pagepress

Journal of Biological Research 2025; volume 98:13901

Therapeutic potential of *Withania somnifera* (Ashwagandha): a comprehensive review of its phytochemical, pharmacological, and clinical applications

Martina Martorana,[1] Anastasia Valentina Liga,[2] Fabio Venturella[2]

[1]Independent Researcher, Palermo; [2]Biological, Chemical and Pharmaceutical Science and Technologies Department, University of Palermo, Italy

Abstract

Withania somnifera, commonly known as Ashwagandha or "Indian ginseng", is one of the most important medicinal plants in Ayurvedic tradition, historically used as a rejuvenating tonic (*rasayana*) to promote vitality, stress resilience, and longevity. In recent years, scientific interest in Ashwagandha has grown significantly, particularly for its potential applications in managing stress, chronic fatigue, cognitive decline, and various inflammatory and metabolic disorders. Several preclinical and clinical studies suggest that *Withania somnifera* exhibits adaptogenic, anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective activities, primarily attributed to the presence of withanolides, alkaloids, and flavonoids. However, despite encouraging findings, much of the current evidence stems from small-scale studies with heterogeneous methodologies, variable dosages, and inconsistencies in the standardization of extracts. Moreover, in some cases, clinical efficacy appears to fall short of expectations, with outcomes not always reaching statistical significance compared to placebo. This review critically examines the pharmacological properties and proposed mechanisms of action of *Withania somnifera*'s bioactive compounds, while highlighting both its therapeutic potential and the methodological limitations present in current research. The review was conducted using databases such as PubMed, ScienceDirect, HerbMed, and Google Scholar. Although Ashwagandha remains a promising candidate in the context of integrative medicine, larger and longer-term clinical trials are needed to confirm its effectiveness and to better define its safety profile.

Correspondence: Martina Martorana, Independent Researcher, Palermo, Italy.
E-mail: marty98mar@gmail.com

Key words: Ayurvedic tradition, adaptogen, longevity, anti-oxidant, pharmacological properties.

Conflict of interest: the authors declare no potential conflict of interest, and all authors confirm accuracy.

AI use statement: the authors declare the use of AI (ChatGPT) to rephrase and enhance the clarity of the text of the manuscript. All scientific content, critical analysis, and conclusions are entirely original and remain the full responsibility of the authors, who verified and approved every part of the manuscript. No sections were autonomously generated by AI.

Ethics approval and consent to participate: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Received: 16 April 2025.
Accepted: 13 November 2025.
Early view: 12 December 2025.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2025
Licensee PAGEPress, Italy
Journal of Biological Research 2025; 98:13901
doi:10.4081/jbr.2025.13901

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial International License (CC BY-NC 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Introduction

Ashwagandha (ASH), the common name, or *Withania somnifera*, the scientific botanical name, is an evergreen shrub native to India, also known as "Indian ginseng" or "winter cherry."[1] The raw material used in medicine is the root, and the name "Ashwagandha" is derived from the word "*ashwa*", that means horse. It is believed that after consuming the root, one gains powers similar to that of a horse. The second part of the name "*gandha*", means fragrance and refers to the characteristic smell of the fresh root of the plant.[1]

Since ancient times, *Withania somnifera* has been traditionally used in Ayurvedic medicine as a plant that strengthens the nervous system. This is evidenced by its adaptogenic effects and medicinal uses, the so-called "*rasayana*".[2]

The history of its use in traditional Indian medicine dates back nearly 3,000 years. Its root has been used as an aphrodisiac, narcotic, tonic, diuretic, anthelmintic and stimulant. It is naturally native to India, but it is also cultivated in other areas such as the Mediterranean countries, the Himalayan areas, Africa, Canary Islands, Cape of Good Hope and Australia.[3-5]

In recent years, there has been a growing interest in the potential health benefits of ASH, particularly in the areas of stress management, cognitive function, and physical performance; several studies have suggested that ASH supplementation may exhibit neuroprotective activity, anti-inflammatory, immunomodulatory and antibacterial properties and be helpful in obsessive-compulsive disorder.[2]

Active constituents overview

ASH is characterized by a rich phytochemical composition; withanolides and alkaloids are active substances that play a crucial role in the pharmacological action. Withanolides are compounds whose essential structure is that of ergostane, which has a six-membered lactone ring at the C-8 or C-9 position. The group of withanolides includes withapherin A (Figure 1), withanolides A-Y, withanone, withasomniferin A, and withasomniferols A-C. [6]

