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Ashwagandha and Chronic Stress: A Review of Its Neuroimmune Modulatory Potential

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ABSTRACT

Introduction: Chronic stress disrupts neuroimmune homeostasis, driving neuroinflammation and neuronal damage. Despite growing interest in natural interventions, comprehensive reviews on ashwagandha's dual neuro-immunomodulatory mechanisms remain limited. This review examines ashwagandha's potential in mitigating chronic stress-induced neuroimmune dysregulation.
Methods: A review was conducted by searching PubMed, Scopus, and Google Scholar for relevant preclinical and clinical studies published between 2015 and 2025. Studies were selected based on their focus on Ashwagandha's effects on the hypothalamic–pituitary–adrenal (HPA) axis, cytokine expression, oxidative stress, and neuroprotection. Data were extracted and synthesized thematically.
Results: Ashwagandha was found to downregulate pro-inflammatory cytokines (TNF-α, IL-6), inhibit NF-κB signaling, and enhance antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). Clinical and animal studies reported cortisol reduction, attenuation of microglial activation, increased brain-derived neurotrophic factor (BDNF) levels, improved T-cell proliferation and NK cell activity, and restoration of Th1/Th2 balance. These mechanisms were associated with improved mood, cognition, and stress resilience.
Conclusion: Ashwagandha demonstrates multimodal neuroimmune modulation, offering a promising natural therapeutic for stress-related disorders. Standardized extracts warrant further investigation for clinical translation.

Keywords: Ashwagandha; chronic stress; immunomodulation; neuroinflammation

INTRODUCTION

Chronic stress is a pervasive condition in modern life, exerting widespread effects on both the nervous and immune systems. Persistent stress can dysregulate the hypothalamic-pituitary-adrenal (HPA) axis, elevate cortisol levels, impair immune responses, and increase vulnerability to neurodegenerative and inflammatory disorders[1,2]. As the understanding of psychoneuroimmunology advances, there is growing interest in natural compounds that can modulate the immune system and protect neuronal integrity under chronic stress conditions. Ashwagandha (*Withania somnifera*), a revered adaptogenic herb in traditional Ayurvedic medicine, has gained attention for its multifaceted therapeutic properties [3]. Ashwagandha is known for ability to enhance resilience against physical and psychological stressors, Its exhibits potent immunomodulatory, antioxidant, and neuroprotective effects.

Emerging preclinical and clinical studies suggest that Ashwagandha may restore HPA axis balance, reduce oxidative stress, regulate pro-inflammatory cytokine expression, and improve cognitive

and emotional well-being[1,4]. Several studies have documented Ashwagandha's neuroprotective effects[5] and its immunomodulatory roles in inflammatory conditions [6] while others have highlighted its impact on mood disorders and sleep disturbances[3,7]. Moreover, there remains a lack of comprehensive synthesis that bridges findings from molecular pathways to physiological and behavioural outcomes across both animal and human studies. This gap underscores the need for a focused review that consolidates existing evidence and provides a clearer understanding of Ashwagandha's dual neuroimmune regulatory roles. Therefore, this review explores the immunological and neuroprotective mechanisms of Ashwagandha in the context of chronic stress. By examining current evidence on its molecular pathways, we aim to highlight its therapeutic potential as a complementary approach to managing stress-induced immune dysregulation and neural impairment.

METHODS

This narrative review was conducted to evaluate current research on the neuroimmune modulatory effects of Ashwagandha (*Withania somnifera*) in the context of chronic stress. A comprehensive literature search was performed using PubMed, Scopus and Google Scholar databases to identify relevant peer-reviewed articles published between 2015 and 2025. The search strategy incorporated a combination of controlled vocabulary and free-text terms using Boolean operators, including: ("Ashwagandha" OR "*Withania somnifera*") AND ("chronic stress" OR "HPA axis") AND ("neuroinflammation" OR "neuroprotection" OR "cytokines" OR "immunomodulation" OR "cortisol"). Articles were included if they met the following criteria: (1) original research published in English; (2) involved either human or animal models exposed to chronic stress without major comorbid conditions; (3) investigated Ashwagandha as the primary intervention; and (4) reported outcomes related to neuroimmune regulation, such as cytokine expression, cortisol levels, HPA axis activity, or microglial function. Review articles, studies unrelated to stress, combined herbal formulations, and those lacking control groups or quantifiable neuroimmune data were excluded. Relevant data, including study design, sample characteristics, Ashwagandha dosage, stress models, and reported biomarkers, were extracted and synthesized qualitatively to identify consistent trends and gaps in the literature. We identified a total of 51 articles through database searching, as illustrated in Figure 1. After removing 16 articles due to duplication and publication year not meeting our eligibility criteria, 35 full text articles were retrieved for eligibility assessment. Of these, 15 articles met all inclusion criteria and were included in the qualitative synthesis, while 20 articles were excluded after eligibility screening and used only as supporting references.

