IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# *Ashwagandha* (Withania Somnifera) In Stress And Neurodegenerative Disorders: A Critical Review

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**Abstract**

**Background:** *Withania somnifera* (*ashwagandha)* is an Ayurvedic adaptogen increasingly studied for stress/anxiety reduction and potential neuroprotective effects. This review critically examines phytochemistry, mechanisms, clinical evidence in stress and anxiety, preclinical and clinical evidence relevant to neurodegenerative disorders, and safety signals. Methods: We searched PubMed/PMC, ClinicalTrials.gov and major journals for randomized clinical trials, systematic reviews, preclinical neuroprotection studies and safety reports up to 2025. Selected high-quality RCTs, systematic reviews and mechanistic papers were prioritized. **Results:** Multiple RCTs and meta-analyses report reductions in perceived stress/anxiety and cortisol with *ashwagandha* extracts (typical doses 225–600 mg/day) versus placebo; effect sizes vary and risk of bias exists in several trials. Preclinical studies show antioxidant, anti-inflammatory, modulation of HPA axis and direct neuronal effects of withanolides; some withanolides cross the blood–brain barrier and show benefit in animal models of Alzheimer's and Parkinson's disease. Safety data is generally favorable in short trials, but recent case series and pharmacovigilance reports describe rare herb-associated liver injury and possible thyroid effects. **Conclusions:** Evidence supports *ashwagandha's* anxiolytic and stress-reducing potential; neuroprotective findings are promising but largely preclinical with limited human data. Larger, standardized, long-term clinical trials and rigorous pharmacovigilance are needed before recommending ashwagandha routinely for neurodegenerative disorders.

**Keywords:** *Ashwagandha; Withania somnifera*; Stress; Neurodegeneration; Withanolides; Neuroprotection; Anxiety; Cognitive impairment.

## Introduction

*Ashwagandha (Withania somnifera*) is a widely used Ayurvedic botanical classified as a *rasayana* and adaptogen. Interest in its psychotropic and neuroprotective potential has increased substantially, with clinical trials reporting benefits in stress, anxiety and sleep and preclinical studies indicating neuroprotection via antioxidant, anti-inflammatory and trophic mechanisms. However, heterogeneity in extracts, doses, study quality and emerging safety reports require a critical appraisal.

## Methods

We searched PubMed/PMC, ClinicalTrials.gov and major publishers for terms: “Withania somnifera”, “*ashwagandha*”, “stress”, “anxiety”, “cognitive”, “Alzheimer”, “Parkinson”, “withanolide”, “neuroprotection”, “randomized”, “trial”, and “liver injury” (searches completed up to March 2026). We prioritized randomized controlled trials (RCTs), systematic reviews/meta-analyses, mechanistic in vivo/in vitro studies, regulatory safety reports and case series. Key sources include Chandrasekhar et al. 2012 (randomized trial), Lopresti et al. 2019 (RCT), Langade et al. 2019 (sleep/anxiety), systematic reviews (2021–2025) and mechanistic reviews on withanolides.

## Phytochemistry and putative mechanisms

Major bioactive constituents are withanolides (steroidal lactones, eg. withaferin A, withanolide A), alkaloids and sitoindosides. Withanolides modulate multiple intracellular pathways (PI3K/Akt/mTOR, NF-κB, Nrf2), inhibit neuroinflammatory signaling, and have antioxidant effects. Some metabolites (e.g., withanolide A derivatives) cross the blood–brain barrier in animal studies and exert direct neuroprotective effects (anti-apoptotic, promoting neurite outgrowth). Ashwagandha also influences the hypothalamic-pituitary-adrenal (HPA) axis (reducing cortisol), GABAergic and serotonergic activity, and may increase neurotrophic factors in preclinical models.

## Clinical evidence — Stress, anxiety, and sleep.

Several RCTs and meta-analyses show reductions in perceived stress, anxiety scales (HAM-A/DASS), and serum cortisol after *ashwagandha* supplementation (common regimens: 300–600 mg/day for 6–12 weeks). Notable trials: Chandrasekhar et al. (2012) double-blind RCT (600 mg/day) — significant reductions in stress and cortisol; Lopresti et al. (2019) randomized trial showed reduced anxiety and HPA modulation; Langade et al. (2019) reported improved sleep parameters and anxiety with 300 mg twice daily. Systematic reviews and recent meta-analyses support overall beneficial effects but highlight heterogeneity and some risk of bias.

## Clinical evidence — Cognitive function & neurodegenerative disorders

Human data for Alzheimer’s disease (AD), Parkinson’s disease (PD) or other neurodegenerative disorders are limited. Small human studies and some open-label trials suggest improvement in attention, memory and executive function in healthy and mild cognitive impairment cohorts, but large RCTs in established AD/PD are lacking. Preclinical studies (rodent, cellular models) demonstrate reduced amyloid-β toxicity, tau hyperphosphorylation attenuation, mitigation of dopaminergic neuronal loss in toxin models, and promotion of synaptic repair — supporting a theoretical benefit for neurodegeneration that requires translation to clinical trials.