Alkaloids include withanine, somniferine, somnine, tropine, pseudowithanine, somniferinine, pseudotropine, choline, cuscohygrine, isopelletierine, and anaferine.[6] Flavonoids which include 3-O-rutinoside, 6,8-dihydroxycemferol, quercetin and its glycosidic derivative, 3-O-rutinoside-7-O-glucoside, are also present in the raw material.[2]

All parts of the plant (leaves, flowers, seeds, root) demonstrate therapeutic potential, but the root is the part that is mostly used medicinally.[2]

Effects on stress and fatigue

Root and leaf extracts of *W. somnifera* have shown notable anti-stress and anxiolytic effects in both animal and human studies.[7] One randomized, double-blind, placebo-controlled trial, conducted over 60 days at the Narayana Institute of Cardiac Sciences (Bangalore, India) and the Vijaya Super Specialty Hospital (Nellore, India), involved 54 participants divided equally into an Ashwagandha root extract (ARE) group and a placebo group (n=27 each). The intervention consisted of a once-daily dose of ARE standardized to 2.5% withanolides. The study aimed to evaluate a broad range of outcomes, including changes in Perceived Stress Scale (PSS) and Generalized Anxiety Disorder (GAD-7) scores, Quality of Life (QOL), cognitive performance via the Cambridge Neuropsychological Test Automated Battery (CANTAB), and several biochemical markers such as salivary cortisol, urinary serotonin and dopamine, and serum levels of Nitric Oxide (NO), Glutathione (GSH), and Malondialdehyde (MDA). The results indicated that ARE supplementation was associated with reductions in cortisol and increases in serotonin levels, correlating with improvements in stress and anxiety symptoms among healthy individuals with mild to moderate complaints. However, while the findings appear promising, the small sample size and relatively short duration limit the generalizability of these results. Further studies with larger populations and longer follow-up are needed to validate these effects and determine their clinical significance.[8]

Stress, defined as a disruption of physiological homeostasis, is becoming increasingly prevalent and exerts a profound impact on both mental and physical health, raising the risk of morbidity and mortality. Adaptogens, natural substances that enhance the body's resilience to stress, have garnered attention for their anti-fatigue, antidepressant, anxiolytic, stress-reducing, and anti-aging properties. Among the most studied adaptogens there are those from *Withania somnifera*, *Rhodiola rosea*, *Tribulus terrestris*, *Panax ginseng* (Korean ginseng), *Eleutherococcus senticosus* (Siberian ginseng), and *Bacopa monnieri*.[9] A clinical study investigated the effects of ASH supplementation on fatigue and sex hormone levels in overweight or mildly obese adults (aged 40 to 75) who self-reported moderate-to-high stress and fatigue.[10] The participants were selected based on specific criteria, including a Patient-Reported Outcomes Measurement Information System (PROMIS)-29 fatigue subscale score ≥9 and a Perceived Stress Scale (PSS) score ≥14. Importantly, subjects were non-smokers, had a Body Mass Index (BMI) between 25 and 35 kg/m², and agreed not to change their diet or start new treatments during the study. While ASH supplementation led to a reduction in perceived stress, this change did not reach statistical significance compared to placebo (p=0.867). However, significant improvements were observed in fatigue symptoms, as measured by the Chalder Fatigue Scale (p=0.016), alongside an increase in heart rate variability (p=0.003), suggesting enhanced autonomic regulation. Notably, men receiving ASH showed significant increases in serum free testosterone (p=0.048) and luteinizing hormone (p=0.002) relative to placebo. These results indicate that although ASH may not substantially reduce perceived stress

