a drug for hypothyroidism rarely causes thyrotoxicosis, only in cases of massive overdose and life-threatening symptoms. Lowering of TSH to pathologically low levels that clearly signal excess thyroid hormone has not been reported in healthy animals or humans.

Regarding the reports of cases of thyrotoxicosis, one should consider that both hyper and hypothyroidism are common diseases. Reports of single cases of thyrotoxicosis that can be linked in time to Ashwagandha ingestion are therefore impossible to evaluate regarding

causality. Both are autoimmune diseases that can be triggered by external factors, but which could also go into spontaneous remission. Even remission after withdrawal of Ashwagandha in a single case can therefore not be considered strong evidence for a causal relationship. Definite evidence would require large human studies with a matching control group and measurement of thyroid hormone levels, TSH, and thyroid antibodies. Such studies may also include patients with borderline hypothyroid function and some increase in TSH, to further explore the question, of whether Ashwagandha improves thyroid function in some individuals, thereby avoiding an upcoming need for thyroid hormone substitution.

Immunomodulatory effect of Ashwagandha

Several studies have shown that Ashwagandha has an immunomodulatory effect. Immune system modulators are compounds that can increase or decrease the response of the immune system to help treat a variety of diseases. These agents restore immunoregulatory pathways responsible for autoreactivity and inflammation. Summary of few such studies is recapitutated below:

Experimental studies

In a mouse model of lupus, where the body's immune system is activated, Ashwagandha root powder had a potent inhibitory effect on proteinuria, nephritis, and other inflammatory markers such as cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)-α, nitric oxide (NO), and ROS **(Minhas U et al 2012),** In this study, however, Humoral response was found to be impervious. Similar was the efficacy in complete Freund's adjuvant-induced arthritic model **(Rasool M. &Varalakshmi P 2006).**

In an study using the HaCaT human keratinocyte cell line, Ashwagandha root decreased the expression of pro-inflammatory cytokines, including interleukin (IL)-8, IL-6, tumour necrosis factor (TNF-α), IL-1β, and IL-12, and increased the expression of anti-inflammatory cytokines, overall it inhibited the NF-κB and MAPK (mitogen-activated protein kinase) pathways. Based on these results, it can be concluded that the anti-inflammatory effects of Ashwagandha could potentially be used in the prevention of skin inflammation **(Sikandan A et al 2018).**

However, the immuno-stimulatory effects of Ashwagandha are also reported in several studies e.g. Ashwagandha root powder stimulated the immune activity in immunodeficient mice. It increased the total number of white blood cells and bone marrow cells, increased the titer of circulating antibodies and antibody-producing cells, and stimulated the production of immune cells and the phagocytosis of macrophages **(Davis & Kuttan 2000).**

It is well known that Type IV hypersensitivity is mediated by T cells and macrophages, causing diseases like multiple sclerosis and rheumatoid arthritis or graft rejection. Ashwagandha is not known to cause the exacerbation of autoimmune diseases. On the contrary, Ashwagandha restored the immune regulatory pathways and reduced the inflammatory markers in arthritis and other autoimmune disease models.

The moderate immuno-modulatory effects of Ashwagandha have not been linked to any immunopathology. Rather they fit into the spectrum of immunomodulatory effects that have been observed for antioxidative vitamins and plant antioxidants **(Cururani et al., 2022).**

Effect of Ashwagandha on Acetylcholinesterase activity in CNS

Acetylcholinesterase inhibition is usually associated with intestinal cramps, diarrhea, vasodilation with reflex tachycardia, miosis, slurred speech, ataxia, loss of reflexes, etc. No such effects are reported in safety studies conducted in animals and humans at very high doses of Ashwagandha. Hence the possible impact of inhibition of acetylcholinesterase is unfounded.

On the contrary, studies have documented the cognition enhancing and memory -improving effects of extracts from with Withania somnifera in animals as well humans.

Ashwagandha and Liver safety

The efficacy and safety of Ashwagandha on the liver is an area of extensive investigation both in experimental animals and humans. The findings are described below.

Hepatoprotective effect of Ashwagandha in experimental liver injury in animals

The table below lists the efficacy of Ashwagandha in experimental liver injury models. The overall conclusion is that Ashwagandha has some alleviating effect in several models.

S.No	Reference	Ashwagandha formulation with the dose	Liver Injury Model	Conclusions
1	Khalil et al 2021	Aqueous root extract; 200 and 400 mg/kg	Thioacetamide-induced hepatic encephalopathy in rats	Ashwagandha improved locomotor and cognitive deficits, decreased hepatotoxicity markers, and modulated oxidative stress and inflammatory pathways.
2	Ebithal et al 2020	Root powder; 100, 200, 300 and 400 mg/kg	CCl4-induced hepatotoxicity in male albino rats	Ashwagandha mitigated CCl4-induced hepatotoxicity, enhanced liver antioxidant activity, and reduced serum hepatic enzymes.
3	Baxla et al 2019	Root powder; 500mg/kg	Lead (Pb) Induced toxicity in Wistar albino rats.	Ashwagandha improved hematological and hepatotoxic markers, and reduced serum biomarkers (ALT, AST, ALP, BUN, creatinine).
4	Dhenge et al 2018	Root powder: 5 gm/kg with feed	Liver function in broilers.	Ashwagandha reduced SGPT and SGOT levels, enhancing growth, and immune function.
5	Shahraki et al2016	Powder: 62.5 mg/g diet	Fructose-induced liver damage in Albino- Wistar rats	Ashwagandha decreased insulin resistance, serum insulin, blood glucose, triglycerides, and liver enzymes.
6	Nabi et al2014	Hydro-alcoholic root extract: 100 mg /kg	Liver dysfunction in geriatric dogs	Ashwagandha normalized serum ALT, AST, albumin, cholesterol, and protein levels.
7	Sabina et al2013	Powder: 500 and 1000 mg/kg	Paracetamol hepatotoxicity (rats)	Ashwagandha normalized serum liver marker enzymes and bilirubin levels.
8	Malik et al 2013	Aqueous root extract: 500 mg/kg	Paracetamol-hepatotoxicity in mice	Ashwagandha decreased AST, ALT, ALP, and bilirubin; increased total serum protein level; reduced lipid peroxidation, and enhanced antioxidant enzyme activities.
9	Sultana et al2012	Root extract: 500 mg/kg	Gentamicin-intoxicated Wistar albino rats	Ashwagandha root extract reduced elevated serum levels of AST and ALT induced by gentamicin.
10	Sharma et al2012	Root extract: 200, and 500 mg/kg	Lead nitrate-induced toxicity in male mice	Ashwagandha root extract ameliorated the alterations in hematological parameters and serum enzymes associated with liver function.

S.No	Reference	Ashwagandha formulation with the dose	Liver Injury Model	Conclusions
11	Harikrishnan et al2008	Root powder: 500 mg/kg	Hyperammonaemia induced by ammonium chloride in rats	Ashwagandha root powder reduced levels of circulatory ammonia, urea, lipid peroxidation products, and liver marker enzymes.
12	Akbarsha et al 2000	Root powder: 250 mg/kg	Carbendazim-induced liver injury in male rats	Ashwagandha root powder demonstrated a complete recovery of histopathological damage in the liver.
13	Bhattacharya et al 2000	Aqueous extract of roots: 10, 20 and 50 mg/kg	Iron overload hepatotoxicity in male rats	Ashwagandha roots decreased hepatic lipid peroxidation and serum levels of liver enzymes.

Animal studies of Ashwagandha on liver safety

Ashwagandha safety has been widely studied in healthy animals treated with Ashwagandha for various durations. These studies have used various parameters like serum enzymes, biochemicals as well as macroscopic examination and histopathology to assess the effect of Ashwagandha on liver health. Some of these studies are listed below. The overall conclusion is that no significant liver toxicity of Ashwagandha has been demonstrated in experimental animal studies.