**Preclinical neuroprotective evidence**

- Withanolides inhibit oxidative stress and neuroinflammation, upregulate antioxidant defenses (Nrf2 pathway) and modulate apoptotic signaling.
- Withanolide A and derivatives have shown BBB penetration and protection in Alzheimer's/Parkinson's animal models, improving behavioral and histological outcomes.

**Safety, adverse events and regulatory notes**

Short-term clinical trials (6–12 weeks) generally report mild, transient adverse events (GI upset, drowsiness) and favourable lab safety profiles. However, case series and pharmacovigilance have reported rare herb-associated liver injury and isolated thyroid perturbations; regulatory safety reviews (e.g., AYUSH safety report and LiverTox summary) urge careful monitoring and quality control of commercial products. Interactions with sedatives, immunosuppressants, antithyroid drugs, and serotonergic agents are potential concerns. Quality of commercial preparations (root vs whole plant extract, standardization of withanolide content) affects efficacy and safety.

**Tables**

**Table 1 — Selected randomized clinical trials of ashwagandha for stress/anxiety/sleep (representative)**

| Study (year) | Design | Dose & Duration | Population | Primary outcome (result) |
|---|---|---|---|---|
| Chandrasekhar et al., 2012. (India) | RCT, double-blind, placebo | 300 mg twice daily (600 mg/day), 60 days | Adults under chronic stress | ↓ Perceived stress scale and ↓ serum cortisol vs placebo |
| Lopresti et al., 2019. | RCT, double-blind | 240–600 mg/day, 60 days (formulation dependent) | Adults with stress/anxiety | ↓ HAM-A, ↓ cortisol; effect vs placebo |
| Langade et al., 2019. | RCT, double-blind | 300 mg twice daily, 10 weeks | Insomnia patients | Improved PSQI and HAM-A scores vs placebo |
| Leonard et al., 2024. | Randomized, crossover | 225 mg, acute & repeated dosing | Healthy adults | Some improvements in memory, attention; ↓ tension/fatigue |
| Deshpande et al., 2020. | RCT | varied brands/doses | Healthy adults | Improved sleep quality in some formulations |

**Table 2 — Representative preclinical neuroprotection studies**

| Model | Intervention | Key findings |
|---|---|---|
| 6-OHDA SH-SY5Y PD model | KSM-66 root extract | Reduced oxidative stress, improved cell survival, altered redox proteins. |
| Transgenic/amyloid models | Withanolide-A, derivatives | Reduced amyloid toxicity, improved memory tasks in rodents. |
| Cell culture neurotoxicity models | Withanolide derivatives (CR-777) | Protection against diverse neuronal stressors; proposed roles in antioxidation and chaperone modulation. |

**Table 3 — Safety signals and regulatory / case reports (selected)**

| Source | Finding |
|---|---|
| LiverTox / NIH summary (2024) | Generally safe in trials but case reports of herb-associated liver injury exist; advise vigilance. |
| Iceland / US DILIN case series (Björnsson et al., 2020) | Case series documenting clinically apparent liver injury temporally associated with *ashwagandha* products. |
| AYUSH safety report (2024) | 90-day toxicity studies show limited adverse effects in animals at high doses; notes possible thyroid effects in case reports. |
| Recent RCT safety analyses (Verma et al., 2021; other RCTs) | Short-term use well tolerated in trial settings; longer duration data limited. |

## Discussion

1. **Efficacy for stress/anxiety**: Multiple RCTs and meta-analyses consistently show *ashwagandha* reduces perceived stress, anxiety scores and cortisol relative to placebo, with moderate effect sizes. However, heterogeneity in extract type (full-spectrum vs standardized KSM-66 etc.), doses (225–600 mg/day), trial quality and small sample sizes limit certainty.
2. **Promise for neurodegeneration but limited human evidence**: Robust preclinical data supports neuroprotective mechanisms (antioxidant, anti-inflammatory, chaperone modulation, promotion of neurite outgrowth). Yet clinical evidence in AD/PD patients is minimal; well-designed RCTs in MCI/early AD/PD are needed. Extrapolation from healthy or MCI subjects to frank neurodegenerative disease is premature.
3. **Safety and product quality**: Short-term RCTs indicate tolerability, but mounting case reports of liver injury and isolated thyroid effects underscore the importance of product quality (contaminants, adulterants), correct botanical identification, and post-marketing surveillance. Clinicians should ask patients about herbal use and monitor liver/thyroid tests if long-term use is considered.
4. **Research gaps**: Standardize extracts (report withanolide content), define optimal dose/duration, undertake long-term safety studies, and perform RCTs in neurodegenerative populations with clinically meaningful endpoints (cognition, function, biomarkers). Mechanistic human studies (imaging, CSF biomarkers) would help translation.