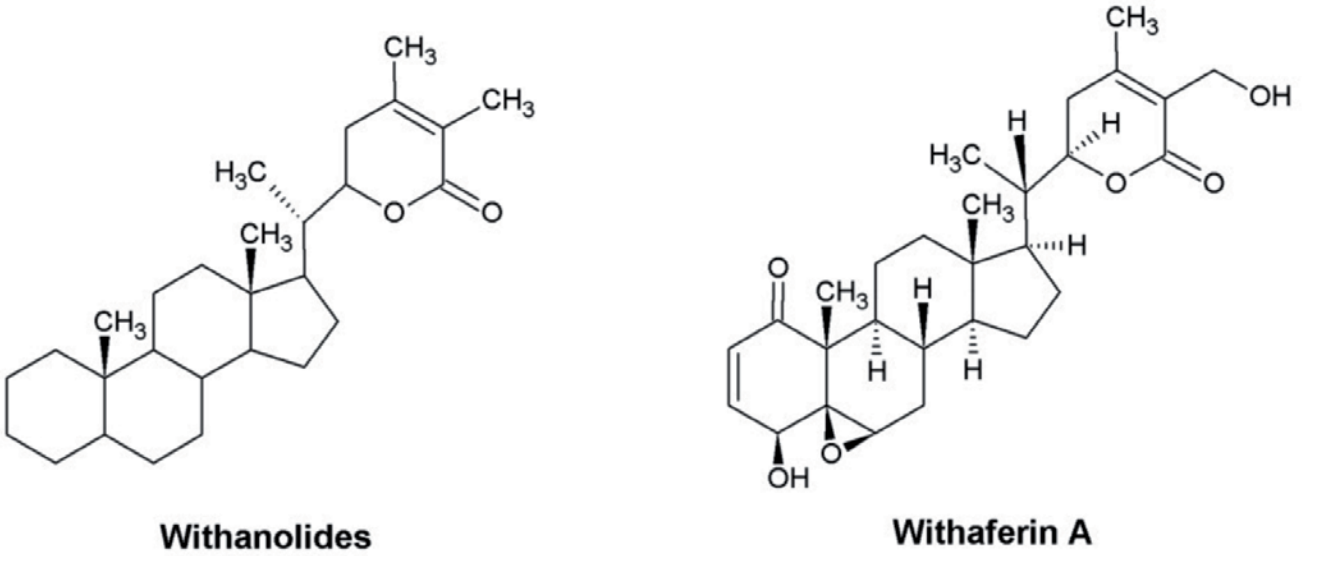

Figure 1. Structures of Withanolides and Withaferin A.

beyond placebo effects, it exerts promising anti-fatigue and hormonal effects, potentially mediated by modulation of the autonomic nervous system.[10]

In a subsequent 60-day randomized, double-blind, placebo-controlled trial, the stress-relieving and pharmacological effects of a standardized ASH extract (Shoden®, Arjuna Natural Pvt. Ltd., Aluva, Kerala, lndia) were evaluated in healthy adults experiencing stress. Sixty participants were randomly assigned to receive either 240 mg of the ASH extract or a placebo once daily. The study assessed outcomes using the Hamilton Anxiety Rating Scale (HAM-A), the Depression, Anxiety, and Stress Scale-21 (DASS-21), and hormonal markers including cortisol, dehydroepiandrosterone-sulphate (DHEA-S), and testosterone. All participants completed the trial without any reported adverse events. Compared to placebo, ASH supplementation produced a statistically significant reduction in anxiety as measured by HAM-A ($p=0.040$) and showed a trend towards improvement in DASS-21 scores ($p=0.096$). Additionally, ASH intake was linked to significantly greater decreases in morning cortisol ($p < 0.001$) and DHEA-S ($p=0.004$) levels compared to placebo. Although testosterone levels increased over time in men receiving ASH ($p=0.038$), this change did not reach statistical significance when compared to placebo ($p=0.158$), and no changes were observed in women ($p=0.989$).[11] These findings support ASH's potential role in reducing anxiety and modulating stress-related hormonal pathways, though some hormonal effects, particularly on testosterone, warrant further investigation with larger sample size.