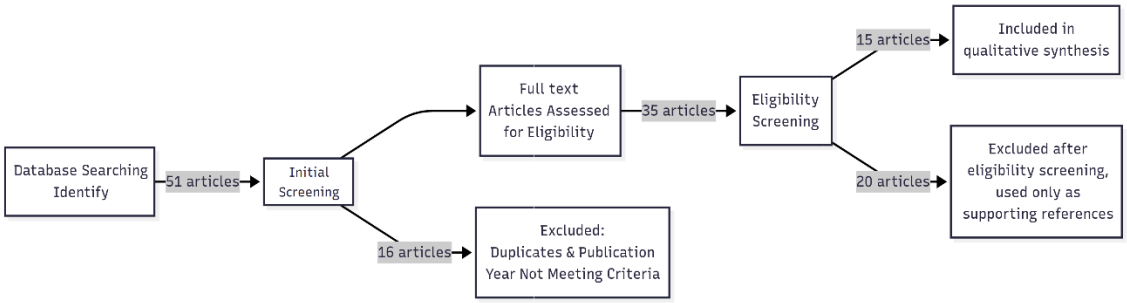

Figure 1. PRISMA Flowchart Illustrating the Identification, Screening, and Inclusion of Studies for this review

RESULT

Pathophysiology of Chronic Stress

Chronic stress is characterized by prolonged activation of the body's stress response system, particularly the HPA axis and the sympathetic-adrenal-medullary (SAM) axis. Under normal conditions, these systems help maintain homeostasis by responding to acute stressors. However, when stress

becomes persistent, it leads to maladaptive changes that negatively affect multiple physiological systems, including the nervous, endocrine, and immune systems [8,9]. The HPA axis becomes hyperactive during chronic stress, resulting in sustained release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and ultimately elevated levels of cortisol. While cortisol has beneficial anti-inflammatory effects in the short term, chronic elevation leads to glucocorticoid receptor resistance, impaired negative feedback, and widespread physiological dysregulation. High cortisol levels also contribute to hippocampal atrophy, memory deficits, mood disturbances, and increased vulnerability to neurodegeneration[1,10].

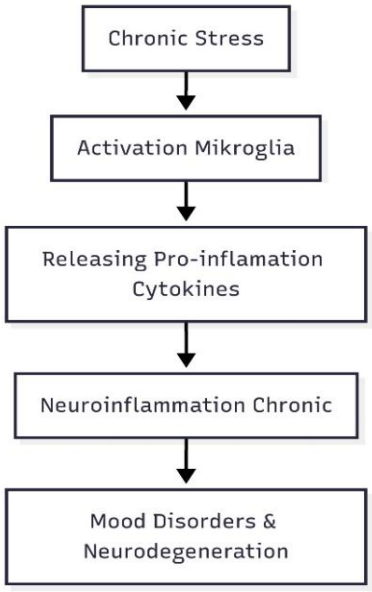

Figure 2. Chronic Stress-Induced Neuroinflammatory Cascade. Schematic flowchart illustrating how persistent activation of the body's stress-response systems precipitates central immune activation and downstream neuropathology. Chronic stress triggers microglial activation in the brain, leading to the release of pro-inflammatory cytokines. Sustained cytokine signaling drives chronic neuroinflammation, which over time contributes to the development of mood disorders and accelerates neurodegenerative processes.

