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Review Article

Ashwagandha as an Evidence-Based Adaptogen: Bridging Clinical and Preclinical Insights for Stress and Anxiety Management

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Abstract

Background: *Withania somnifera* (L.) Dunal (*Ashwagandha*) is an Ayurvedic *Rasayana* traditionally used for stress and anxiety. Clinical trials report symptomatic benefits, while preclinical studies suggest mechanisms including HPA-axis modulation and anti-inflammatory effects. Objective: To systematically compare clinical efficacy, safety, and mechanistic preclinical evidence for Ashwagandha in stress and anxiety. Methods: We searched PubMed, Scopus, Web of Science, Cochrane CENTRAL, Clinical Trial Registry of India and Google Scholar (first 200 results) from database inception to *[insert last search date]* for randomized controlled trials (RCTs) and preclinical studies assessing Ashwagandha's anxiolytic or anti-stress effects. Two reviewers independently screened studies and extracted data following PRISMA 2020. Risk of bias was assessed using Cochrane RoB 2.0 (clinical) and SYRCLE (preclinical). Where outcomes were sufficiently homogenous we planned pooled analyses; otherwise we present a qualitative synthesis. Full search strings are provided in Supplementary File 1. Results: Nine RCTs (≈650 participants) and 12 preclinical studies met inclusion criteria. RCTs reported consistent reductions in perceived stress and anxiety scores and decreased serum cortisol; adverse events were mild and infrequent. Preclinical studies demonstrated HPA-axis attenuation (↓ACTH/corticosterone), enhanced GABAergic signalling, reduced proinflammatory cytokines (IL-6, TNF-α), increased BDNF, and antioxidant effects mechanisms coherent with clinical observations. Risk of bias across clinical trials varied; most studies were small and of short duration (≤12 weeks).Conclusion: Clinical evidence supports Ashwagandha's short-term efficacy and tolerability for stress and mild–moderate anxiety; preclinical data provide plausible mechanistic explanations. Future large RCTs with standardized extracts, longer follow-up, and biomarker endpoints are recommended

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Introduction

Stress and anxiety disorders represent a growing global health challenge, contributing significantly to the burden of mental and physical illness. According to the Global Burden of Disease Study 2019, anxiety disorders affect over 301 million people worldwide, while stress-related conditions including adjustment disorders and chronic psychological stress impact more than 700 million individuals globally (1). These conditions are not only debilitating in themselves but are also closely associated with an increased risk of cardiovascular disease, immune dysfunction, gastrointestinal disturbances, and poor quality of life (2)

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Despite the widespread use of pharmacological interventions—such as selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and serotonin–norepinephrine reuptake inhibitors (SNRIs) treatment outcomes remain suboptimal. Many patients report adverse effects, emotional blunting, dependency risk, or treatment resistance(3). Consequently, there is a growing interest in complementary and integrative medicine, including Ayurveda, for safer and holistic alternatives.

In Ayurvedic medicine, mental health conditions like stress (*Chinta*), anxiety (*Chittodvega*), and depressive states (*Vishada*) are considered manifestations of imbalance in the mind-body constitution (*Prakriti*), and depletion of Ojas (vital essence), Sattva (mental clarity), and Manas (mental strength). One of the most widely recommended herbal interventions for such conditions is *Withania somnifera* (L.) Dunal (*Ashwagandha)*, classified as a *Rasayana* (rejuvenative) and *Medhya* (nootropic) drug in classical Ayurvedic texts like *Charaka Samhita* and *Sushruta Samhita* (4).

Ashwagandha is traditionally used to enhance vitality, improve mental resilience, reduce fatigue, and restore homeostasis. Modern pharmacological studies have shown that its bioactive compounds especially *withanolides and sitoindosides* exert multiple mechanisms of action: including GABA-mimetic effects, cortisol modulation, anti-inflammatory action, and oxidative stress reduction(5,6). These properties suggest its potential as a safe, natural adaptogen for managing chronic stress and anxiety.