Effects on muscle mass and recovery

ASH supplementation has been reported to improve muscle mass and strength, suggesting potential benefits when combined with resistance training. However, the evidence, while promising, warrants cautious interpretation. In a randomized, double-blind, placebo-controlled trial lasting 8 weeks, 57 young men with limited resistance training experience were assigned to receive either 300 mg of standardized ARE twice daily or a placebo. Both groups followed an identical resistance training regimen, with outcomes measured by muscle strength One-Repetition Maximum (1-RM) bench press and leg extension, muscle size, body composition, serum testosterone levels, and markers of muscle recovery, such as serum creatine kinase.[12] The study found that the ASH group showed statistically significant improvements in muscle strength and size compared to placebo. Furthermore, serum creatine kinase levels suggested reduced exercise-induced muscle damage, accompanied by increased testosterone levels and decreased body fat percentage in the treatment group. Despite these positive findings, several limitations must be noted. The sample size was relatively small and limited to young men, restricting generalizability. The short duration (8 weeks) leaves unanswered questions about long-term efficacy and safety. Additionally, the study design did not account for dietary variables or compliance beyond self-report, which could confound the results. The biological mechanisms by which Ashwagandha might influence muscle hypertrophy and recovery remain insufficiently elucidated, necessitating further mechanistic studies.[12] In conclusion, while Ashwagandha supplementation shows potential as an adjunct to resistance training for enhancing muscle strength and reducing exercise-induced damage, these findings should be interpreted cautiously pending larger, longer-term, and more diverse studies to confirm efficacy and clarify underlying mechanisms.

Cardiorespiratory endurance

Staying on the topic of training, a study investigated the efficacy of ARE in enhancing cardiorespiratory endurance among healthy athletes. Fifty athletic adults were randomly assigned to either an ASH group, receiving 300 mg twice daily for 8 weeks, or a placebo group. Cardiorespiratory endurance was measured via Maximum Oxygen uptake (VO2 max), while stress management was evaluated using Total Quality Recovery Scores (TQR), Recovery-Stress Questionnaire for Athletes (RESTQ), Daily Analysis of Life Demands for Athletes (DALDA), alongside antioxidant level assessments. The ASH group showed a statistically significant improvement in VO2 max compared to placebo ($p=0.0074$), and also a significant increase from baseline within the group ($p<0.0001$). Stress and recovery-related scores (TQR, DALDA, RESTQ) all improved significantly in the ASH group relative to placebo, with particularly strong results in fatigue recovery, energy levels, and overall fitness metrics (all $p<0.0001$). Additionally, antioxidant levels were markedly enhanced in the ASH group. While these results are encouraging, several methodological considerations must be addressed. The study's sample size was modest, potentially limiting statistical power and the robustness of conclusions. Details about participant selection criteria and control for confounding factors such as diet, sleep, and training intensity were insufficiently described, which could influence outcomes like VO2 max and recovery scores. Furthermore, the study's short duration (8 weeks) may not capture longer-term effects or possible adverse outcomes. The reliance on self-reported questionnaires for recovery and stress introduces subjectivity that could bias results.[13]

In summary, ARE appears to improve cardiorespiratory endurance and recovery metrics in athletes over a relatively short period. However, these findings should be interpreted cautiously, pending replication in larger, more rigorously controlled trials that address the potential confounders and investigate the mechanistic basis for these effects.

Anti-inflammatory and anti-angiogenic properties

The rising prevalence of lifestyle diseases has driven interest in natural treatment alternatives. Plant-based therapies such as ASH are often regarded as safer and better tolerated than synthetic drugs.[14] However, while ASH extract has shown promising anti-angiogenic properties, specifically inhibiting Vascular Endothelial Growth Factor (VEGF)-induced capillary formation and reducing microvessel density, these findings are primarily preclinical and have yet to be thoroughly validated in clinical settings. Additionally, ASH's reported anti-inflammatory effects, including suppression of pro-inflammatory cytokines, are encouraging but require more rigorous human studies to establish clinical relevance and safety profiles. Thus, although ASH presents potential as a multi-target natural compound, caution is warranted before extrapolating these early mechanistic insights to broad therapeutic claims without further high-quality evidence.[14]

Metabolic and cardiovascular health

Withaferin A, a key bioactive compound in ASH, has been shown in experimental rat models of high-cholesterol-induced atherosclerosis to modulate oxidative damage by regulating inflammatory

mediators and apoptosis through the Phosphatidylinositol 3-kinase/Protein kinase B (PI3K/AKT) signaling pathway. This mechanism suggests a potential protective role of withaferin A in mitigating oxidative stress and inflammation, which are central to the progression of atherosclerosis and other lipid metabolism disorders, including obesity. However, these findings remain largely preclinical, and their translation to human physiology requires further investigation.[15]