Chronic stress also disrupts immune system balance, promoting pro-inflammatory cytokine production such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)[5]. These inflammatory mediators contribute to systemic inflammation and are closely linked to conditions like cardiovascular disease, metabolic syndrome, and depression. Furthermore, stress can suppress adaptive immunity by decreasing lymphocyte proliferation, reducing natural killer (NK) cell activity, and shifting the balance from Th1 to Th2 immune responses, leading to increased susceptibility to infections and impaired immune surveillance [9]. Chronic stress increases oxidative stress, mitochondrial dysfunction, and excitotoxicity, particularly via overactivation of the glutamatergic system. These effects impair synaptic plasticity and reduce levels of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which are essential for neuronal survival and regeneration[11,12]. Chronic stress induces a cascade of neuroendocrine and immunological changes that promote neuroinflammation, immune dysfunction, and neuronal damage. These pathophysiological changes form the basis for stress-related disorders and highlight the need for interventions that can regulate the HPA axis, reduce inflammation, and protect the nervous system [9,10].

Chronic stress can trigger a cascade of detrimental effects within the brain. This prolonged stress response often leads to chronic neuroinflammation, a state where the brain's immune cells become overactive, causing persistent inflammation[13]. This sustained inflammation can damage neurons and disrupt critical neurotransmitter systems, ultimately increasing vulnerability to mood disorders like

depression and anxiety as illustrated in Figure 2. Furthermore, chronic neuroinflammation is a significant contributor to neurodegeneration, accelerating the loss of brain cells and potentially paving the way for conditions such as Alzheimer's disease and other forms of dementia[13,14].

Neuroprotective Effects of Ashwagandha

Ashwagandha has emerged as a potent neuroprotective agent, particularly beneficial in mitigating the damaging effects of chronic stress on the brain and nervous system. Chronic stress contributes to neuronal atrophy, oxidative damage, neuroinflammation, and dysregulation of neurotransmitters, all of which are linked to cognitive impairment, mood disorders, and neurodegenerative diseases[15]. Ashwagandha counters these effects through a combination of antioxidant, anti-inflammatory, and neurotrophic mechanism[3,16]. Ashwagandha enhances the body's antioxidant defence systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). These enzymes neutralize reactive oxygen species (ROS), which accumulate during chronic stress and contribute to neuronal cell damage. The withanolides in Ashwagandha are especially effective at scavenging free radicals, thereby reducing lipid peroxidation and preserving neuronal membrane integrity[17].

Ashwagandha particularly those rich in withaferin A have demonstrated the ability to modulate the NF-κB signaling pathway, a key regulator of inflammation. One of the primary mechanisms involves the inhibition of IκBα phosphorylation and degradation. Under normal conditions, IκBα binds to NF-κB and prevents its translocation to the nucleus; its degradation allows NF-κB activation. By stabilizing IκBα, Ashwagandha effectively suppresses NF-κB activation, thereby reducing the expression of pro-inflammatory cytokines. Additionally, withaferin A has been reported to directly bind to IKKβ, a central kinase responsible for initiating NF-κB signaling, and inhibit its activity. Through these mechanisms as illustrated in Figure 3, Ashwagandha helps attenuate inflammation, a hallmark of various chronic diseases and stress-related disorders[18,19].

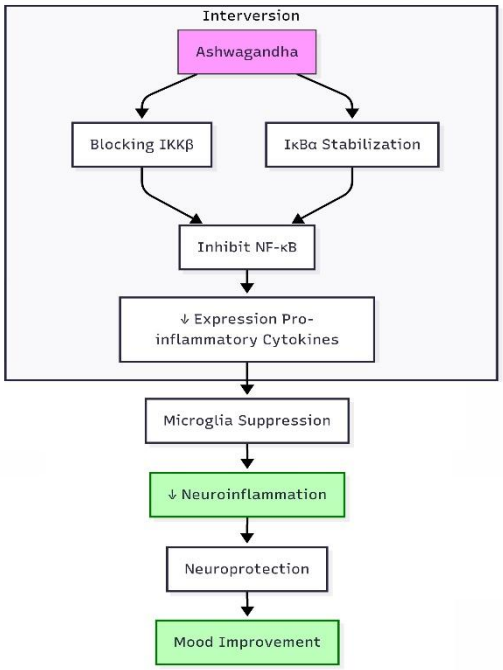

Figure 3. Mechanistic overview of Ashwagandha's anti-inflammatory and neuroprotective actions in chronic stress-mediated neuroinflammation, culminating in mood improvement. Ashwagandha intervention targets the NF-κB pathway as a key therapeutic mechanism. By modulating the activity of IKKβ and stabilizing IκBα, Ashwagandha effectively inhibits NF-κB translocation and activation. This inhibition subsequently reduces the expression of various pro-inflammatory cytokines. The resulting cascade leads to the suppression of microglial

activation, a reduction in overall neuroinflammation, and ultimately contributes to neuroprotection and an improvement in mood.