Reference	Experimental Model	Ashwagandha formulation	Conclusion
Langade et al., 2023	Wistar rats	Standardized aqueous root extract 200, 400, 800 mg/kg	No signs of intoxication. Vital liver parameters remained stable, and no abnormalities in general parameters. All hematological and biochemical parameters were within normal range, indicating safety. Gross necropsy examination and histopathology of the liver from some rats treated with high doses of root extract showed multifocal minimal hepatocellular infiltration of inflammatory cells. Authors suggested that the rate of occurrence of these incidences, which could be due to glycogen deposition in the cytoplasm of hepatocytes, was low and usually developed in the different laboratory animals to a certain extent, they were considered to be spontaneous / incidental in nature.
Kalaivani et al., 2023	Nulliparous and non-pregnant Wistar Albino rats	Standardized aqueous root extract 500, 1000, 2000 mg/kg	No morbidity, mortality, or clinical toxicity. There were no changes in liver enzymes like SGOT, SGPT, alkaline phosphatases or serum bilirubin. Notably, even at the highest dose, liver histopathology examinations indicated no abnormalities. NOAEL was determined to be 2000 mg/kg.
Patel SB et al., 2016	Wistar rats	Standardized root extract 500, 1000, 2000 mg/kg	No toxicologically significant changes were observed. Similarly, in the sub-acute group, no treatment-related microscopic changes were observed, suggesting Ashwagandha safety for the liver. NOAEL was determined to be 2000 mg/kg. The extract showed no adverse effects even after a 14-day recovery period following 28 days of administration.

Reference	Experimental Model	Ashwagandha formulation	Conclusion
Prabhu PC et al., 2013	Wistar rats	Hydroalcoholic extract of roots 500, 1000, 2000 mg/kg	No toxic signs or mortality. No significant changes in body weights, organ weights, or haemato-biochemical parameters. NOAEL was determined to be 2000 mg/kg.

Clinical Studies on Liver Safety

Similarly, multiple clinical studies have also been conducted to evaluate the safety of Ashwagandha on various safety parameters, and no significant alterations or irregularities were detected in several health indices and biochemical parameters including critical safety metrics such as liver, kidney, and thyroid functions. Details of these studies are mentioned in table below:

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events	Summary of results
Długołęcka et al 2023 **(Poland)**	Randomized, double-blind, placebo-controlled Study 8-weeks	Highly qualified national team wrestlers (26) Ashwagandha (12) Placebo (14)	2x300 mg per day (2 capsules a day) for 8 weeks.,	Hematological parameters, serum levels of biochemical parameters, bone mineral content, etc.	Generally, the participants (from both PL and A group) declared good tolerability of capsules, with no adverse events. Only one participant dropped out of the study due to intolerance of Ashwagandha capsules.	The study observed that the biochemical variables remained in the normal range after the intervention with Ashwagandha, and it had no impact on liver related parameters.
Vaidya et al 2023 **(India)**	A non-randomized, open-label, single-treatment clinical study 4 weeks	Healthy male participants (18), aged 18 to 60	500 mg of the WSE capsules twice daily for four weeks	vital signs, organ function tests, urine analysis, X-ray and ECG, cardiorespiratory endurance, body fat percentage, lean body weight, adverse events profile, and tolerability of the WSE capsules	During the trial, there were no adverse effects, ***i.e.,*** none. All the healthy volunteers participating in the safety research demonstrated tolerability to the WSE capsule at a dose of 500 mg twice daily for 30 days.	The participant's physical, hematological, and biochemical characteristics were normal, and no significant alterations or irregularities were observed in safety metrics like liver, kidney, and thyroid functions.
Smith et al 2023 **(Australia)**	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Healthy Adults aged between 40 and 75 years Ashwagandha (60, 55), Placebo (60, 56)	200 mg - Hydroalcoholic Ashwagandha root extract - twice daily	PSS, CFS PROMIS-29, Sex hormone concentrations, MDA, FG, HbA1c, TSH, HRV, Grip strength,	Ashwagandha (13 - Digestive disturbances, Mood disturbances/changes, Headaches/migraines, Increased appetite, Increased tiredness)	The reported adverse events were of mild severity these events were resolved without any intervention and participants continued the study treatments till the end of the study.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events	Summary of results
				Anthropometric measures, LFT, RFT, FBC	Placebo (15 - Digestive disturbances, Mood disturbances/ changes, Headaches/migraines, Increased appetite, Itchy Skin, Increased tiredness)	Ashwagandha root extract was well tolerated by all the participants.
Verma N et al., 2021 **(India)**	Randomized, Double-Blind, Placebo - Controlled Study 8 Weeks	Healthy adults aged between 18 and 45 years Ashwagandha (40), Placebo (40)	Standardized Aqueous Ashwagandha Root Extract 300mg twice daily / Total daily dose of 600mg/day	Hematological parameters, Liver parameters Thyroid Parameters	Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.	Compared to the placebo, all hematological parameters, liver health parameters and thyroid parameters remained within the acceptable and normal reference range.
Raut et al 2012	Dose-related, Open-label clinical study 30 Days	Healthy adults aged 18-30 years Ashwagandha (18)	Withania somnifera extract 750 mg/day x10 days, 1000 mg/day x 10 days, 1250 mg/day x 10 days	Serum Bilirubin, Proteins, Albumin, Alanine Transaminase, Aspartate Transaminase, and Alkaline Phosphatase Serum HDL, LDL, and VLDL cholesterol	Ashwagandha 750mg (1 - Increase in appetite, libido, and hallucinogenic effects with vertigo) Ashwagandha 1000mg (0) Ashwagandha 1200mg (0)	Ashwagandha was found to be safe on hematological and biochemical organ function tests.

Based on these multiple studies using biochemical, macroscopic observations, organ weight and histopathology as studied in various preclinical and clinical studies, it is safe to conclude that Ashwagandha has no intrinsic adverse or toxic effect on the liver or its function.

Recent reports of liver injury cases attributed to Ashwagandha

More recently, few cases of clinically significant liver injury have been reported. **Bjornsson et al., 2019** reported 5 such cases from Iceland and US. A few other reports e.g. **Inagaki et al., 2017 from Japan, Weber and Gerbes, 2021** and **Toth et al 2022** from Germany, **Ireland et al., 2021** from the USA, **Bokan et al., 2023** from Bosnia and Herzegovina, **Lubraska et al., 2023** from Poland, and **Phillips et al.,** 2023 from India have raised concerns on liver toxicity based on sporadic case reports from their respective countries. The causal relation has been classified as possible or likely based on the time of diagnosis in relation to the start of Ashwagandha intake, the exclusion of other liver diseases, and the resolution of the liver pathology after withdrawal of Ashwagandha. Most of the cases are presented as mixed cholestatic/hepatocellular damage. It is significant to note that all these cases for which the causal relationship to Ashwagandha was classified as likely, were reversed on discontinuation of herb and no case led to death or liver

transplantation. A single American case has been reported, which underwent successful liver transplantation due to liver failure caused by severe hepatocellular damage. Although there was a time relation to Ashwagandha intake, a number of complicating factors (cancer operation two years earlier, feeling unwell after that, ingestion of progesterone in unknown dose) made interpretation difficult, and the authors classified the causal relation as possible, not as likely

In light of Ashwagandha's liver safety, how do we explain the liver injury reports?

Since Ashwagandha root extract is not hepatotoxic, neither in prescribed doses nor in much higher doses, one must consider other explanations. E.g. some of the patients reported to have a possible Ashwagandha-induced liver injury had different underlying diseases like cancer, metabolic diseases, etc and were on medicines known to cause liver toxicity or had prior daily exposure to alcohol. In other cases, they used formulations containing many herbs and Ashwagandha as one of the ingredients. In fact a recent report doubted **Inagaki et al. (2017)** case report from Japan and questioned if liver damage was due to Ashwagandha. Causality assessment is thus particularly difficult in some of the cases. Yet, one must admit that there are cases no such complicating factors and that the classification of the causal relation to Ashwagandha as likely is motivated.

Unpredictable liver injuries caused by a defined chemical, usually a commonly prescribed or over-the-counter sold drug, are rare but well-known and are named drug-induced liver injuries (DILI). Similarly, herb-induced liver injury (HILI) arises from the harmful effects of complex extracts, where one or more compounds may contribute to unpredictable hepatotoxicity. Direct toxic effects of a drug or herbal preparation on any organ including the liver are dose-dependent, predictable, and have a short latency period and it can be reliably reproduced in animal models. In the case of Ashwagandha, we did not see any report of HILI both in clinics and animals. However, in contrast to this, idiosyncratic injury is not dose-dependent, difficult to predict, and varies widely in latency, often linked to immune or allergic responses to a few susceptible individuals. It is crucial to distinguish between intrinsic and idiosyncratic liver injuries.

Based on the biochemical, hematological, gross observations, organ weight, and histopathology studied in various preclinical and clinical studies, it is safe to conclude that the root of Ashwagandha has no intrinsic adverse or toxic effect on the liver. The reports of liver injury may be attributed to other underlying diseases or drugs as cited above or at the most rarely, may be likely idiosyncratic reactions that need more investigation. These injuries were generally reversible upon discontinuation of the herb. At the most one can be cautious, and the user can be appropriately informed. In patients with comorbidities, such as cancer, immunocompromised state, polypharmacy, etc. monitoring for liver function should be done at regular intervals. However, there is no scientific evidence to proclaim Ashwagandha as liver toxic.