## Conclusion

Ashwagandha shows consistent evidence for stress and anxiety reduction in short-term randomized trials and has promising neuroprotective actions in preclinical models. However, heterogeneity of products, limited long-term human data, and rare but notable safety reports (liver, thyroid) necessitate cautious optimism. High-quality, standardized, long-term clinical trials are required before routine recommendation for neurodegenerative disorders.

## References


1. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum Ashwagandha root extract in reducing stress and anxiety in adults. *Indian J Psychol Med*. 2012;34(3):255–262.
2. Lopresti AL, Smith SJ, Drummond PD. 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(37):e17186.
3. Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and safety of Ashwagandha (Withania somnifera) root extract in insomnia and anxiety: a double-blind, randomized, placebo-controlled study. *J Ethnopharmacol*. 2019;? (published online) — see PubMed.
4. Speers AB, et al. Effects of Withania somnifera (Ashwagandha) on stress and mental health: a systematic review. *Complement Ther Clin Pract*. 2021;? (systematic review).
5. Mikulska P, et al. Ashwagandha (Withania somnifera)—Current Research on Its Neuroprotective Potential. *Phytother Res*. 2023;XX:XX–XX.
6. White PT, et al. Natural withanolides in the treatment of chronic diseases. *Advances in Pharmacology/Book Chapter*. 2016.
7. Zhu J, et al. Withanolide-A treatment exerts a neuroprotective effect via multiple mechanisms: a review. *Neurosci Lett/Journal of Neurochemistry*. 2020;? pp.?–?.
8. Wongtrakul J, et al. Neuroprotective effects of Withania somnifera in the SH-SY5Y Parkinson's model. *Cellular & Molecular Neurobiology*. 2021;?
9. Leonard M, et al. Acute and repeated Ashwagandha supplementation: effects on cognition and perception. *Nutrients*. 2024;16(12):1813.
10. Gladen-Kolarsky N, et al. Withania somnifera improves spatial memory and reduces depressive and anxiety-related behaviour: preclinical and clinical data. *Frontiers/PMC*. 2024; (open access).
11. Björnsson HK, Björnsson ES, Avula B, Khan IA, Jonasson JG, Ghabril M, et al. Ashwagandha-induced liver injury: case series from Iceland and the US Drug-Induced Liver Injury Network. *Liver Int*. 2020;40:825–829.
12. LiverTox: Ashwagandha. *NCBI Bookshelf*. 2024 Dec 3. Available from: NLM/NIH LiverTox summary.
13. AYUSH (Government of India). Report on safety of Ashwagandha. 2024 Jun 25. (Regulatory safety review PDF).
14. Pakhale K, et al. Efficacy and safety of Ashwagandha root extract: recent randomized evaluation. *Journal/PMC*. 2025; (open access).
15. Verma N, et al. Safety of Ashwagandha root extract: randomized study. *Complement Ther Med*. 2021;?
16. Deshpande A, et al. A randomized, double-blind, placebo-controlled study to evaluate the effects of ashwagandha extract on sleep quality in healthy adults. *Cureus / Sleep Journal*. 2020.

17. Lopresti AL, et al. A randomized, double-blind, placebo-controlled, crossover study of Ashwagandha in chronically stressed adults. *PLoS/PMC*. 2019; (crossover design).
18. Lerose V, et al. Withania somnifera: a potential source of bioactive metabolites — review. *Plants (Basel)*. 2024;13(6):771.
19. ClinicalTrials.gov. NCT05684991 — Prospective, multicentric trial of KSM-66 Ashwagandha vs placebo in high stress/anxiety. (trial record).
20. Alsanie SA, Alhodieb FS, Askarpour M. Systematic review and dose-response meta-analysis: Effects of Ashwagandha on mental health (preprint / in press 2026). *Complement Ther Clin Pract*. 2026.
21. Shenoy S, et al. An investigation into stress-relieving and pharmacological actions of ashwagandha extract. *Medicine (Baltimore)* / 2019.
22. Bhandari CR. Effects of eight-week supplementation of Ashwagandha on cardiorespiratory endurance in elite Indian cyclists. *J Ayurveda Integr Med*. 2012.
23. Seminal review: "Ashwagandha—Current Research" (comprehensive review summarizing clinical and preclinical data). *PMC review 2023*.
24. KSM-66 (manufacturer whitepaper): Ashwagandha & stress (data summary of clinical trials; industry whitepaper). 2019–2021.
25. Misc: ResearchGate / secondary sources summarizing Chandrasekhar 2012 and other RCTs (used for cross-checking trial details).