Chronic stress leads to microglial activation and the release of pro-inflammatory cytokines in the brain, contributing to neuroinflammation and behavioral changes. Ashwagandha has been shown to suppress microglial activation and reduce levels of inflammatory mediators such as IL-1β, TNF-α, and NF-κB, which are implicated in both mood disorders and neurodegenerative conditions[19]. Ashwagandha influences key neurotransmitter systems, including GABAergic, serotonergic, and dopaminergic pathways, which are often disrupted in stress-related disorders. It also helps normalize serotonin and dopamine levels, which are essential for mood regulation and motivation[3,7].

Ashwagandha promotes the expression of brain-derived neurotrophic factor (BDNF), a crucial neurotrophin involved in neurogenesis, synaptic plasticity, and neuronal survival[5]. Increased BDNF levels are associated with improved learning, memory, and emotional resilience, all of which are negatively affected by chronic stress. Preclinical studies suggest that Ashwagandha can protect against β-amyloid toxicity, tau protein aggregation, and mitochondrial dysfunction pathological features linked to Alzheimer's disease and Parkinson's disease. It also helps maintain mitochondrial membrane potential, thereby preserving cellular energy and reducing apoptosis in neuronalf cells[3,20].

Immunomodulatory Effects of Ashwagandha

Ashwagandha exhibits significant immunomodulatory properties, which play a central role in its adaptogenic and therapeutic potential, particularly in the context of chronic stress[1,5]. Chronic stress is impairing immune function by suppressing protective immune responses and enhancing inflammation. Ashwagandha acts to restore immune balance by modulating both innate and adaptive immunity[21]. One of the primary mechanisms by which Ashwagandha exerts its immunomodulatory effects is through the regulation of pro- and anti-inflammatory cytokines[6].

Ashwagandha has been reported to stimulate lymphocyte proliferation, increase natural killer (NK) cell activity, and enhance the cytotoxic response of T cells, thereby strengthening cell-mediated immunity. This is particularly important in stress-induced immunosuppression, where the body's ability to defend against infections and abnormal cells is weakened. Prolonged stress often leads to an imbalance between T-helper 1 (Th1) and T-helper 2 (Th2) responses, skewing the immune system toward Th2 dominance, which is associated with increased susceptibility to infections and allergies. Ashwagandha has been shown to restore Th1/Th2 balance, helping to maintain immunological homeostasis[6,22]. Extracts of Ashwagandha have been found to stimulate macrophage activation, increase phagocytic activity, and enhance the release of ROS and nitric oxide (NO), which are essential for the elimination of pathogens[3,23]. These effects further contribute to the herb's protective role against microbial infections and immune compromise. Animal studies have demonstrated that Ashwagandha can reverse immunosuppression caused by stress hormones like corticosterone. It helps maintain white blood cell counts, spleen weight, and antibody production in stressed models, suggesting a robust protective effect against stress-induced immune decline[17,24].

Study investigated the immunomodulatory effects of Ashwagandha in healthy adults and found significant enhancements in immune function among those receiving the extract. Participants in the Ashwagandha group demonstrated notable increases in key immune components, including immunoglobulins (IgA, IgM, and IgG), cytokines such as IFN-γ and IL-4, as well as immune cell populations including T cells, B cells, and natural killer (NK) cells [21,22,25]. In contrast, the placebo group exhibited a decline in immune cell counts. Continued supplementation with Ashwagandha resulted in further immune enhancement over time. Notably, no adverse effects were reported during the study period. These findings indicate that Ashwagandha extract may effectively support both innate and adaptive immune responses, contributing to a strengthened overall immune system[21].