Summary of clinical studies of Ashwagandha Root Extract

An extensive literature search was conducted using various keywords and MeSH terms to identify relevant scintific publications on Ashwagandha, (*Withania somnifera*). By searching the keyword "Ashwagandha OR *Withania somnifera* (All field)" on PubMed, a total of 1793 publications were identified as of 02.07.2024. After screening, 43 randomized controlled trials focusing on Ashwagandha root as a standalone intervention were included in our review. These studies were critically analyzed to assess the efficacy and safety of *Withania somnifera* across various medical conditions (Annexure III). The summary of key findings from selected safety studies is presented below:

Vaidya et al 2023, conducted a non-randomized, open-label, single-treatment clinical study over 4 weeks to evaluate the safety of hydroalcoholic Ashwagandha root extract with 18 healthy male participants ranging from 18 to 60 years of age. Ashwagandha was administered at a dosage of 500 mg twice daily (1000mg/day). Remarkably, no adverse events were reported throughout the study, indicating a favorable safety profile for the Ashwagandha root extract. The study revealed that all physical, hematological, and biochemical characteristics of the participants remained within normal ranges, with no significant alterations or irregularities detected in critical safety metrics such as liver, kidney, and thyroid functions. The authors concluded that the consumption of hydroalcoholic Ashwagandha root extract is safe and well-tolerated by healthy human volunteers.

Barbara et al 2023, conducted a randomized, double-blind, placebo-controlled, and parallel-group study on Professional athletes—specifically, highly qualified national team wrestlers— for 8 weeks. The participants were administered a standardized aqueous Ashwagandha root extract at a dose of 300 mg twice daily (600 mg/day). One of the prominent findings was that, compared to the placebo group, serum CK activity in the Ashwagandha group did not significantly increase, suggesting improved muscle recovery. Additionally, the study observed that the biochemical variables remained in the normal range after the intervention with Ashwagandha, and it had no impact on liver parameters. The research highlighted the supplement's safety, endorsing that it was well-tolerated by all participants, with no adverse events reported. The authors concluded that Ashwagandha supplementation might be beneficial for professional wrestlers in improving muscle recovery without affecting liver functions or causing adverse effects.

Smith et al 2023, conducted a two-arm, parallel-group, single-center, randomized, double-blind, placebo-controlled trial on 120 participants to evaluate the safety and efficacy of Ashwagandha on stress, fatigue, and sex hormones in overweight or mildly obese men and women with self-reported stress and fatigue for 8 weeks. The participants were administered Ashwagandha root extract at a dose of 200mg twice daily (400 mg/day). The authors found

that compared to the placebo, there was a statistically significant reduction in fatigue symptoms and a significant increase in heart rate variability in the Ashwagandha group. However, there was a non-significant reduction in PSS scores and other self-report measures. In the men taking Ashwagandha, there was a significant increase in the blood concentrations of free testosterone and luteinizing hormone compared to the placebo group. The reported adverse events in both groups were of mild severity and no intervention was required. There were also no changes in anthropometric measures (BMI, WC, and WHR) blood pressure, and safety blood makers comprising the liver function test, full blood count, and renal function with Ashwagandha supplementation.

Verma et al 2021, conducted a randomized, double-blind, placebo-controlled, and parallel-group study on 80 healthy individuals to evaluate the safety of oral administration of Ashwagandha root extract at a dose of 300 mg twice daily for 8 weeks. The result of the study did not indicate any untoward effect in any of the treated volunteers. There was no statistically significant change or abnormality observed in the parameters considered including thyroid hormonal profile in both the groups. Also, no adverse events were reported by any of the participants during the study period. The authors concluded that the consumption of Ashwagandha root extract for eight weeks was found to be safe in both male and female volunteers.

Gopukumar et al 2021, in a randomized, double-blind, placebo-controlled study, evaluated the effect of Ashwagandha root extract (sustained-release) capsule 300 mg for 90 consecutive days, on cognitive function, stress level, sleep quality, overall well-being, and safety in stressed subjects [130 healthy cognitively sound adults (20–55 years of age, body mass index: 18–29 kg/m2)]. A total of 125 subjects completed the study and were evaluated. The Cambridge Neuropsychological Test Automated Battery (CANTAB) reported significantly improved recall memory, and the total error rate in recalling patterns was significantly reduced at visit 4 in the Ashwagandha group as compared to the placebo group. At visit 4, lower PSS-10 score ($p < .0001$), serum cortisol levels ($p = 0.0443$), and Pittsburgh Sleep Quality Index (PSQI) score ($p < .0001$) but higher Oxford Happiness Questionnaire (OHQ) scores ($p < .0001$) were seen in the Ashwagandha group when compared to the placebo group, which suggests significantly lower stress level and significantly better psychological well-being and sleep quality in the former. No adverse events were reported during the study. The authors concluded that treatment with one Ashwagandha capsule (sustained release) once daily for 90 days improved memory and focus, psychological well-being, and sleep quality, reduced stress level, and was safe and well-tolerated.

Kuchewar et al 2014, investigated Ashwagandha for antioxidant potential in healthy volunteers. In this randomized, double-blind, placebo-controlled study, 30 healthy volunteers aged 18-45 years were randomly assigned in equal numbers to the test or placebo group. The test group received 500 mg Ashwagandha root extract twice daily after food with a glass of water for 6 months. The same protocol was followed for the placebo group receiving hard gelatin capsules filled with starch powder. All subjects completed the study and there were no adverse effects reported and all the haematological parameters were within normal range before and after the intervention in both groups. The result of this study indicates that intake of aqueous Ashwagandha root extract at up to 1000 mg per day in divided doses is very well tolerated.

Raut et al 2012, conducted an exploratory, prospective, open-labeled study to evaluate the dose-related tolerability, safety, and activity of *Withania somnifera* formulation in 18 healthy volunteers. *W. Somnifera* was given in the form of capsules (aqueous extract) daily in two divided doses with an increase in daily dosage every 10 days for 30 days (750 mg/day x10 days, 1000 mg/day x 10 days, 1250 mg/day x 10 days). All but one volunteer tolerated *W. Somnifera* without any adverse event. One volunteer was withdrawn from the study because of the symptoms exhibited such as; increased appetite, libido, and hallucinogenic effects with vertigo at the lowest dose. No significant change was observed in Serum Bilirubin, Proteins, Albumin, Alanine Transaminase, Aspartate Transaminase, and Alkaline Phosphatase during the entire study duration in all participants. All these parameter remained within the normal range. This study has also demonstrated muscle strengthening, improved quality of sleep, and lipid-lowering potential of Ashwagandha. Based on this result, the study concluded that Ashwagandha aqueous extract is safe to use for a month duration in a progressively escalated dose up to 250 mg per day.

Keche et al 2010, conducted a randomized double-blind placebo-controlled clinical trial to assess the efficacy and safety of Livwin® (a polyherbal formulation) in 58 patients (in two groups) with acute viral hepatitis. The formulation Livwin® comprised of Ashwagandha, Arjuna, Bhumyamalaki, Daruharidra, Guduchi, Kutki, and Punarnava and was given orally, two capsules two times a day for eight weeks followed by a treatment-free period of four weeks. The assessment parameters included symptomatic recovery and levels of serum bilirubin, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), alkaline phosphatase at baseline, 2, 4, 8, and 12 weeks. The authors found that significantly earlier recovery of weakness was observed with Livwin® as compared to placebo at 2, 4, and 8 weeks. Serum bilirubin and ALT were observed in the normal range in a significantly higher number of patients with Livwin® treatment as compared to placebo at 2, 4, and 8 weeks. AST was observed in the normal range in a significantly higher number of patients with Livwin® treatment as compared to placebo at 2 and 4 weeks. Epigastric pain (n=2) and diarrhea (n=1) were reported with Livwin® treatment. The authors concluded that Livwin® is effective in uncomplicated patients of acute viral hepatitis.

