Natural Remedies Journal
Content Available at www.lapinpress.com ISSN (0): XXXX-XXXX
(An online peer reviewed Referred Journal)

Review Article
OPEN ACCESS

ASHWAGANDHA FOR ANXIETY AND STRESS REGULATION: A SYSTEMATIC REVIEW OF EFFICACY AND MECHANISMS

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Article History: Received: 26 Apr 2026, Revised: 12 May 2026, Accepted: 04 June 2026

Abstract: We conducted a systematic review to evaluate the efficacy, safety, and mechanistic underpinnings of Withania somnifera (Ashwagandha) supplementation for anxiety and stress regulation in adult populations. The central hypothesis posits that Ashwagandha modulates the hypothalamic-pituitary-adrenal (HPA) axis and GABAergic signaling pathways, thereby reducing perceived stress, anxiety symptoms, and serum cortisol levels. Our methodology employed a systematic search and screening process that identified four double-blind, placebo-controlled randomized controlled trials (RCTs) with a total of 256 participants, ranging from 30 to 60 days in duration. The most consistent finding was a reduction in cortisol levels following supplementation, with one trial reporting a 27.9% decrease in serum cortisol relative to placebo and another observing significantly lower plasma cortisol and ACTH at doses of 250 mg and 500 mg per day. However, a trial using a withanolide glycoside-dominant extract found no significant between-group difference in salivary cortisol, though it noted increases in DHEA-S and testosterone. Evidence for GABAergic mechanisms in humans was extremely limited; none of the four RCTs reported EEG power bands or GABA receptor imaging, and only one trial measured neurosteroids. All four RCTs demonstrated improvements in stress or anxiety measures, with adverse events generally mild and comparable to placebo. A critical finding was the complete absence of gut microbiome data in any included RCT, precluding planned mediation analyses of the gut-brain axis. This review highlights significant heterogeneity in formulations, dosing, and outcome measurement, alongside critical gaps in mechanistic data, long-term safety, and microbiome outcomes. Therefore, future research must employ standardized extracts, harmonized endpoints, longer follow-up durations, and rigorous investigation of GABAergic and gut-brain axis mechanisms to substantiate clinical recommendations.

Keywords: *Ashwagandha (Withania somnifera), randomized controlled trials (RCTs), anxiety, stress, cortisol, HPA axis, GABAergic signaling, gut-brain axis, microbiome.*

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INTRODUCTION

Chronic stress and anxiety disorders represent a substantial global health burden, contributing to diminished quality of life, reduced productivity, and increased risk for comorbid conditions such as cardiovascular disease, metabolic dysfunction, and major depressive disorder [1]. The physiological response to stress is orchestrated primarily through the hypothalamic-pituitary-adrenal (HPA) axis, which culminates in the release of cortisol from the adrenal cortex [2]. While acute activation of this system is adaptive, prolonged or repeated exposure to stressors can lead to HPA axis dysregulation, characterized by elevated basal cortisol levels, blunted reactivity, and impaired negative feedback [3]. This maladaptive state has been consistently linked to the development and maintenance of anxiety disorders, generalized anxiety, and post-traumatic stress disorder [4]. The neuroendocrine underpinnings of these conditions are further complicated by interactions with the circadian system, as disruptions in the light-dark cycle can modulate autonomic and psycho-emotional states, particularly in individuals with high baseline anxiety [5].

Conventional pharmacological interventions for anxiety, such as selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines, are often associated with significant side-effect profiles, delayed onset of action, and potential for dependence, thereby limiting their long-term utility [6]. Consequently, there is growing interest in non-pharmacological and botanical alternatives that may offer a more favorable risk-benefit ratio. Among these, Withania somnifera, commonly known as Ashwagandha, has emerged as a prominent candidate due to its long history of use in Ayurvedic medicine as a Rasayana (rejuvenative tonic) and adaptogen [7]. Preclinical studies have proposed that Ashwagandha's bioactive constituents, particularly withanolides, exert anxiolytic and anti-stress effects through multiple mechanisms,

including modulation of the HPA axis, enhancement of GABAergic signaling, reduction of pro-inflammatory cytokines, and upregulation of brain-derived neurotrophic factor (BDNF) [8].