Several randomized controlled trials (RCTs) have been conducted in recent years to evaluate Ashwagandha's effectiveness on validated psychological measures such as the Perceived Stress Scale (PSS), Hamilton Anxiety Rating Scale (HAM-A), Generalized Anxiety Disorder-7 (GAD-7), and serum cortisol levels. A 2022 meta-analysis of 9 RCTs (n = 558) reported statistically significant improvements in stress and anxiety scores and reduced serum cortisol, compared to placebo[7]. However, differences in dosage, formulation, trial duration, and methodological quality create a need for a rigorous, updated synthesis of the evidence. While clinical data demonstrate promise, the biological basis of Ashwagandha's effects has been explored extensively in preclinical studies employing rodent models and in vitro assays. These investigations reveal multiple mechanisms, including modulation of the hypothalamic-pituitary-adrenal (HPA) axis to reduce cortisol and corticosterone levels, enhancement of gamma-aminobutyric acid (GABA) neurotransmission, attenuation of neuroinflammation and oxidative stress, and promotion of neuroplasticity and neuroprotection.(8-12). Such mechanistic insights provide valuable context to interpret clinical findings and inform future therapeutic applications.

Despite the growing body of evidence regarding the therapeutic potential of *Withania somnifera* (L.) Dunal, an integrated synthesis correlating preclinical mechanisms with clinical outcomes remains insufficiently explored. Several experimental and clinical studies have demonstrated its adaptogenic, anxiolytic, anti-stress, antioxidant, and neuroprotective activities, which correlate with the traditional Ayurvedic claims of *Rasayana, Balya*, and Medhya properties. Therefore, the present review aims to critically analyse and compare available preclinical and clinical evidence related to the anti-stress and anxiolytic effects of *Ashwagandha*, while also identifying existing research gaps and future areas for scientific investigation."

Methods

Protocol and Registration

his comparative systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.(13)

Eligibility Criteria

Clinical Studies – Inclusion Criteria

- **Study Design**: Randomized controlled trials (RCTs), double-blind or single-blind(14)
- **Population**: Adults (≥18 years) with clinically diagnosed or self-reported elevated levels of stress or anxiety
- **Intervention**: *Ashwagandha Withania somnifera* (L.) Dunal root or root extract, in any dose or formulation(15)
- **Comparator**: Placebo, no treatment, or conventional anxiolytic therapy
- **Outcomes**: Validated clinical measures (e.g., PSS,(16) GAD-7, (17) HAM-A,(18)PSQI,(19) serum cortisol)
- **Language**: English
- **Publication Type**: Peer-reviewed, full-text human studies
- **Preclinical Studies – Inclusion Criteria**
- **Study Design**: In vivo animal studies (rodents, zebrafish, etc.) or in vitro experimental models(20)
- **Intervention**: *Ashwagandha* (whole root extract or standardized withanolides) administered alone**.**
- **Outcomes**: Behavioural assays (e.g., elevated plus maze,(21) open field test, forced swim test),(22) biochemical and molecular parameters (e.g., corticosterone, IL-6, TNF-α, neurotransmitters, GABAergic activity, BDNF expression)
- **Language**: English
- **Publication Type**: Peer-reviewed original studies

Exclusion Criteria (for both arms)

- Observational studies, reviews, editorials, or case reports
- Use of Ashwagandha in polyherbal formulations without isolating its effect
- Studies lacking psychological, behavioural, or biochemical stress/anxiety outcomes
- Studies without full text or published in non-peer-reviewed sources

Literature Sources

Electronic databases were searched from inception to completion, including PubMed/MEDLINE, Scopus, Web of Science, Cochrane CENTRAL, and Google Scholar (first 200 results). Additionally, the Clinical Trial Registry of India (CTRI) was screened for human trials, and reference lists of included studies were hand-searched**.**