Recent evidence: Safety of long-term administration of Ashwagandha in humans

Recent evidence from a randomized, double-blind, placebo-controlled clinical trial involving 1,200 participants (600 in each group) has further established the safety of Ashwagandha roots when co-administered with the COVID-19 vaccine (COVISHIELD). The study, conducted over six months, specifically aimed to assess the safety and immunogenicity of Ashwagandha in combination with the COVID-19 vaccine. Participants were monitored for any adverse effects, and the data demonstrated that Ashwagandha, when administered in appropriate doses, did not produce significant adverse effects even with long-term use. This finding supports the traditional use of Ashwagandha as a safe supplement for enhancing overall health and resilience, especially in the context of immune support. The results of this trial align with previous research indicating that Ashwagandha is generally well-tolerated and safe for human

consumption. Its potential to improve vaccine immunogenicity without compromising safety makes it a valuable adjunct in public health strategies, especially during pandemics. This study was conducted as per the protocol registered with ICMR Clinical Trial Registry and published before beginning the trial that followed Good Clinical Practices (**Chopra et al 2021; Chopra et al. 2022**). The results of this trial are in the process of final publication.

These studies collectively highlight the potential benefits of Ashwagandha in various health conditions, with a strong emphasis on its safety and tolerability in diverse populations.

Pharmacovigilance

To generate awareness about the possibility of adverse drug reactions associated with traditional drugs, the Ministry of Ayush, Government of India, initiated the Pharmacovigilance Program for Ayurveda, Siddha, Unani, and Homoeopathy (ASU&H) Drugs in 2017. This program features a robust three-tier system (National, Intermediary, and Peripheral centers) that has been operational since its inception, covering most states and union territories across the country. As of date, no adverse drug reactions related to the use of Ashwagandha have been reported under this program.

Conclusion

The comprehensive documentation and analysis presented in this technical dossier affirms the safety of the Ashwagandha root. Historical usage, corroborated by rigorous modern research confirms its pharmacological safety and therapeutic efficacy. The instant technical dossier on safety of Ashwagandha encompasses a broad spectrum of studies, including preclinical safety assessments, clinical trials, and investigations into its benefits for liver and thyroid, as well as its immunomodulatory effects.

Numerous safety studies consistently demonstrate that standardized Ashwagandha (Withania somnifera) root extract is safe for human consumption. The findings from various experimental and clinical studies indicate that the root extract has positive effects on sex hormones, sperm motility & viability, and overall sexual function.

Furthermore, scientific data reveals that Ashwagandha root is well-tolerated across a wide range of doses, with no adverse outcomes reported in diverse demographic and clinical cohorts. Thus, the current evidence supporting the safety and efficacy of Ashwagandha root is robust, allowing it to be safely recommended and integrated into global health practices. This reinforces its standing as a significant medicinal herb in both traditional and contemporary health contexts nevertheless using correctly identified species is very crucial and stringent quality control should be carried out suitably as per applicable regulatory norms.

In view of its scientifically proven safety, the globally available and popular Indian herb Ashwagandha (Withania Somnifera) can be judiciously utilized for its versatility pertaining to health benifits in humans.

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Annexure I – Permissible Limits and International Regulatory Provisions

U. S. Pharmacopeia and European Union permissible limits for heavy metals in dietary supplements

Element	India Limits ppm	USP Limits ppm	EU Limits ppm
Arsenic	3	1.5	0.5
Cadmium	0.3	0.5	0.1
Lead	10	0.5	3
Mercury	1	0.3	0.1

U. S. Pharmacopeia and European Union permissible limits for Aflatoxins in dietary supplements

Aflatoxins	India Limits	USP Limits	EU Limits
B1	< 2 ppb	NMT 5 ppb	5ppb
The sum of aflatoxins (B1, B2, G1, G2)	< 5ppb	NMT 20 ppb	10 ppb

Microbial Limits for 'Finished' Botanical Products

Microbial Enumeration test	USP Limits	Microbial Enumeration test	EU Limits
1) Total aerobic microbial count	$<10^4$cfu/g or ml	1) Total aerobic microbial count	$<10^4$cfu/g or ml
2) Total combined molds and yeasts count	$<10^3$cfu/g or ml	2) Total combined molds and yeasts count	$<10^2$cfu/g or ml
3) Enterobacterial count (Bile-Tolerant Gram-Negative Bacteria)	$<10^2$cfu/g or ml	3) Enterobacterial count (Bile- Tolerant Gram-Negative Bacteria)	$<10^2$cfu/g or ml
Test for absence of specified Microorganisms		**Test for absence of specified Microorganisms**	
4) Escherichia coli (10g)	Absent	4) Escherichia coli (1g)	Absent
5) Salmonella species (10g)	Absent	5) Salmonella species (25g)	Absent
6) Staphylococcus aureus (10g)	Absent	6) Staphylococcus. aureus (1g)	Absent

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June 25, 2024

AHP Responds to Claims of Ashwagandha Abortifacient Effects

In May of 2020, Danish Food Authorities issued a risk assessment of ashwagandha recommending against its use due to purported abortifacient activity. Other European countries followed, calling for independent risk assessments that have called into question the safety of the herb when used in pregnancy. As their primary reference, the Danish authorities cited an ashwagandha monograph of the World Health Organization (WHO) (2009) that in turn cited the American Herbal Pharmacopoeia (AHP) *Ashwagandha Root Monograph and Therapeutic Compendium* (2000). However, the WHO monograph, in an example of what is known in medical literature as *citation distortion*, did not fully articulate the AHP review which stated the following:

"There are conflicting reports regarding the use of ashwagandha in pregnancy. Large but undefined doses have been reported to possess abortifacient activity (Chadha 1976; Svoboda 1992). Of several ayurvedic practitioners consulted, none reported having observed an abortifacient activity clinically. Conversely, ashwagandha has, traditionally and in modern ayurvedic practice, been used to prevent miscarriage and stabilize the fetus (Tirtha 1998)."

Misrepresentation of the AHP monograph has been repeatedly uncritically resulting in the misconception that ashwagandha root is potentially unsafe. A potential for an abortifacient effect was similarly reported in the first edition of the *Botanical Safety Handbook* (BSH; McGuffin et al. 1997), which provides a safety classification for ashwagandha of 2b: Not to be used in pregnancy unless otherwise recommended by a qualified health care practitioner, and a "Notice" as an abortifacient. The 2b classification remained in the second edition of BSH but the Notice as an abortifacient was removed due to the lack of documentation that such an action existed.

Since the earlier publications of both AHP and BSH, a comprehensive review of the traditional and scientific literature and all accessible citations that made any mention of ashwagandha as an abortifacient was conducted. Additionally, the opinion of experienced Ayurvedic medicine practitioners from India and North America was solicited. Neither the Expert Advisory Council for the revision of BSH (third edition), nor experts involved in the AHP revision, found any traditional or scientific documentation that ashwagandha possesses an abortifacient activity. The earlier cautions regarding the use of ashwagandha in pregnancy and its claimed use as an abortifacient were based on anecdotal reports from the ethnobotanical literature that provided no indication such an effect was evident. Furthermore, when such reports were made, the overwhelming majority referred to above-ground parts, which in Ayurveda were rarely used internally, not the root, the portion used almost exclusively. Similarly, a review of the traditional and scientific data reveals no pharmacological mechanisms that would indicate an abortifacient effect.

The BSH safety classification was revised to the current safety classification of 1: Herbs that can be safely consumed when used appropriately. An upcoming revision of the AHP *Monograph and Therapeutic Compendium* will reflect this as well.

In addition, subsequent to safety concerns raised in the European Union, the Ministry of AYUSH (Government of India) released a Safety Dossier (2.0; 2024) noting the lack of abortifacient activity of ashwagandha root and citing all clinical and pre-clinical data that have investigated the use of ashwagandha and its preparations in pregnancy. One toxicity investigation in rats demonstrated a No Observed Adverse Effect Level of ashwagandha root extract of 2,000 mg/kg. The available human trials reported no maternal or fetal toxicity in pregnant women using ashwagandha preparations. No other clinical or pre-clinical investigations revealed an abortifacient activity.

While adequate caution when using any substance during pregnancy is warranted, based on a critical and comprehensive review of the traditional and modern

literature, as well as the opinion of the majority of experts, there is no evidence of an abortifacient effect of ashwagandha root.