Table 1. Study Summary Table of Neuroprotective and Immunomodulatory Effects of Ashwagandha

No.	Author (Year)	Study Design	Subjects or Model	Ashwagandha Intervention	Dosage (mg/kg)	Main Neuroimmune Outcomes
1	Er B et al. (2025)	Animal trial	Sleep-deprived rats	Novel formulation	100	↓ Oxidative stress, ↑ cognitive function
2	Kim et al. (2025)	Animal trial	Mice under chronic stress	Root extract with withanolide A	a) 60, b) 100	↑ BDNF, ↓ depression-like behavior
3	Dawane et al. (2024)	Animal trial	Stress-tested Wistar Rats	Root extract	a) 27 b) 54 c) 108	↓ Anxiety (EPM), ↓ depression (FST/SPT), ↑ monoamine
4	Sood et al. (2024)	Animal trial	Ischemic stroke rats	Root extract	100	Neuroprotection via ↓ inflammation, ↑ neurotransmitters
5	KrishnaRaju et al. (2023)	Animal trial	Chronic unpredictable stress rats	Sustained-release formulation	100	↓ IL-6, ↓ TNF-α, ↓depression/anxiety
6	Gupta & Kaur (2019)	Animal trial	Systemic inflammation rats	Root extract	100	Ameliorated neurodegeneration, ↓ cognitive deficits
7	Elhadidy et al. (2018)	Animal trial	AlCl3-exposed rats	Root extract	100	↑ Antioxidant enzymes, ↓ lipid peroxidation, ↓ TNF-α/IL-1β, prevented neurodegeneration
8	Puttaswamy et al. (2025)	Clinical trial	Healthy adults	Ashwagandha extract	300	↑ Energy and endurance
9	Leonard et al. (2024)	Clinical trial	Adults	Root extract	450	↑ Cognitive function, ↑ mood
10	Tiwari et al. (2021)	Clinical trial	Athletic adults	Root extract	600	↑ Cardiorespiratory endurance
11	Tharakan et al. (2021)	Clinical trial	Healthy adults	Water extract of Ashwagandha	600	↑ IgA, ↑ IgG, ↑ IFN-γ, ↑ NK cell activity
12	Gopukumar et al. (2021)	Clinical trial	Stressed adults	Root extract	300	↑ Cognitive functions
13	Kelgane et al. (2020)	Clinical trial	Older adults	Root extract	600	↑ BDNF serum, ↑ cognition, ↓ CRP
14	Salve et al. (2019)	Clinical trial	Healthy adults	Root extract	600	Adaptogenic and anxiolytic effects
15	Lopresti et al. (2019)	Clinical trial	Stressed adults	Ashwagandha extract	240	↓ Stress, ↑ Sleep quality

DISCUSSION

Ashwagandha's Therapeutic Potential in Chronic Stress: A Multifaceted Neuroimmune Modulator

Ashwagandha (*Withania somnifera*) demonstrates significant therapeutic potential in counteracting the detrimental effects of chronic stress through multiple, well-documented mechanisms, making it a compelling focus for this review. As a prominent adaptogen, Ashwagandha plays a crucial role in helping the body maintain physiological balance during prolonged stress exposure. Its

established ability to modulate the Hypothalamic-Pituitary-Adrenal (HPA) axis is key; it has consistently been shown to normalize elevated cortisol levels one of the primary biomarkers of chronic stress thereby restoring hormonal equilibrium and reducing the systemic impact of stress on the body [4,19,24].

Ashwagandha at the molecular level exhibits potent anti-inflammatory properties by interfering with core pro-inflammatory signaling pathways such as NF-κB and COX-2[26]. This action leads to a significant decrease in the production and release of key pro-inflammatory cytokines, which are typically upregulated during chronic stress-induced neuroinflammation. Furthermore, its capacity to enhance the body's endogenous antioxidant defenses, via increasing the activity of enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, effectively mitigates the pervasive oxidative damage associated with chronic stress[27]. These profound biochemical effects manifest in observable behavioral improvements, as evidenced in both preclinical animal models and human clinical studies. Supplementation with Ashwagandha has been associated with reduced anxiety, improved sleep quality, enhanced memory, and better emotional regulation[4,28,29]. Ashwagandha demonstrated ability to support neurogenesis and preserve microglia homeostasis (shifting from pro-inflammatory M1 to anti-inflammatory M2 phenotypes) further strengthens its comprehensive neuroprotective profile, highlighting its central role in maintaining brain health under stress[29,30].