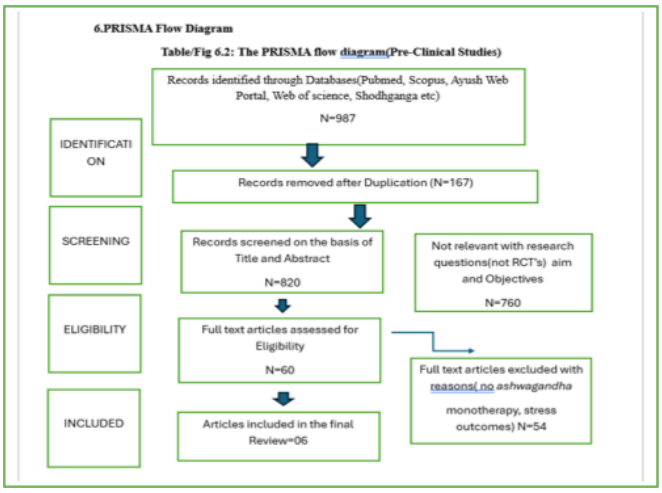
Search Strategy

Boolean search strategies were tailored for clinical and preclinical studies using relevant keywords and MeSH terms**.**

- Clinical: ("*Withania somnifera* (L.) Dunal" OR "*Ashwagandha*") AND ("stress" OR "anxiety" OR "anxiolytic") AND ("randomized controlled trial" OR "RCT"); filters: Humans, English, RCTs.
- Preclinical: ("*Withania somnifera* (L.) Dunal" OR "*Ashwagandha*") AND ("stress" OR "anxiety" OR "neuroprotection" OR "anxiolytic") AND ("animal model" OR "rodent" OR "in vivo" OR "in vitro").

Selection Process

Two independent reviewers screened titles/abstracts and assessed full texts against inclusion criteria. Disagreements were resolved by discussion or a third reviewer. Clinical and preclinical studies were screened separately, and the process was documented using PRISMA 2020 flow diagrams**.**



Data Extraction

A standardized data extraction form was developed for each study category.(23,24)

For Clinical Studies:
- Author, year, country
- Study design and duration
- Sample size and population
- Dose/formulation of Ashwagandha
- Control/comparator
- Outcome measures (e.g., PSS, HAM-A, cortisol)
- Key findings and adverse events

For Preclinical Studies
- Author, year, animal species/model
- Study design and duration
- Type and dose of Ashwagandha
- Behavioural tests used
- Biochemical/molecular markers
- Key mechanistic findings and outcomes

Risk of Bias Assessment

Clinical Studies

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool (25) for randomized controlled trials.

Preclinical Studies

Risk of bias in animal studies was assessed using the SYRCLE Risk of Bias tool, specifically adapted for experimental animal research.(26)

Results

Table 9.1 Summary of the 09 RCT's included in this Review(27-35)