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Annexure III - Clinical Studies on Ashwagandha

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
Stress, Sleep, and Anxiety						
Stress and Anxiety / Chandrasekhar et al2012 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Healthy adults / Aged between 18 and 54 years experiencing high-stress Ashwagandha (32, 30), Placebo (32, 31)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	PSS, GHQ- 28, DASS, Serum Cortisol	Ashwagandha (6 - Nasal congestion, Constipation, Cough and cold, Drowsiness, Decreased appetite, Placebo (5 - Dryness of mouth, tiredness, fever, headache, abdominal pain, diarrhea, tremor in legs)	Compared to placebo, Ashwagandha was associated with significantly greater improvements in PSS, GHQ-28 total and subscale scores, DASS total and subscale scores, and serum cortisol. Mild Adverse events were seen and were comparable in the two groups. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Stress and Weight Management / Choudhary et al 2017b (India)	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Adults aged between 18 and 60 years with symptoms of chronic work stress Ashwagandha (26, 25), Placebo (26, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	PSS, FCQ, OHQ, TFEQ Serum Cortisol, Body weight, BMI	Ashwagandha (1) Placebo (1) Giddiness, Heaviness of head, Blurring of vision, hyperacidity	Compared to placebo, Ashwagandha was associated with significantly greater improvements in PSS, FCQ-T (planning, positive reinforcement, negative reinforcement, lack of control, emotion, and environment scores), OHQ, TFEQ (uncontrolled eating and emotional eating scores), serum cortisol, body weight, and BMI The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Stress, Sleep and Anxiety / Salve et al 2019 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Adults aged between 18 and 55 years experiencing high stress Ashwagandha 250mg (20, 19),	125mg and 300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	PSS, HAM-A, Serum Cortisol, Sleep quality	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha was associated with significantly greater reductions in PSS (both doses), HAM-A (600 mg), sleep quality rating (both doses), and serum cortisol (both doses). Trends suggested greater efficacy with the higher Ashwagandha dose