Table 2. Summary of Key Mechanisms of Ashwagandha in Modulating Neuroimmune Responses to Chronic Stress

No.	Mechanism	Action/Outcome	Target
1	HPA Modulation[1,24]	↓ Cortisol, balance HPA	CRH/ACTH
2	NF-κB Inhibition[19,27]	↓ TNF-α, IL-1β	IKKβ, COX-2
3	BDNF ↑[5]	↑ Neurogenesis, plasticity	Neurons
4	Antioxidant Enzymes ↑[17]	↓ Lipid peroxidation	ROS
5	Th1/Th2 Balance[6]	↑ NK cells, ↑ IFN-γ	T-cells

Critical Analysis, Limitations, and Contradictions in Current Research

While the evidence is largely supportive, a critical examination of the existing literature reveals several important nuances and limitations. A major challenge lies in the heterogeneity of study designs and the lack of standardization across research. Specifically, significant variations in Ashwagandha extract formulations and dosage regimens are prevalent across clinical trials[27,31,32]. This variability makes direct comparisons between studies difficult and complicated the establishment of optimal therapeutic doses. For instance, while most studies concur on Ashwagandha anxiolytic and stress-reducing effects, the magnitude and onset of these benefits can differ, potentially influenced by the extract type and duration of intervention[31].

The predominance of short-term clinical trials also includes as the limitation, typically lasting only 4-12 weeks. While these durations are sufficient to demonstrate acute effects on stress markers and mood, they offer limited insight into the long-term sustainability of Ashwagandha's immunomodulatory and neuroprotective effects, or its potential for preventing chronic disease progression[21,33]. Furthermore, many studies rely heavily on self-reported questionnaires for psychological outcomes, which, while valuable, can be subject to placebo effects and participant bias. The translation of findings from preclinical animal models to human physiology also requires careful consideration, given interspecies differences in stress responses, neurobiology, and drug metabolism. While the overall picture is consistent, minor contradictions sometimes emerge regarding specific cytokine profiles or immune cell shifts, which could be attributed to these methodological differences,

varied baseline health statuses of participants, or genetic polymorphisms affecting individual responses[32].

Clinical Implications

Based on the current body of evidence, Ashwagandha holds significant promise as a valuable complementary therapeutic agent for individuals experiencing chronic stress-induced neuroimmune alterations. From a clinical perspective, Ashwagandha generally favorable safety profile at commonly studied doses is a major advantage, making it a viable option for long-term use compared to some pharmaceutical interventions. However, clinicians must emphasize the importance of using standardized Ashwagandha extracts with clearly defined active compounds like a guaranteed percentage of withanolides to ensure product quality, consistency, and predictable efficacy. While no universal "optimal dose" has been definitively established, the effective doses in most positive clinical trials fall within the around 240-600 mg range of standardized root extract[34,35].

CONCLUSION

Chronic stress triggers complex neuroimmune dysregulation, leading to neuroinflammation, oxidative damage, and increased vulnerability to neuropsychiatric disorders. Ashwagandha demonstrates significant immunomodulatory and neuroprotective effects across preclinical and clinical studies. It downregulates pro-inflammatory cytokines, balances microglial activity, and enhances antioxidant defences collectively supporting cognitive resilience and stress adaptation. Clinical evidence suggests reductions in cortisol levels and improved mood, though findings on long-term immune outcomes remain limited. Overall Ashwagandha shows promising potential as a natural therapeutic agent for managing stress-induced neuroimmune alterations. Its ability to target multiple stress-related pathways highlights its value as a complementary therapeutic candidate in the broader context of integrative neuroscience and psychoneuroimmunology. Future research should prioritize standardized extract formulations, dose optimization, and longitudinal trials across diverse populations to confirm and expand its clinical efficacy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCE

1. Pandit S, Srivastav AK, Sur TK, Chaudhuri S, Wang Y, Biswas TK. Effects of Withania somnifera Extract in Chronically Stressed Adults: A Randomized Controlled Trial. Vol. 16, Nutrients. 2024.

2. P Sharan, Vellapandian C. Hypothalamic-Pituitary-Adrenal (HPA) Axis: Unveiling the Potential Mechanisms Involved in Stress-Induced Alzheimer's Disease and Depression. Cureus. 2024 Aug;16(8):e67595.

3. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, Pesta K, et al. Ashwagandha (Withania somnifera)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics. 2023 Mar;15(4).

4. Er B, Ozmen B, Sahin E, Orhan C, Sahin N, Morde AA, et al. A Novel Ashwagandha (Withania somnifera) Formulation Mitigates Sleep Deprivation-Induced Cognitive Impairment and Oxidative Stress in a Rat Model. Biomolecules. 2025 May;15(5).

5. Kim H, Choi HS, Han K, Sim W, Suh HJ, Ahn Y. Ashwagandha (Withania somnifera (L.) dunal) root extract containing withanolide a alleviates depression-like behavior in mice by enhancing the brain-derived neurotrophic factor pathway under unexpected chronic mild stress. J Ethnopharmacol [Internet].

2025;340:119224. Available from: https://www.sciencedirect.com/science/article/pii/S037887412401523X

6. Alanazi HH, Elfaki E. The immunomodulatory role of withania somnifera (L.) dunal in inflammatory diseases. Front Pharmacol. 2023;14:1084757.

7. Speers AB, Cabey KA, Soumyanath A, Wright KM. Effects of Withania somnifera (Ashwagandha) on Stress and the Stress-Related Neuropsychiatric Disorders Anxiety, Depression, and Insomnia. Curr Neuropharmacol. 2021;19(9):1468–95.

8. Ghasemi Farshad, Beversdorf David Q, Herman Keith C. Stress and stress responses: A narrative literature review from physiological mechanisms to intervention approaches. J Pacific Rim Psychol [Internet]. 2024 May 1;18:18344909241289224. Available from: https://doi.org/10.1177/18344909241289222

9. Balakin E, Yurku K, Ivanov M, Izotov A, Nakhod V, Pustovoyt V. Regulation of Stress-Induced Immunosuppression in the Context of Neuroendocrine, Cytokine, and Cellular Processes. Vol. 14, Biology. 2025.

10. Sic A, Bogicevic M, Brezic N, Nemr C, Knezevic NN. Chronic Stress and Headaches: The Role of the HPA Axis and Autonomic Nervous System. Vol. 13, Biomedicines. 2025.

11. Dawane J, Seok S, Dhande P, Langade D, Han H, Kim SB, et al. Evaluation of the Anxiolytic and Antidepressant Effects of Standardized Ashwagandha (Withania somnifera) Root Extract in Wistar Rats. Prev Nutr Food Sci. 2024;29:414–21.

12. Kelgane SB, Salve J, Sampara P, Debnath K. Efficacy and Tolerability of Ashwagandha Root Extract in the Elderly for Improvement of General Well-being and Sleep: A Prospective, Randomized, Double-blind, Placebo-controlled Study. Cureus. 2020 Feb;12(2):e7083.

13. Sic A, Cvetkovic K, Manchanda E, Knezevic NN. Neurobiological Implications of Chronic Stress and Metabolic Dysregulation in Inflammatory Bowel Diseases. Dis (Basel, Switzerland). 2024 Sep;12(9).

14. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Front Aging Neurosci. 2024;16:1347987.

15. Krasner H, Ong CV, Hewitt P, Vida TA. From Stress to Synapse: The Neuronal Atrophy Pathway to Mood Dysregulation. Int J Mol Sci. 2025 Mar;26(7).

16. Juszczyk G, Mikulska J, Kasperek K, Pietrzak D, Mrozek W, Herbet M. Chronic Stress and Oxidative Stress as Common Factors of the Pathogenesis of Depression and Alzheimer's Disease: The Role of Antioxidants in Prevention and Treatment. Antioxidants (Basel, Switzerland). 2021 Sep;10(9).

17. Guo S, Rezaei MJ. The benefits of ashwagandha (Withania somnifera) supplements on brain function and sports performance. Front Nutr [Internet]. 2024;Volume 11. Available from: https://www.frontiersin.org/journals/nutrition/articles/10.3389/fnut.2024.1439294

18. White PT, Subramanian C, Motiwala HF, Cohen MS. Natural Withanolides in the Treatment of Chronic Diseases. Adv Exp Med Biol. 2016;928:329–73.

19. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, Liss S, Szyperski P, Szambelan M, et al. Ashwagandha's Multifaceted Effects on Human Health: Impact on Vascular Endothelium, Inflammation, Lipid Metabolism, and Cardiovascular Outcomes—A Review. Vol. 16, Nutrients. 2024.

20. Zieneldien T, Kim J, Cao C. The Multifaceted Role of Neuroprotective Plants in Alzheimer's Disease Treatment. Geriatr (Basel, Switzerland). 2022 Feb;7(2).

21. Tharakan A, Shukla H, Benny IR, Tharakan M, George L, Koshy S. Immunomodulatory Effect of Withania somnifera (Ashwagandha) Extract-A Randomized, Double-Blind, Placebo Controlled Trial with an Open Label Extension on Healthy Participants. J Clin Med. 2021 Aug;10(16).

22. Pushpakaran AMK, Singh J, Rasane P, Kaur S, Kaur J, Kaur J, et al. Immunomodulatory effect of ashwagandha (Withania somnifera(L.) Dunal) and its impact on COVID-19. Foods Raw Mater. 2024;13(1):46–57.

23. Elhadidy ME, Sawie HG, Meguid NA, Khadrawy YA. Protective effect of ashwagandha (Withania somnifera) against neurotoxicity induced by aluminum chloride in rats. Asian Pac J Trop Biomed [Internet]. 2018;8(1). Available from: https://journals.lww.com/aptb/fulltext/2018/08010/protective_effect_of_ashwagandha__withania.10.aspx

24. Wiciński M, Fajkiel-Madajczyk A, Kurant Z, Kurant D, Gryczka K, Falkowski M, et al. Can Ashwagandha Benefit the Endocrine System?-A Review. Int J Mol Sci. 2023 Nov;24(22).

25. 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 Ethnopharmacol [Internet]. 2021;272:113929. Available from: https://www.sciencedirect.com/science/article/pii/S0378874121001550

26. Das R, Rauf A, Akhter S, Islam MN, Emran TB, Mitra S, et al. Role of Withaferin A and Its Derivatives in the Management of Alzheimer's Disease: Recent Trends and Future Perspectives. Vol. 26, Molecules. 2021.

27. KrishnaRaju AV, Somepalli V, Thanawala S, Shah R. Efficacy and Anti-Inflammatory Activity of Ashwagandha Sustained-Release Formulation on Depression and Anxiety Induced by Chronic Unpredictable Stress: in vivo and in vitro Studies. J Exp Pharmacol. 2023;15:291–305.

28. Akhgarjand C, Asoudeh F, Bagheri A, Kalantar Z, Vahabi Z, Shab Bidar S, et al. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. Phyther Res. 2022;36:4115–24.

29. Gupta M, Kaur G. Withania somnifera (L.) Dunal ameliorates neurodegeneration and cognitive impairments associated with systemic inflammation. BMC Complement Altern Med. 2019 Aug;19(1):217.

30. Sood A, Mehrotra A, Dhawan D, Sandhir R. Neuroprotective effects of Withania somnifera on ischemic stroke are mediated via anti-inflammatory response and modulation of neurotransmitter levels. Neurochem Int. 2024;180:105867.

31. 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 Sep;98(37):e17186.

32. Puttaswamy N, Singh G, Mayachari A, Parameswaran M, Kudiganti V. Efficacy of Ashwagandha Extract Formulation (ASVAMAN®) on Improvement of Energy and Endurance: A Randomized, Double-blind, Placebo-controlled Clinical Study in Healthy Adults. Eur J Med Heal Sci. 2025;7(2):88–93.

33. Gopukumar K, Thanawala S, Somepalli V, Rao TSS, Thamatam VB, Chauhan S. Efficacy and Safety of Ashwagandha Root Extract on Cognitive Functions in Healthy, Stressed Adults: A Randomized, Double-Blind, Placebo-Controlled Study. Evid Based Complement Alternat Med. 2021;2021:8254344.

34. 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 Dec;11(12):e6466.

35. Leonard M, Dickerson B, Estes L, Gonzalez DE, Jenkins V, Johnson S, et al. Acute and Repeated Ashwagandha Supplementation Improves Markers of Cognitive Function and Mood. Nutrients [Internet]. 2024;16(12). Available from: https://www.mdpi.com/2072-6643/16/12/1813