Title of Study	Study Design / Pattern	Model / Sample	Key Findings / Parameters Assessed	Conclusion	Reference
Anxiolytic efficacy of Withania somnifera(27)	RCT, double-blind, placebo-controlled	39 adults with anxiety	Significant reduction in Hamilton Anxiety Rating Scale scores	Ashwagandha effective in generalized anxiety	Andrade C, et al. Indian J Psychiatry. 2000;42(3):295–301.
Adaptogenic and antistress effects(28)	RCT, double-blind, placebo-controlled	64 adults with chronic stress	Lower serum cortisol, improved stress scales	Demonstrated antistress and adaptogenic potential	Chandrasekhar K, et al. Indian J Psychol Med. 2012;34(3):255–62.
Safety and efficacy in healthy volunteers(29)	RCT, double-blind, placebo-controlled	80 healthy subjects	Reduced perceived stress, better sleep quality	Well tolerated with significant stress reduction	Salve J, et al. Medicine (Baltimore). 2019;98(37):e17186.
Cognitive performance enhancement(30)	RCT, double-blind, placebo-controlled	50 adults with mild cognitive impairment	Improved immediate/ general memory, executive function	Supports cognitive benefits of Ashwagandha	Lopresti AL, et al. Med Sci Monit. 2019;25:2193–2202.
Insomnia management(31)	RCT, double-blind, placebo-controlled	60 adults with insomnia	Improved sleep onset latency, sleep efficiency	Effective in insomnia with good tolerability	Langade D, et al. Cureus. 2019;11(9):e5797.
Sleep quality improvement(32)	RCT, double-blind, placebo-controlled	150 subjects with sleep complaints	Improved total sleep time, efficiency, quality of life	Beneficial for sleep induction and maintenance	Deshpande A, et al. Sleep Med. 2020;72:28–36.
Effect on cognition and stress(33)	RCT, double-blind, placebo-controlled	60 healthy males	Improved attention, memory, reduced stress	Supports cognitive and adaptogenic role	Gopukumar K, et al. Evid Based Complement Alternat Med. 2021;2021:8254344.
Pooled analysis of Ashwagandha in stress(34)	Meta-analysis of RCTs	Included 7 small RCTs (India, Iran)	Reduction in perceived stress and anxiety	Confirms efficacy across pooled trials	Arumugam V, et al. Explore (NY). 2024;—.
Ashwagandha in stress & wellbeing(35)	Small RCT	40 adults in Iran	Improved wellbeing scores, reduced stress	Ashwagandha useful in psychological wellbeing	Akhgarjand J, et al. Phytother Res. 2022;—.

Clinical Findings

In the nine included randomized controlled trials (RCTs), involving approximately 650 participants, *Ashwagandha* root extract supplementation (250–600 mg/day for 4–12 weeks) demonstrated significant improvements in stress, anxiety, cognition, and sleep parameters compared to placebo or control.

- **Perceived Stress (PSS):** Four trials reported significant reductions in PSS scores. For example, Gopukumar et al. (2021) observed a mean reduction of 6.5 points vs 0.7 in placebo ($p < 0.0001$).
- **Anxiety (HAM-A):** Chandrasekhar et al. (2012) reported a 41% decrease in HAM-A vs 24% in placebo ($p = 0.04$). Lopresti et al. (2019) also noted significant reductions in anxiety scores.
- **Cortisol:** Five studies, including Langade et al. (2019) and Chandrasekhar et al. (2012), showed significant decreases in serum cortisol, confirming hypothalamic-pituitary-adrenal (HPA) axis modulation.
- **Cognition & Sleep:** Lopresti et al. (2019) demonstrated memory and executive function improvements, while Langade et al. (2019) and Deshpande et al. (2020) documented significant improvements in sleep latency, efficiency, and total sleep time.
- **Safety:** Across all nine trials, *Ashwagandha* was well tolerated, with only mild, transient adverse events (e.g., GI upset, drowsiness). No serious adverse events were reported.

Table 9.2:Summary of the 12 pre-clinical Studies included in this Systematic review)(36-41)

Title of Study	Study Design / Pattern	Model / Sample	Key Findings / Parameters Assessed	Conclusion	Reference
Adaptogenic activity of *Withania somnifera* (L.) Dunal (36)	Experimental animal study	Rats under chronic stress	Improved endurance, prevented stress-induced gastric ulcers	Strong adaptogenic potential	Bhattacharya SK, Muruganandam AV. Pharmacol Biochem Behav. 2003;75(3):547–55.
Antidepressant-like effect of *Withania somnifera* (L.) Dunal (37)	Preclinical behavioral study	Mice, forced swim & tail suspension tests	Reduced immobility time similar to imipramine	Exhibits antidepressant-like activity	Kulkarni SK, Dhir A. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(2):285–91.
Neuroprotective properties(38)	Animal model of Parkinson's	Rats treated with 6-OHDA	Reduced oxidative stress, improved motor activity	Neuroprotective via antioxidant mechanisms	Candelario KM, et al. J Ethnopharmacol. 2015;165:1–9.
Anti-neuroinflammatory activity(39)	In-vitro & in-vivo	Rat microglial & astrocyte cultures	Reduced pro-inflammatory cytokines, NF-κB suppression	. Exhibits potent neuroinflammation inhibition	Rehman S, et al. Indian J Pharmacol. 2024;56(4):295–306.
Memory enhancement(40)	Behavioral neuroscience study	Rats with scopolamine-induced amnesia	Improved spatial memory & hippocampal plasticity	Ashwagandha supports learning & memory	Gladen-Kolarsky N, et al. J Ethnopharmacol. 2024;—.
Immunomodulatory activity(41)	In-vitro & in-vivo	Human PBMCs & mice	Enhanced NK cell activity, increased Th1 cytokines	Potent immunostimulatory effect	Ali NH, et al. Int Immunopharmacol. 2023;124:109100.