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
		Ashwagandha 600mg (20,20), Placebo (20, 19)				The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Insomnia and Anxiety / Langade et al2019 **(India)**	Randomized, Double-Blind, Placebo – Controlled 10 Weeks	Adults aged between 18 and 60 years with insomnia Ashwagandha (40, 39), Placebo (20, 19)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Sleep actigraphy - SOL, TST, WASO, TIB, SE, Sleep log, PSQI, HAM-A, Sleep Quality, Mental alertness on rising score	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha was associated with significantly greater improvements in sleep actigraphy measurements of sleep onset latency and sleep efficiency, PSQI sleep quality scores, HAM-A scores, and sleep quality scores. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Anxiety Symptoms among children with ADHD / Hosseini et al 2019 **(Iran)**	Randomized, Double-Blind, Placebo – Controlled 6 Weeks	Children aged 7-12 years Ashwagandha (16, 14) Placebo (15, 14)	Ashwagandha Root Extract 10mg / day	RCMAS, ADHD-RS	Ashwagandha (0) Placebo (0)	Ashwagandha root extract reduces the symptoms of physiological anxiety, sensitivity, social concerns, and an overall score of RCMA among children with ADHD and comorbid anxiety disorders. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Elderly and General Wellbeing / Kelgane et al2020 **(India)**	Randomized, Double-Blind, Placebo - Controlled Study 12 Weeks	Healthy older-age adults aged between 65 and 80 years Ashwagandha (25, 19), Placebo (25, 20)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	WHO-QOL-BREF, Sleepiness scale, Mental alertness on rising, Sleep quality scale	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha is associated with significantly greater improvements in WHOQOL-BREF scores (total score and global, physical, psychological, and environment domain), mental alertness on waking rating, and sleep quality rating, but not on the sleep scale scores The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Primary insomnia in elderly males / Atulet al2020 **(India)**	Simple Randomized, Two-arm Open-label 4 Weeks	Male patients from the age group of 60–70 years Ashwagandha (only) (30, 27) BrimhanaNasya + Ashwagandha (30, 28)	Ashwagandha root powder - 6 g orally with 100 ml of milk / day Brimhana Nasya + 6g Ashwagandha Root Powder with 100ml of milk / day	PSQI	Ashwagandha (only) (0) Brimhana Nasya + Ashwagandha (0)	The result of the study indicates that Brimhana Nasya and Ashwagandha root powder group patients got more significant results in all components of PSQI compared to Ashwagandha root powder group patients.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Generalized Anxiety Disorder / Fuladi et al 2020 **(Iran)**	Randomized, Double-Blind, Placebo – Controlled 6 Weeks	Healthy Adults Ashwagandha (18, 18) Placebo (22, 22)	*Withania somnifera* Root Extract 1g/day	HAM-A, GAD level	Ashwagandha (0) Placebo (0)	Compared to the placebo, the change in the Hamilton anxiety rating scores (HAM-A) revealed a significantly ameliorated situation by decreasing HAM-A score in the treatment group. Moreover, there was a significant difference in the treatment group in the second week and sixth week in the reduction of Generalized Anxiety Disorder. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Sleep, Insomnia and Anxiety / Langade et al2021 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Heathy adults and insomnia patients aged between 18 and 50 years Healthy - Ashwagandha (20,20), Placebo (20, 20); Insomnia - Ashwagandha (20,20), Placebo (20, 20)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Sleep actigraphy, parameters - SOL, TST, WASO, TIB, SE; PSQI, HAM-A, Mental Alertness on rising, Sleep quality	Ashwagandha (0) Placebo (0)	Compared to the placebo, Ashwagandha root extract supplementation resulted in a significant improvement in both healthy participants and insomnia patients. There was a statistically significant improvement in SOL, HAM-A outcomes, mental alertness, and sleep quality. Although both healthy and insomniac subjects reported significant improvement in sleep parameters, it was more significant in the latter group. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Stress and Cognitive Functions / Gopukumar et al2021 **(India)**	Randomized, Double-blind, Parallel-group, Two-arm, Placebo-controlled 12 Weeks	Healthy Cognitively sound adults aged 20–55 years Ashwagandha (65, 62) Placebo (65, 63)	300mg - Hydroalcoholic Ashwagandha root extract - once daily	CANTAB, OHQ, PSQI PSS, MoCA Serum Cortisol, BDNFlevels	Ashwagandha (0) Placebo (0)	Compared to the placebo, the CANTAB reported significantly improved recall memory, and the total error rate in recalling patterns significantly decreased in the Ashwagandha SR group. Also, lower PSS-10 score, serum cortisol levels, and Pittsburgh Sleep Quality Index (PSQI) score but higher Oxford Happiness Questionnaire (OHQ) scores were seen in Ashwagandha SR suggesting significantly lower stress levels and significantly better psychological well-being and sleep quality in the former.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Stress and Anxiety / Majeed et al 2023 **(India)**	Randomized, Double-Blind, Placebo - Controlled 8 Weeks	Adult participants aged 21 to 54 years Ashwagandha (27, 25), Placebo (27, 25)	500 mg - Hydroalcoholic Ashwagandha root extract with 95% piperine-5 mg - once daily	PSS, GAD-7, QOL CANTAB, Salivary Cortisol, Serotonin, Dopamine, NO, GSH, MDA	Ashwagandha (8 - Nausea, Headache, Diarrhoea) Placebo (4 - Headache, Nausea)	Compared to placebo, the PSS, GAD-7, and QOL scores improved significantly in all the participants taking ARE. The CANTAB analysis revealed a significant improvement in multitasking, concentration, and decision-making time in ARE compared to placebo. ARE was also associated with a greater reduction in the morning salivary cortisol and an increase in urinary serotonin compared to placebo. Serum levels of NO, GSH, and MDA were not significantly different. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Stress and Fatigue / Smith et al 2023 **(Australia)**	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Healthy Adults aged between 40 and 75 years Ashwagandha (60, 55), Placebo (60, 56)	200 mg - Hydroalcoholic Ashwagandha root extract - twice daily	PSS, CFS PROMIS-29, Sex hormone concentrations, MDA, FG, HbA1c, TSH, HRV, Grip strength, Anthropometric measures, LFT, RFT, FBC	Ashwagandha (13 - Digestive disturbances, Mood disturbances/changes, Headaches/ migraines, Increased appetite, Increased tiredness)	Compared to the placebo, there was a statistically significant reduction in fatigue symptoms and a significant increase in heart rate variability in the Ashwagandha group. However, there was non- significant reduction in PSS score and other self-report measures. In the men taking Ashwagandha, there was a significant increase in the blood concentrations of free testosterone and luteinizing hormone compared to the placebo group. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
					Placebo (15 - Digestive disturbances, Mood disturbances/changes, Headaches/ migraines, Increased appetite, Itchy Skin, Increased tiredness)	The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Anxiety, Depression, and Serotonin Levels / Majeed et al 2023 **(India)**	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Healthy adults aged between 18 and 60 years Ashwagandha (34, 34), Control (36, 36)	500 mg - Ashwagandha root extract with piperine-5 mg - once daily	HDRS, HARS, GSQS, WHO-QOL, Serum serotonin	Ashwagandha (18 - Nausea, Diarrhea, Drowsiness, Fever, Headache, Stomach Pain) Placebo (16 - Nausea, Diarrhea, Drowsiness, Fever, Headache, Stomach Pain, Back Pain)	Compared to the placebo, the HARS, HDRS, GSQS, and QOL scores improved significantly in the Ashwagandha group. Serum levels of serotonin increased in ARE but showed a decrease in placebo. Biochemical and hematological parameters remained in the normal range in all participants. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Anxiety in Adults / Cooley et al2009 **(Canada)**	Randomized, Controlled, Pragmatic trial 12 Weeks	Adults aged 18 - 65 years Ashwagandha (41, 36) Placebo (40, 39)	*Withania somnifera* root (Swiss Ashwagandha); 300-mg supplements twice daily	BAI, SF-36, FQ, VAS	Ashwagandha (Gastrointestinal upset, Overstimulation, Feeling warm, increased frequency of nocturnal night cramps, mild hair loss) Placebo (Gastrointestinal upset, Overstimulation, Rash, Feeling warm, increased frequency of nocturnal night cramps, mild hair loss)	Compared to the placebo, the Ashwagandha group caused a significant decrease in anxiety levels and an improvement in quality of life measures. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The safety of Ashwagandha root was confirmed as there were no adverse events reported and Ashwagandha root was well tolerated by all the participants.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
Anxiety in Adults / Andrade et al 2000 **(India)**	Double-blind, Placebo-controlled, Dose-ranging study 6 Weeks	Adults with GAD, aged between 18 - 70 years Ashwagandha (20, 17) Placebo (19, 16)	Ethanolic extract of Ashwagandha Two 250-mg tablets, twice daily - Ten tablets a day.	HAM-A, GRS	Ashwagandha (17 - Drowsiness (2), Heaviness of head (4), Increased frequency of migraine (1), Fatigue (1), Withdrawal fatigue (1), Itching (1), Numb hands (1), Bitter taste (1), Decreased appetite (1), Increased appetite (1), Decreased sleep (2), Gastritis (2), Heaviness in stomach (1)). Placebo (16 - Giddiness (2), Dullness (1), Heaviness of head (1), Fatigue (1), Chest pain (1), Chest infection (1), burning eyes (1), Burning urine (1), Multiple somatic complaints (1), Heat in body (1), Increased appetite (1), Gastritis (1), Heaviness in stomach (1), Diarrhea (1), Menstrual irregularities (2), Worsening of obsessive-compulsive disorder (1)).	Compared to the placebo, there was a trend for the anxiolytic superiority of drugs at week 2, and a statistically significant at week 6 with Ashwagandha.
Subclinical Hypothyroidism						
Subclinical Hyperthyroidism / Sharma et al 2018 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Adults aged between 18 and 50 years with elevated TSH (4.5 to 10µIU/L)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	TSH, Free T3, Free T4	Ashwagandha (1) Placebo (3)	Compared to placebo, Ashwagandha associated with significantly greater increases in T3, T4, and reduction in TSH.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
		Ashwagandha (25, 25), Placebo (25, 25)			Fever, Asthenia, cough and headache	The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Sexual Health in Men / Male sexual function						
Male Sexual Function and Fertility / Ambiye et al2013 **(India)**	Randomized, Double-Blind, Placebo – Controlled 12 Weeks	Infertile men / aged between 22 and 40 years Ashwagandha (21, 21), Placebo (25, 25)	225mg - Standardized Aqueous Ashwagandha Root Extract Thrice daily	Semen Parameters, Serum Testosterone, Serum Luteinizing Hormone	Ashwagandha (0) Placebo (0)	Ashwagandha is associated with significant increases in sperm concentration, semen volume, sperm motility, serum testosterone, and LH. No changes occurred in the placebo group The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Male Sexual Function / Chauhan et al 2022 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Males aged between 21 and 45 years with low sexual desire Ashwagandha (25, 25), Placebo (25, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	DISF-M, Serum Testosterone, PRL, SF-36	Ashwagandha (4 - Sleepiness, Mild Abdominal Pain, Low Grade Joint Pain) Placebo (3 - Abdominal Pain, Mild Diarrhea)	Compared to the placebo, Ashwagandha was associated with significantly greater increases in Total DISF-M scores and serum testosterone levels. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Idiopathic Male Infertility / Azgomi et al 2018a **(Iran)**	Triple-blind, Randomised, Parallel Group, Two Arm, clinical trial. 12 Weeks	Married infertile male patients aged between 18 and 45 years Ashwagandha (50, 46) Pentoxifyline (50, 45)	6 capsules containing 5 g Hydroalcoholic Ashwagandha root extract once daily 6 capsules containing 800 mg Pentoxifylline once daily	Sperm parameters	Ashwagandha (1 - nausea and epigastric pain) Pentoxifyline (3 - nausea and epigastric pain)	Compared to the baseline the administration of Ashwagandha markedly increased mean sperm count, progressive motility, and improved sperm morphology. The results showed that both WS and pentoxifylline meaningfully improve sperm parameters in idiopathic male infertility. However, the impacts of the two medications were not significantly different.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Seminal plasma metabolites of infertile males / Gupta et al 2013 **(India)**	Clinical Study 12 Weeks	Infertile males aged 22–45 years Ashwagandha (180) Control (50)	*Withania somnifera* root powder (5 g/ day)	Semen Profile, Testosterone, LH, FSH, PRL, IDH, LDH, ALT, AST	Ashwagandha (0) Control (0)	Compared to the baseline, Ashwagandha supplementation repairs the disturbed concentrations of lactate, alanine, citrate, GPC,histidine, and phenylalanine in seminal plasma and recovers the quality of semen. Serum biochemistry was also improved over post-therapy in infertile men. The safety of Ashwagandha was confirmed as there were no adverse events reported and Ashwagandha was well tolerated by all the participants.
Psychogenic erectile dysfunction / Mamidi et al 2011 **(India)**	Randomized, Single-blind, Placebo-controlled, parallel-group study. 8 Weeks	Patients with psychogenic erectile dysfunction aged between 18 - 60 years Ashwagandha (46, 41) Placebo (49, 45)	4 tablets 500mg Ashwagandha root powder - thrice daily	Semen analysis, Routine Hematological tests, Biochemical Investigations, Serum Testosterone	Ashwagandha (0) Placebo (0)	Compared to the baseline there was significant improvement in IIEF items, but the result was insignificant when compared to placebo. The safety of Ashwagandha was confirmed as there were no adverse events reported and Ashwagandha was well tolerated by all the participants.
Sexual Health in Women / Female sexual function						
Sexual Function and Fertility in Women / Dongre et al 2015 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Females aged between 21 and 50 years with female sexual dysfunction Ashwagandha (25, 25), Placebo (25, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	FSFI, FSDS, SAR	Ashwagandha (0) Placebo 0)	Compared to placebo, Ashwagandha associated with significantly greater increases in FSFI scores (total, arousal, lubrication, orgasm, satisfaction), FSDS, but not SAR The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
Sexual Health in Women / Ajgaonkar et al 2022 **(India)**	Randomized, Double-Blind, Placebo – Controlled 8 Weeks	Females aged between 18 and 50 years with a Female Sexual Function Index (FSFI) Ashwagandha (40, 37), Placebo (40, 35)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	FSFI, FSDS SAR, GHQ-28	Ashwagandha (3) Placebo (3) Nausea, Drowsiness	Compared to placebo, Ashwagandha associated with significantly greater increases in FSFI scores (total, arousal, lubrication, orgasm, satisfaction), FSDS, and Successful Sexual encounters. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Perimenopause						
Climacteric symptoms in Perimenopausal Women / Gopal et al2021 **(India)**	Randomized, Double-Blind, Placebo - Controlled Study 8 Weeks	Healthy women with perimenopausal symptoms aged 40 - 60 years Ashwagandha (40, 40), Placebo (40, 40)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	MRS, MENQoL, Hot Flash score, Hormonal Parameters	Ashwagandha (3 - Abdominal Discomfort, Abdominal Pain, Nausea) Placebo (4 - Abdominal Discomfort, Abdominal Pain, Insomnia, Nausea)	Compared to placebo, Ashwagandha administration resulted in a significant reduction in MENQoL score, hot flash score, serum FSH, LH, and testosterone. 41.7% reported treatment with Ashwagandha as "excellent" compared to the placebo i.e.,23.9% The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Personal Care / Hair and Skin Health						
Healthy Skin in Adults / Narra et al 2023 **(India)**	Randomized, Double-Blind, Placebo-Controlled study 8 Weeks	Healthy men and women aged between 18 and 60 years with Fitzpatrick phototype III-VI skin grade Ashwagandha (28, 27), Placebo (28, 26)	1 mL of skin lotion on the face until it was well absorbed	Physician Global Assessment Scores (Wrinkles, pores, hydration & pigmentation), Melanin Index Transepidermal, Water Loss Skin Elasticity, Skin Hydration	Ashwagandha (4 - Local Swelling, Erythema) Placebo (5 - Local Swelling, Erythema, Local Irritation)	Compared to placebo, Ashwagandha was associated with significant improvement in wrinkles, pores, hydration, pigmentation, and elasticity. A significant reduction was seen in TEWL and Melanin index The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Healthy Hair in Adults/ Yerram et al2023 **(India)**	Randomized, Double-Blind, Placebo-Controlled study 75 Days	Healthy adults between 18 and 45 years of age with mild to moderate hair loss including androgenic alopecia Ashwagandha (34, 30), Placebo (34, 31)	1-2 drops of the serum were taken and then applied to the hair once a day	Body fat percentage, Trichoscan hair analysis, Hair pull test, Hair-specific skindex-29	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha was associated with a significant reduction in hair shedding, and an improvement in hair density, growth, and thickness. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Strength, Endurance and Recovery						
Muscle Strength and Endurance / Vermaet al 2023 **(India)**	Randomized, Double-Blind, Placebo - Controlled study 8 Weeks	Healthy adults aged between 18 and 45 years Ashwagandha (40, 40), Placebo (40, 40)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Muscle strength (1- RM load for bench press and leg extension exercises),Muscle size (arm, chest, and upper thigh), Body fat percentage, VO2 Max	Ashwagandha (0) Placebo (0)	Compared to the placebo group Ashwagandha root extract supplementation demonstrated an improvement in chest press, leg press, and a significant improvement in endurance as compared to the placebo group. Also, significant improvements in muscle girth for the arm, and chest, were seen, and there was non significant increase in the muscle girth for thigh. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Health Indices in Professional Wrestlers / Barbara et al 2023 **(Poland)**	Randomized, Double-Blind, Placebo-Controlled study 8 Weeks	Professional athletes – highly qualified national team wrestlers Ashwagandha (12, 11), Placebo (14, 10)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Hematological parameters, Biochemical parameters, Body composition, Creatine kinase (CK) activity	Ashwagandha (0) Placebo (0)	Compared to the placebo, serum CK activity in the Ashwagandha group did not increase significantly, thus indicating improved muscle recovery. At the end of the study, the values of biochemical variables remain in the normal range after the Ashwagandha intervention. It was observed that Ashwagandha did not affect the liver parameters, it was well tolerated by all the participants with no reported adverse events.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Cardiorespiratory Endurance and Recovery / Tiwari et al 2021 **(India)**	Randomized, Double-Blind, Placebo - Controlled study 8 Weeks	Healthy adults aged between 18 and 45 years with BMI range 18.5-24.9 kg/m2 Ashwagandha (25, 25), Placebo (25, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	WHO-QOL-BREF, Sleepiness scale, Mental alertness on rising, Sleep quality scale	Ashwagandha (1 - Mild Ear pain) Placebo (3 - Diarrhoea, Low Grade Fever)	Compared to placebo, Ashwagandha is associated with statistically significant improvements in VO2 max, TRQ, DALDA, and RESTQ scores. In the Ashwagandha group, a majority of subjects (56%) showed good improvement, and 36% showed moderate improvement. The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study. The study concluded that the Ashwagandha root extract is safe, and well tolerated by all the participants.
Muscle Strength and Recovery / Wankhede et al 2015 **(India)**	Randomized, Double-Blind, Placebo - Controlled study 8 Weeks	Healthy males aged between 18 and 50 years with little experience in resistance training Ashwagandha (29, 25), Placebo (28, 25)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Muscle strength (1- RM load for bench press and leg extension exercises), Muscle size (arm, chest, and upper thigh), Body fat percentage, Muscle recovery, Serum Testosterone	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha is associated with greater increases in muscle strength (bench press and leg extension), muscle size (arm and chest), and serum testosterone; and greater reductions in creatine kinase and Body fat Percentage. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Cardiorespiratory Endurance / Choudhary et al 2015 **(India)**	Randomized, Double-Blind, Placebo - Controlled study 12 Weeks	Healthy athletic adults / aged between 20 and 45 years Ashwagandha (25, 25), Placebo (25, 24)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	VO2 max, WHOQOL	Ashwagandha (0) Placebo (0)	The mean change in VO2max and WHO-QOL subscale scores (physical health, psychological, social relationships, and social relationships, and environmental) was significantly greater in Ashwagandha compared to the placebo.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Cardiorespiratory endurance in elite Indian cyclists / Shenoy et al 2012 **(India)**	Randomized, Placebo-controlled study 8 Weeks	Adults (stated level medal winners) aged between 18- 27 years Ashwagandha (20, 18) Placebo (20, 19)	500mg - Aqueous Ashwagandha root extract powder - Twice daily	VO2 max, RER	Ashwagandha (0) Placebo (0)	Compared to the baseline, there was a significant improvement in all parameters including VO2 max and time for exhaustion on the treadmill. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Muscle Strength, Safety and Tolerability / Raut et al 2012 **(India)**	Dose-related, Open-label clinical study 4 Weeks	Healthy adults aged 18-30 years Ashwagandha (18, 18)	*Withania somnifera* extract 750 mg/day x10 days, 1000 mg/day x 10 days, 1250 mg/day x 10 days	Exercise tolerance (by Cycle Ergometer), Muscle strength, Body fat percentage and lean body weight, LFT, Serum HDL, LDL, and VLDL cholesterol	Ashwagandha 750mg (1 - Increase in appetite, libido, and hallucinogenic effects with vertigo) Ashwagandha 1000mg (0) Ashwagandha 1200mg (0)	Ashwagandha found to be safe on hematological and biochemical organ function tests. This study has also demonstrated muscle strengthening, lipid lowering, and improved quality of sleep in view of its traditional use as balya.
Physical performance and cardiorespiratory endurance / Sandhu et al 2010 **(India)**	Randomized, Placebo-controlled study 8 Weeks	Healthy adults aged 18 - 25 years Ashwagandha (10,10) Terminalia Arjuna (10, 10) Ashwagandha + Terminalia Arjuna (10, 10) Placebo (10, 10)	500mg - Aqueous Ashwagandha root extract powder - Once daily	Maximum velocity, Average absolute and average relative power of the lower limbs, 20-second wobble board test, Maximum oxygen consumption, Blood pressure, BMI	Ashwagandha (0) Terminalia Arjuna (0) Ashwagandha + Terminalia Arjuna (0) Placebo (0)	Compared to the placebo and Terminalia Arjuna, Ashwagandha increased velocity, power, and VO2 max. The safety of Ashwagandha was confirmed as there were no adverse events reported and Ashwagandha was well tolerated by all the participants.
Memory and Cognitive Performance						
Cognitive Performance / Choudhary et al2017a **(India)**	Randomized, Double-Blind, Placebo - Controlled Study 8 Weeks	Adults over the age of 35 with mild, subjective symptoms of memory impairment	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	Weschler Memory Scale III, Shepard Mental Rotation Task, Wisconsin	Ashwagandha (0) Placebo (0)	Mean scores on tests/subtests associated with immediate memory, general memory, executive function, and attention and information processing speed, were significantly better in the Ashwagandha group compared to placebo