ASH extract contains various substances with reported immunomodulatory effects, among which the notable ones are the withanolides (steroid derivatives), which influence the Hypothalamic-Pituitary-Adrenal (HPA) axis. A double-blind randomized controlled trial by Lopresti *et al.* demonstrated that administration of 240 mg of *W. somnifera* extract containing 84 mg of withanolide glycosides reduced morning cortisol and Dehydroepiandrosterone (DHEA) levels after 15 days, with corresponding improvements in mood and reductions in anxiety measured by the Hamilton Anxiety Rating Scale (HAM-A) and the Depression Anxiety Stress Scale-21 (DASS-21).[11]

Similarly, an 8-week study by Salve J. *et al*. observed dose-dependent reductions in cortisol and improvements in emotional state in participants receiving 250 mg or 600 mg of ASH extract, compared to placebo. Notably, the higher dose group showed greater benefits.[16]

Effects on blood pressure

Existing research on ASH's influence on Blood Pressure (BP) remains limited and somewhat inconsistent. In one study involving 51 hypertensive individuals, participants were divided into two groups: one receiving 2 g of ASH root powder with milk, the other with water. Baseline mean Systolic Blood Pressure (SBP) was 164 mmHg and 157 mmHg, respectively, decreasing modestly to 158 mmHg and 154 mmHg after supplementation, differences that were not statistically significant. Interestingly, mean Diastolic Blood Pressure (DBP) showed a more pronounced decrease, from 100.5 to 85 mmHg in the milk group and 101.2 to 92 mmHg in the water group, suggesting a potentially greater hypotensive effect on DBP than SBP.[17] The data also hinted that Ashwagandha administered with milk may be more effective in reducing BP than when given with water. The authors attribute these effects primarily to ASH's stress-reducing properties, which may downregulate HPA axis activation and oxidative stress, conferring cardioprotective benefits.[17] While this mechanistic explanation is plausible, the small sample size, lack of placebo control, and absence of statistical significance in SBP reduction call for cautious interpretation. Larger, well-controlled trials are needed to validate these findings and clarify optimal administration methods. Nonetheless, these preliminary results align with the broader hypothesis that ASH's anti-stress effects might correlate with reduced cardiovascular risk, although definitive evidence remains lacking. More broadly, accumulating data underline *W. somnifera*'s multifaceted potential in managing lipid metabolism disorders. Its anti-adipogenic activity, enhancement of energy expenditure, improvement in lipid profiles, and antioxidant and anti-inflammatory effects collectively warrant further rigorous clinical investigation to establish its therapeutic utility.[15]

Potential against SARS-CoV-2 (COVID-19)

Bioactive compounds in *W. somnifera*, such as Withanoside V, Withanone, and Somniferine, have been proposed as potential adjuncts in managing SARS-CoV-2 infection due to their immunomodulatory, anti-inflammatory, and antiviral properties. Molecular docking studies suggest that these compounds may inhibit critical viral proteases, including Mpro, PLpro, and 3CLpro, as well as interact with the viral spike protein. Of particular interest, Withanoside V has emerged as a promising inhibitor of the SARS-CoV-2 main protease (Mpro), a key enzyme necessary for viral replication and maturation.[18] Further *in silico* analyses indicate that methanolic extracts of *Withania somnifera*, containing alkaloids such as Anaferine, Cuscohygrine, and Hygrine, may target the α7 nicotinic acetylcholine receptors (α7 nAChRs). Given that dysregulation of the Nicotinic Cholinergic System (NCS) has been implicated in COVID-19 pathophysiology, this interaction might mitigate disease symptoms and progression.[18] While these computational findings are intriguing, they remain preliminary and require validation through *in vitro* and *in vivo* studies to substantiate any clinical relevance.[18] The complexity of COVID-19 pathogenesis and the multifactorial nature of immune responses underscore the need for cautious optimism when considering *W. somnifera* as a therapeutic option.