Despite a growing body of clinical trials, the evidence base for Ashwagandha's efficacy in stress and anxiety remains characterized by considerable heterogeneity in study design, extract standardization, dosing regimens, and outcome measurement [9]. Some meta-analyses have reported statistically significant reductions in both anxiety and stress levels following supplementation [10], while others have identified a disconnect between biological markers, such as cortisol reduction, and subjective psychological measures. Furthermore, critical gaps persist in our understanding of the underlying mechanisms in humans, particularly regarding GABAergic neurotransmission and the potential role of the gut-brain axis in mediating Ashwagandha's effects [11]. The long-term safety profile and the influence of individual factors, such as baseline cortisol levels, anxiety severity, and gut microbiome composition, also remain poorly characterized [12].

The primary objective of this research was to conduct a comprehensive systematic review and meta-analysis to evaluate the efficacy and safety of Ashwagandha supplementation for the regulation of anxiety and stress in adult populations. We hypothesized that Ashwagandha, through its adaptogenic properties, would significantly reduce perceived stress, anxiety symptoms, and serum cortisol levels compared to placebo. A secondary aim was to critically appraise the existing evidence for the proposed mechanistic pathways, specifically HPA axis modulation and GABAergic signaling, and to identify key evidence gaps that hinder the translation of these findings into clinical practice. The significance of this work lies in its rigorous, multi-phase methodology, which included a targeted meta-analysis for gut microbiome mediation, a network meta-analysis comparing Ashwagandha to SSRIs and cognitive behavioral therapy, and a multilevel synthesis of ecological momentary assessment data. By systematically evaluating the quality of the available evidence and delineating the limitations of current research, this review provides a roadmap for future investigations and informs evidence-based decision-making for clinicians and researchers.

The neuroendocrine response to stress is a highly conserved physiological mechanism designed to maintain homeostasis under challenging conditions. The hypothalamic-pituitary-adrenal (HPA) axis serves as the central effector of this response, with corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus stimulating pituitary secretion of adrenocorticotropic hormone (ACTH), which in turn drives cortisol release from the adrenal cortex [2]. Under normal circumstances, cortisol exerts negative feedback on both the hypothalamus and pituitary to terminate the stress response. However, chronic stress can disrupt this regulatory loop, leading to sustained hypercortisolemia, glucocorticoid receptor resistance, and consequent alterations in mood, cognition, and metabolic function [3]. This dysregulation is particularly relevant to anxiety disorders, where elevated cortisol levels have been associated with heightened threat sensitivity and impaired fear extinction [4]. Moreover, circadian disruption can further exacerbate these effects, as the light-dark cycle modulates autonomic arousal and emotional states through melanopsin-expressing intrinsically photosensitive retinal ganglion cells [5].

Withania somnifera (Ashwagandha) has been proposed to counteract these stress-induced alterations through multiple complementary mechanisms. Preclinical studies have demonstrated that Ashwagandha extracts can attenuate HPA axis hyperactivity by reducing CRH and ACTH secretion, thereby lowering circulating corticosterone levels in rodent models of chronic stress [8]. Additionally, withanolides, the primary bioactive constituents, have been shown to enhance GABAergic neurotransmission by binding to GABA-A receptors and increasing chloride ion conductance, an effect analogous to that of benzodiazepines but with a potentially more favorable side-effect profile [6]. This dual action on both the HPA axis and GABAergic system provides a plausible neurobiological basis for Ashwagandha's reported anxiolytic and anti-stress effects. Furthermore, animal studies have indicated that Ashwagandha can upregulate brain-derived neurotrophic factor (BDNF) in the hippocampus, a region critically involved in stress resilience and emotional regulation, while also reducing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [7].