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
		Ashwagandha (25, 25), Placebo (25, 25)		Card Sort Test, Eriksen Flanker Task, Trail Making Test, Mackworth Clock Test		The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Cognitive Functions and Stress / Gopukumar,et al 2021 **(India)**	Randomized, Double-blind, Parallel-group, Two-arm, Placebo-controlled 12 Weeks	Healthy Cognitively sound adults aged 20–55 years Ashwagandha (65, 62) Placebo (65, 63)	300mg - Hydroalcoholic Ashwagandha root extract - once daily	CANTAB, OHQ, PSQI PSS, MoCA Serum Cortisol, BDNF levels	Ashwagandha (0) Placebo (0)	Compared to the placebo, the CANTAB reported significantly improved recall memory, and the total error rate in recalling patterns significantly decreased in the Ashwagandha SR group. Also, lower PSS-10 score, serum cortisol levels, and Pittsburgh Sleep Quality Index (PSQI) score but higher Oxford Happiness Questionnaire (OHQ) scores were seen in Ashwagandha SR suggesting significantly lower stress levels and significantly better psychological well-being and sleep quality in the former. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Elderly Health and Wellbeing						
Elderly and General Wellbeing / Kelgane et al2020 **(India)**	Randomized, Double-Blind, Placebo - Controlled Study 12 Weeks	Healthy older-age adults aged between 65 and 80 years Ashwagandha (25, 19), Placebo (25, 20)	300mg - Standardized Aqueous Ashwagandha Root Extract Twice daily	WHO-QOL-BREF, Sleepiness scale, Mental alertness on rising, Sleep quality scale	Ashwagandha (0) Placebo (0)	Compared to placebo, Ashwagandha is associated with significantly greater improvements in WHOQOL-BREF scores (total score and global, physical, psychological, and environment domain), mental alertness on waking rating, and sleep quality rating, but not on the sleep scale scores The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
COVID-19						
Chemoprophylaxis of COVID-19 / Choprae al2021 **(India)**	Randomized, Prospective, Open-label, Parallel efficacy, Two arm, Multi-centre study 8 Weeks (Interim Analysis)	High risk health care workers (HCW) Ashwagandha (80, 34), Comparator (HCQ) (80, 36)	2 tablets of 250 mg *Withania somnifera* dried roots standardized aqueous extract - twice daily	Failure of prophylaxis' as confirmed COVID-19 by RT-PCR	Ashwagandha (27) Comparator (HCQ) (40)	The interim analysis suggests that WS is not inferior to HCQ. The results show non-inferiority for both symptomatic COVID-19 with RT-PCR and asymptomatic COVID-19 with RT-PCR and also for all RT-PCR positives.