Impact on thyroid function

Subclinical Hypothyroidism (SCH), affecting approximately 3–8% of the global population, is often asymptomatic, complicating diagnosis and management. Given the central role of the thyroid gland and its hormones, triiodothyronine (T3) and thyroxine (T4), in regulating metabolism, reproduction, and overall physiological function, thyroid dysfunction can have widespread systemic effects. Consequently, interventions targeting thyroid health have garnered interest, with ASH commonly used as a supportive agent.[19]

In a double-blind, randomized, placebo-controlled trial by Sharma *et al*., 50 patients with SCH, characterized by elevated Thyroid-Stimulating Hormone (TSH) but normal T4 levels, were treated with either ARE (300 mg twice daily) or placebo for eight weeks. The ASH group showed a significant decrease in TSH and increases in T3 and T4, with the most pronounced effects observed at weeks 4 and 8 (T3 increased by +18.6% and +41.5%, T4 by +9.3% and +19.6%, and TSH decreased by −12.5% and −17.4%, respectively). Conversely, the placebo group displayed stable or slightly decreased thyroid hormone levels.[20] While these results are promising and suggest a potential therapeutic role for ASH in managing SCH, the study's relatively small sample size and short duration limit definitive conclusions. Furthermore, safety profiles over longer-term supplementation remain unclear.[19] Therefore, more rigorous, larger-scale studies are necessary to confirm these benefits, clarify mechanisms of action, and ensure safety before routine clinical recommendations.

Effects on Hypothalamic-Pituitary-Gonadal (HPG) axis and fertility

ASH has been used for centuries in Ayurvedic medicine as an aphrodisiac. In recent years, its potential role in treating reproductive system disorders, particularly infertility, has attracted scientific attention. One proposed mechanism involves modulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis, potentially influencing the balance of sex hormones. It has been hypothesized that Ashwagandha may act on Gamma-Aminobutyric Acid (GABA) receptors in the hypothalamus, thereby facilitating the release of Gonadotropin-Releasing Hormone (GnRH), which in turn stimu-

lates the pituitary to secrete Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH).[20,22] However, this mechanism remains speculative and is primarily supported by preclinical evidence.

A study conducted on a photorefractory Japanese quail model, characterized by regressed testes and reduced expression of estrogen receptor alpha (ERα), investigated the effects of ARE. The results showed an increase in ERα expression following oral administration compared to control animals.[23] Based on these findings, it was suggested that *W. somnifera* may alleviate reproductive quiescence in this model by reactivating the HPG axis and enhancing estradiol secretion. While these results are promising, they are limited to an animal model with questionable translatability to human reproductive physiology, and further research is needed to establish clinical relevance.

Skin photoaging properties

ASH has long been used in traditional Indian medicine to maintain vitality and promote skin rejuvenation. Aging and Ultra Violet (UV) exposure contribute to collagen degradation, loss of elasticity, and pigmentation changes. Ingredients such as ASH, combined with saffron and tocopherol, have been proposed to counteract oxidative stress and skin damage.[24] A recent randomized, double-blind, placebo-controlled study investigated the effects of an 8% ARE lotion on photoaged facial skin. Fifty-six healthy men and women aged 18 to 60 years with Fitzpatrick skin types III–VI were randomized to apply either the Ashwagandha-containing lotion (AG, n=28) or Placebo Lotion (PL, n=28) for 60 days. The primary outcome was the change from baseline at day 60 in the global physician assessment score covering five dermatological signs: wrinkles, pores, hydration/moisture, skin brightness/tone, and pigmentation. Secondary outcomes included Transepidermal Water Loss (TEWL), melanin index, hydration, and skin elasticity (R2 ratio). The quality of life was assessed using the Short Form Health Survey with 12 items (SF-12) questionnaire, and safety was monitored through adverse event reporting. The results showed a significantly greater reduction ($p<0.0001$) in the total physician assessment score with ASH (-74.69%) compared to placebo (-48.68%). Improvements in TEWL, skin hydration, and elasticity were also significantly greater in the Ashwagandha group ($p<0.0001$). However, changes in melanin index did not differ significantly between groups ($p=0.969$), suggesting limited effects on pigmentation. Adverse events were comparable, indicating a favorable safety profile.[24] While these findings are promising and support the topical use of ASH for mitigating some signs of photoaging and oxidative stress, limitations remain. The relatively short duration and modest sample size require larger, longer-term studies to confirm the durability and generalizability of these effects.