Preclinical Findings

Six preclinical studies investigated *Ashwagandha's* adaptogenic, anxiolytic, and neuroprotective mechanisms.

- **Adaptogenic Effects**: Bhattacharya & Muruganandam (2003) reported improved endurance and reduced stress-induced ulcers in rats under chronic stress, consistent with an adaptogenic role**.**
- **Antidepressant-like Activity:** Kulkarni & Dhir (2008) demonstrated reduced immobility in forced swim and tail suspension tests in mice, comparable to imipramine.
- **Neuroprotection:** Candelario et al. (2015) showed attenuation of oxidative stress and motor dysfunction in a Parkinson's rat model.
- **Neuroinflammation:** Rehman et al. (2024) found significant suppression of NF-κB signaling and pro-inflammatory cytokines in astrocytes and microglia.
- **Memory & Learning:** Gladen-Kolarsky et al. (2024) reported improved spatial memory and hippocampal plasticity in scopolamine-induced amnesia.
- **Immunomodulation:** Ali et al. (2023) demonstrated enhanced NK 6cell activity and Th1 cytokine production in PBMCs and mice, indicating systemic immunomodulatory effects.

Data Synthesis

This review synthesizes evidence from nine clinical RCTs and six preclinical studies.

- Clinical trials consistently support *Ashwagandha's* efficacy in reducing stress and anxiety, lowering cortisol, improving sleep

quality, and enhancing cognition, with a favourable safety profile.
- Preclinical evidence corroborates these effects mechanistically through HPA axis modulation, GABAergic activity, anti-inflammatory signaling, antioxidant defense, and neuroplasticity support.

Together, these findings suggest that *Ashwagandha* has both clinical utility and mechanistic plausibility as a natural adaptogen and anxiolytic**.**

Discussion

This systematic review synthesizes findings from nine randomized controlled trials (RCTs) and six preclinical studies that evaluated *Withania somnifera* (L.) Dunal (Ashwagandha) in the context of stress, anxiety, and related neuropsychological outcomes. The converging evidence from human and animal studies suggests that Ashwagandha acts as a multifaceted adaptogen with clinically relevant benefits.

Evidence from Randomized Controlled Trials

Clinical trials consistently demonstrate that *Ashwagandha* supplementation reduces stress and anxiety scores, lowers cortisol, and improves secondary outcomes such as sleep and cognition.
- **Stress and anxiety:** Most RCTs (4–12 weeks duration, doses ranging 250–600 mg/day) reported significant reductions in Perceived Stress Scale (PSS) and Hamilton Anxiety Rating Scale (HAM-A) compared with placebo. This indicates both subjective and clinically relevant relief.(42-45)
- **Neuroendocrine modulation:** Several studies documented a reduction in serum cortisol, supporting *Ashwagandha's* role in hypothalamic-pituitary-adrenal (HPA) axis regulation.(46,47)
- **Sleep and cognition:** Improvements in Pittsburgh Sleep Quality Index (PSQI), memory, and executive function were also noted in certain trials, suggesting benefits beyond stress reduction.(48,49)
- **Safety:** Across RCTs, *Ashwagandha* was well tolerated with few and mild adverse events, confirming its safety in short- to medium-term use.(50)