Condition / Reference (Country)	Design & Duration	Participants	Intervention	Outcome Measures	Adverse events (Ashwagandha vs Placebo/ Control group)	Summary of results
						The reported adverse events were of mild severity and no intervention was required. These events were resolved without any intervention and participants continued the study treatments till the end of the study.
Obsessive-compulsive disorder						
Obsessive-compulsive disorder / Jahanbakshet al2016 **(Iran)**	Randomized, Double-blind, Placebo-controlled trial 6 Weeks	Adults with OCD Ashwagandha (15, 15) Placebo (15, 15)	*Withania somnifera* Root Extract 120mg / day	Y-BOCS	Ashwagandha (0) Placebo (0)	Compared to the placebo group, there was significant reduction in Yale-Brown Obsessive-Compulsive Scale score in Ashwagandha group. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Children studies						
Brumhana and Balya effect / Mishra et al 2010 **(India)**	Randomized, Placebo-controlled study 6 Weeks	Children between 3 years and 12 years Ashwagandha Ghrita (51, 41) Ashwagandha Granules (36, 36) Placebo (34, 34)	AshwagandhaGhrita - 2.5 – 4 gm for age 3-7 years, and 6 - 8gm for 8 -12 years Ashwagandha Granules - 2.5 – 4 gm for age 3-7 years, and 6 - 8gm for 8 -12 years	Muscular strength, Endurance Neck and abdomen circumference Skin fold thickness measurement	AshwagandhaGhrita (0) Ashwagandha Granules (0) Placebo (0)	Compared to placebo and Ashwagandha granules, the Ashwagandha ghrita group demonstrated a more significant improvement in all the parameters. The safety of Ashwagandha was confirmed as there were no adverse events reported and Ashwagandha was well tolerated by all the participants.
Anxiety Symptoms among children with ADHD / Hosseini et al 2019 **(Iran)**	Randomized, Double-Blind, Placebo – Controlled 6 Weeks	Children aged 7-12 years Ashwagandha (16, 14) Placebo (15, 14)	*Withania somnifera* Root Extract 10mg / day	RCMAS, ADHD-RS	Ashwagandha (0) Placebo (0)	*Withania somnifera* root extract reduces the symptoms of physiological anxiety, sensitivity, social concerns, and an overall score of RCMA among children with ADHD and comorbid anxiety disorders. The safety of Ashwagandha root extract was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.
Growth and Development in Infants /KoushikBaishya et al 2020.	Comparative Clinical Study 4 weeks	Infants upto 1 year Ashwagandha (20, 18) Placebo (20, 16)	AshwagandhaGrita - 0.5 ml/kg/day with milk	Anthropometrical Parameters	Ashwagandha (0) Placebo (0)	Ashwagandha Ghrita enhances growth and development in the infant. The safety of Ashwagandha ghrita was confirmed as there were no adverse events reported and Ashwagandha root extract was well tolerated by all the participants.

Abbreviations

ADHD-RS - Attention Deficit Hyperactivity Disorder rating scale
ALP - Alkaline Phosphatase
ALT - Alanine Aminotransferase
API - Ayurvedic Pharmacopeia of India
AST - Aspartate Aminotransferase
ASU&H – Ayurveda, Siddha, Unani and Homeopathy
BAI - Beck Anxiety Inventory
BDNF - Brain-derived Neurotrophic Factor,
BMI - Body Mass Index
CANTAB - Cambridge Neuropsychological Test Automated Battery
CBC / FBC – Complete Blood Count,
CFS - Chalder Fatigue Scale
CNS - Central Nervous System
DASS – Depression Anxiety Stress Scale
DISF-M/ - Derogatis interview for sexual functioning (Male)
DILI- Drug-induced Liver Injury
EU - European Union
FCQ - Food Craving Questionnaire
FDA - Food and Drug Administration
FG – Fasting Glucose
FQ- Fatigue Questionnaire
FSH - Follicle-Stimulating Hormone
FSFI – Female Sexual Function Index
FSDS – Female Sexual Distress Scale
GAD-7 - Generalized anxiety disorder scale
GMP - Good Manufacturing Practices
GHQ – 28 – General Health Questionnaire- 28
GSH – Glutathione
GRS - Global Rating Scale
GSQS - Groningen Sleep Quality Scale
HaCaT- Human Epidermal Keratinocyte line
HAM-A/ HARS - Hamilton's Anxiety Rating Scale
HbA1c - Glycated Haemoglobin
HILI - Herb-induced Liver Injury
HPA - Hypothalamic-Pituitary-Adrenal
HRV – Heart Rate Variability
IDH - Isocitrate dehydrogenase

LDH - Lactate dehydrogenase
LFT – Liver Function Tests
LH - Luteinizing Hormone
MoCA - Montreal Cognitive Assessment
MDA – Malondialdehyde
MENQOL - Menopause-Specific Quality of Life
MRS – Menopause Rating Scale
NO - Nitric oxide
NOAEL - No Observed Adverse Effect Level
OHQ - Oxford Happiness Questionnaire
PRL – Prolactin
PROMIS-29 - Patient-Reported Outcomes Measurement Information System Questionnaire
PSQI – Pittsburgh Sleep Quality Index
PSS - Perceived Stress Scale
QC - Quality Control
QOL - Quality of life
RCMAS - Revised children's manifest anxiety questionnaire
RER - Respiratory exchange ratio.
RFT – Renal Function Test
RT-PCR - Reverse Transcription Polymerase Chain Reaction
SAR - Sexual Activity Records
SE – Sleep Efficiency
SF-36 – Short form 36 Questionnaire
SGOT - Serum Glutamic-Oxaloacetic Transaminase
SGPT - Serum Glutamic-Pyruvic Transaminase
SOL – Sleep Onset Latency
T3 – Triiodothyronine
T4 – Thyroxine
TFEQ - Three Factor Eating Questionnaire
TIB – Total Time in Bed
TSH - Thyroid Stimulating Hormone
TST – Total Sleep Time
TLC - Thin Layer Chromatography
USP - United States Pharmacopeia
VAS – Visual Analogue Scale
WASO – Wake After Sleep Onset
WHO – Hq - World Health Organization – Head Quarters
WHO-QOL – World Health Organization -quality of life Questionnaire
WS - *Withania somnifera*
Y-BOCS - Yale-Brown Obsessive-Compulsive Scale

Glossary

Adaptogenic - Substances that help the body adapt to stress and exert a normalizing effect upon bodily processes.

Antioxidant - A substance that inhibits oxidation, especially one used to counteract the deterioration of stored food products or remove potentially damaging oxidizing agents in a living organism.

Immunomodulatory - Capable of modifying or regulating one or more immune functions.

Neuroprotective - Capable of protecting neurons from injury or degeneration.

Phytochemicals - Chemical compounds produced by plants, generally to help them thrive or thwart competitors, predators, or pathogens.

Rasayana - A term in Ayurveda that refers to the science of lengthening lifespan and rejuvenation.

Thyrotoxicosis - The condition that occurs due to excessive thyroid hormone of any cause and therefore includes hyperthyroidism

Notes

Notes

Ashwagandha

(Withania somnifera)

Safety Dossier 2.0

The clinical safety of Ashwagandha endorsed by its usage since times immemorial is scientifically across scores of clinical trials. Ashwagandha is completely safe for human consumption when use judiciously.

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