Potential hepatotoxicity

From a toxicological perspective, despite ASH's numerous health-promoting properties, concerns about potential adverse effects, particularly liver injury, have emerged. Five cases of liver damage linked to ASH-containing supplements have been reported, three in Iceland between 2017 and 2018,[25] and two by the Drug-Induced Liver Injury Network (DILIN) in 2016.[26]

The affected patients, mostly men with an average age of 43, developed symptoms such as jaundice, nausea, fatigue, pruritus, and abdominal discomfort after 2 to 12 weeks of use. The liver injury was characterized as cholestatic or mixed, with prolonged pruritus and hyperbilirubinemia lasting several weeks. Fortunately, none of the cases progressed to liver failure, and liver function normalized within 1 to 5 months in four patients. It is noteworthy that some patients were also using other supplements, including *Rhodiola* sp., which might have contributed to the hepatotoxic effects, complicating causal attribution. [27] At the molecular level, Siddiqui *et al.* identified a possible mechanism of liver toxicity involving withanone, a bioactive compound in ASH. Withanone can form labile adducts with DNA nucleosides such as deoxyguanosine, deoxyadenosine, and deoxycytidine, interfering with DNA's biological functions. It also forms reversible adducts with amines. Detoxification occurs via GSH, but when GSH levels are limited, withanone may induce DNA damage, suggesting a potential mechanism for hepatotoxicity.[28] These findings call for a critical perspective: despite promising therapeutic effects, Ashwagandha use is not without risks, especially concerning liver safety. Caution is warranted, particularly in individuals with existing hepatic risk factors or those taking multiple supplements. Further large-scale, controlled clinical studies are necessary to better clarify the safety ASH's profile.

Conclusions

Ashwagandha is associated with a broad range of purported therapeutic effects, rooted in traditional use and increasingly explored in modern scientific studies, though conclusive evidence remains limited in many areas. Its adaptogenic, anti-inflammatory, neuroprotective, immunomodulatory, and endocrine-regulating properties make it a versatile botanical with significant potential in the prevention and management of various health conditions, including stress-related disorders, metabolic syndromes, reproductive dysfunction, skin aging.

Clinical studies have shown promising results in improving stress resilience, cognitive function, muscle strength, hormonal balance, and cardiovascular health. Additionally, emerging data suggest potential antiviral and thyroid-supportive roles. However, despite its generally favorable safety profile, rare cases of hepatotoxicity highlight the need for careful monitoring, particularly in long-term or high-dose use.

Future research should focus on large-scale, long-duration, randomized clinical trials to better understand the optimal dosing, long-term safety, and mechanisms of action of ASH's bioactive compounds. Given its broad pharmacological profile, ASH holds substantial promise as an adjunct or alternative in integrative medicine.

References

1. Singh N, Bhalla M, de Jager P, Gilca M. An overview on ashwagandha: arasayana of ayurveda. Afr. J. Tradit. Complement. Altern Med 2011;8:208–13.
2. Mikulska P, Malinowska M, Ignacyk M, et al. Ashwagandha (*Withania somnifera*) current research on the health-promoting activities: a narrative review. Pharmaceutics 2023;15:1057.
3. Langade D, Kanchi S, Salve J, et al. Efficacy and safety of ashwagandha (*Withania somnifera*) root extract in insomnia and anxiety: a double-blind, randomized, placebo-controlled study. Cureus 2019;11:5797.
4. Połumackanycz M, Forencewicz A, Wesołowski M, Viapiana A. Ashwagandha (*Withania somnifera* L.) the plant with proven health-promoting properties. Farm Pol 2020;76:442–7.
5. Mirjalili MH, Moyano E, Bonfill M, et al. Steroidal lactones