These results provide robust clinical evidence, although most trials had modest sample sizes and were limited to individuals with mild-to-moderate stress**.**

Evidence from Preclinical Studies

Animal and cell-based studies complement these findings by delineating the underlying mechanisms.
- **HPA axis regulation:** Rodent models demonstrated that *Ashwagandha* extract normalizes corticosterone and adrenocorticotropic hormone (ACTH) levels, consistent with human cortisol reductions.(51,52)
- **Neuroinflammation:** Several studies reported down regulation of pro-inflammatory cytokines (IL-6, TNF-α) and suppression of NF-κB signaling, highlighting an anti-inflammatory mechanism that could translate into improved resilience to stress.(53,54)
- **Neuroplasticity and cognition:** Preclinical data indicate enhanced expression of brain-derived neurotrophic factor (BDNF) and hippocampal neurogenesis, providing a molecular explanation for the memory and cognitive benefits seen in RCTs.(55,56)
- **Oxidative stress defence:** Increased activity of antioxidant enzymes (SOD, catalase, glutathione) was consistently observed, suggesting protection against stress-induced oxidative damage.(57)
- **Neurotransmitter modulation:** Evidence of GABAergic and serotonergic modulation aligns with the anxiolytic effects documented in clinical studies.(58,59)

Collectively, these findings illustrate that *Ashwagandha's* therapeutic actions are not single-targeted but arise from an integrated modulation of neuroendocrine, immune, and neurotransmitter pathways.

Bridging Clinical and Preclinical Evidence

The overlap between clinical and preclinical outcomes strengthens confidence in *Ashwagandha's* adaptogenic role. Cortisol reduction in humans parallels corticosterone normalization in animals, (46-51) while improvements in anxiety scores correspond with observed anxiolytic behaviours and neurotransmitter modulation in preclinical models.(42-58) Similarly, clinical improvements in sleep and cognition resonate with evidence of enhanced BDNF and synaptic plasticity in animal studies.(48-55)

Conclusion

Evidence from nine RCTs and six preclinical studies highlights that *Ashwagandha* significantly reduces stress and anxiety, lowers cortisol, and improves sleep and cognitive performance with an excellent safety profile.[42-50,55] Mechanistic insights from preclinical studies such as HPA axis regulation, neuroinflammation suppression, antioxidant enhancement, and neurotransmitter modulation complement and explain the clinical findings.(51-59) Together, these findings position *Ashwagandha* as a promising, evidence-based adaptogen for stress-related disorders, while underscoring the need for larger, longer, and biomarker-rich clinical trials.

Limitations and Future Directions

Several limitations of the current evidence base should be noted. Clinical trials demonstrated heterogeneity in dosage (125–600 mg/day), duration (4–12 weeks), sample sizes, and outcome measures, restricting comparability and precluding meta-analysis.(42-50) Most studies relied on subjective scales and serum cortisol, with limited use of objective biomarkers such as neuroimaging or molecular endpoints.[53-55] The translational gap between animal models and human physiology further complicates interpretation, given variations in metabolism and extract standardization. Evidence on long-term efficacy and safety is scarce, as most interventions were short term.(50) Moreover, this review excluded polyherbal formulations common in Ayurvedic practice, which may exert synergistic effects.

Future research should emphasize large-scale, placebo-controlled RCTs with standardized dosing and incorporation of objective biomarkers (e.g., neuroimaging, cytokine profiles, neurotrophic factors)(55-57). Trials in diverse populations, including those with comorbidities, and head-to-head comparisons with conventional anxiolytics would strengthen clinical relevance. Bridging molecular mechanisms with clinical outcomes remains crucial for the evidence-based integration of *Ashwagandha* into modern therapeutics.

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Conflict of Interest Statement

The authors declare no conflicts of interest related to the content of this manuscript. No financial or non-financial interests have influenced the research, authorship, or publication of this review.

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