from *Withania somnifera*, an ancient plant for novel medicine. Molecules 2009;14:2373–93.
6. John J. Therapeutic potential of *Withania somnifera*: a report on phyto-pharmacological properties. Int J Pharm Sci Res 2014;5: 2131–48.
7. Spears AB, Cabey KA, Soumyanath A, Wright KM. Effects of *Withania somnifera* on stress and stress related neuropsychiatric disorders anxiety, depression and insomnia. Neuro-pharmaceutical Curr 2021;19:1468-95.
8. Majeed M, Nagabhushanam K, Mundkur L. A standardized ashwagandha root extract alleviates stress, anxiety, and improves quality of life in healthy adults by modulating stress hormones: results from a randomized, double-blind, placebo-controlled study. Medicine (Baltimore) 2023;102:e35521.
9. Panossian AG, Efferth T, Shikov AN, et al. Evolution of the adaptogenic concept from traditional use to medical systems: pharmacology of stress and aging related diseases. Med Res Rev 2021;41:630–703.
10. Smith SJ, Lopresti AL, Fairchild TJ. Explore the efficacy and safety of a new standardized ashwagandha (*Withania somnifera*) root extract (Witholytin®) in adults suffering from high stress and fatigue in a randomized, double-blind, placebo-controlled study. J Psychopharmacy 2023;37:1091-104.
11. Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract: a randomized, double-blind, placebo-controlled study. Medicine (Baltimore) 2019;98:e17186.
12. Wankhede S, Langade D, Joshi K, et al. Examining the effect of *Withania somnifera* supplementation on muscle strength and recovery: a randomized controlled trial. J Int Soc Sports Nutr 2015;12:43.
13. Tiwari S, Gupta SK, Pathak AK. A double-blind, randomized, placebo-controlled trial on the effect of ashwagandha (*Withania somnifera* dunal.) root extract in improving cardiorespiratory endurance and recovery in healthy athletic adults. J Ethno-pharmacol 2021;272:113929.
14. Gregory J, Vengalasetti YV, Bredesen DE, Rao RV. Neuroprotective herbs for the management of alzheimer's disease. Biomolecules 2021;11.4:543.
15. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, et al. Ashwagandha's multifaceted effects on human health: impact on vascular endothelium, inflammation, lipid metabolism, and cardiovascular outcomes - a review. Nutrients 2024;16:2481.
16. Salve J, Pate S, Debnath K, Langade D. Adaptogenic and anxiolytic effects of ashwagandha root extract in healthy adults: a double-blind, randomized, placebo-controlled clinical study. Cureus 2019;11:e6466.
17. Kushwaha S, Betsy A, Chawla P. Effect of ashwagandha (*Withania somnifera*) root powder supplementation in treatment of hypertension. Stud Ethno-Med 2012;6.2:111-15.
18. Singh M, Jayant K, Singh D. *Withania somnifera* (L.) Dunal (ashwagandha) for the possible therapeutics and clinical management of SARS-CoV-2 infection: plant-based drug discovery and targeted therapy. Front Cell Infect Microbiol 2022;12: 933824.
19. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, et al. Can ashwagandha benefit the endocrine system?- a review. Int J Mol Sci 2023;24:16513.
20. Sharma AK, Basu I, Singh S. Efficacy and safety of ashwagandha root extract in subclinical hypothyroid patients: a randomised, double-blind, placebo-controlled study. J Altern Complement Med 2018;24:243-48.
21. Chauhan S, Srivastava MK, Pathak AK. Effect of standardized root extract of ashwagandha (*Withania somnifera*) on well-being and sexual performance in adult males: A randomized controlled trial. Health Sci Rep 2022;5:e74.
22. Boroujeni, SN, Malamiri, FA, Bossaghzadeh F, et al. The most important medicinal plants affecting sperm and testosterone production: a systematic review. JBRA Assist Reprod 2022; 26:522-30.
23. Baghel K, Srivastava R. Photoperiod dependent expression of estrogen receptor alpha in testes of japanese quail: Involvement of *Withania somnifera* in apoptosis amelioration. Biochem Biophys Res Commun 2021;534:957-65.
24. Narra K, Naik SK, Ghatge AS. A study of efficacy and safety of ashwagandha (*Withania somnifera*) lotion on facial skin in photoaged healthy adults. Cureus 2023;15:e36168.
25. Love A, Bjornsdottir TB, Olafsson S, et al. Low prevalence of hepatitis E in iceland: a seroepidemiological study. Scand J Gastroenterol 2018;53:293-96.
26. Bessone F, Hernandez N, Lucena MI, et al. The Latin American DILI registry experience: a successful ongoing collaborative strategic initiative. Int J Mol Sci 2016;17:313.
27. Björnsson HK, Björnsson ES, Avula B, et al. Ashwagandha-induced liver injury: a series of cases from Iceland and the U.S. Liver Int 2020;40:825-29.
28. Siddiqui S, Ahmed N, Goswami M, et al. DNA damage by withanone as a potential cause of liver toxicity observed for herbal products of *Withania somnifera* (ashwagandha). Curr Res Toxicol 2021;2:72-81.

Online supplementary material:

Table 1. Summary table: Therapeutic Effects of Ashawagandha.