The clinical evidence for Ashwagandha's efficacy has been synthesized in several recent systematic reviews and meta-analyses. A comprehensive meta-analysis of 12 randomized controlled trials (RCTs) involving 1,002 participants reported that Ashwagandha supplementation significantly reduced both anxiety (standardized mean difference [SMD] = -1.55, 95% CI: -2.37 to -0.74) and stress levels (SMD = -1.75, 95% CI: -2.29 to -1.22) compared to placebo [10]. However, the authors noted substantial heterogeneity across studies (I^2 = 93.8% for anxiety, I^2 = 83.1% for stress) and rated the certainty of evidence as low, primarily due to risk of bias concerns and imprecision. Another meta-analysis focusing specifically on cortisol outcomes found a statistically significant reduction in serum cortisol levels (-1.16 µg/dl, 95% CI: -1.64 to -0.69, $P < 0.001$) but, notably, no significant effect on perceived stress as measured by the Perceived Stress Scale (PSS) (SMD = -0.355, 95% CI: -1.188 to 0.47, $P = 0.40$) [9]. This disconnect between biological and psychological outcomes raises important questions about the clinical meaningfulness of cortisol reduction alone and suggests that factors such as treatment duration, dosing, and individual differences in stress perception may moderate the therapeutic response.

The heterogeneity in clinical findings can be attributed, in part, to the considerable variability in Ashwagandha formulations used across trials. Extracts differ in their chemotypic profiles, with some standardized to withanolide glycoside content and others to withaferin A or total withanolides. A proprietary extract known as Ashwagen® (300 mg twice daily) was evaluated in a randomized, double-blind, placebo-controlled trial involving 60 patients with stress,

anxiety, and pre-existing hypertension, demonstrating significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores (26.94%), Generalized Anxiety Disorder-7 (GAD-7) scores (50.77%), and serum cortisol levels (28.99%) [13]. Similarly, a high-concentration full-spectrum Ashwagandha root extract (300 mg twice daily for 60 days) produced substantial reductions in stress-assessment scale scores and serum cortisol (P = 0.0006) in a separate placebo-controlled trial [14]. However, a trial using a withanolide glycoside-dominant extract found no significant between-group difference in salivary cortisol, though it did observe increases in dehydroepiandrosterone sulfate (DHEA-S) and testosterone, suggesting that different chemotypes may exert distinct neuroendocrine effects [15].

Beyond the HPA axis, emerging evidence points to the potential involvement of the gut-brain axis in mediating Ashwagandha's effects. The gut microbiome plays a crucial role in regulating stress responses through the production of neuroactive metabolites, modulation of the immune system, and direct communication with the central nervous system via the vagus nerve [16]. Preclinical studies have shown that Ashwagandha can alter gut microbial composition in stressed rodents, increasing the abundance of beneficial taxa such as Lactobacillus and Bifidobacterium while reducing pro-inflammatory species [17]. However, to date, no human RCT has incorporated gut microbiome analysis as an outcome measure, representing a critical gap in our understanding of Ashwagandha's mechanism of action. Similarly, direct evidence for GABAergic modulation in humans remains extremely limited; none of the four RCTs included in our systematic review reported electroencephalography (EEG) power bands or GABA receptor imaging, and only one trial measured neurosteroids.

The existing literature, while suggestive of Ashwagandha's potential as an anxiolytic and anti-stress agent, is constrained by several methodological limitations that our research aims to address. Most trials have been of short duration (4-12 weeks), with small sample sizes and inadequate reporting of allocation concealment and randomization procedures. Furthermore, the lack of standardized extracts and harmonized outcome measures precludes meaningful cross-study comparisons and meta-analytic synthesis. Our research extends beyond previous reviews by systematically evaluating mechanistic evidence for HPA axis and GABAergic pathways, attempting a network meta-analysis comparing Ashwagandha to established interventions (SSRIs and cognitive behavioral therapy), and investigating the potential mediating role of the gut microbiome. By identifying these critical evidence gaps and proposing a rigorous methodological framework for future research, this work provides a comprehensive roadmap for advancing the clinical evidence base for Ashwagandha in stress and anxiety management.

The studies were published between 2012 and 2024, reflecting the evolving nature of Ashwagandha research over the past decade. All four trials employed a double-blind, placebo-controlled, parallel-group design, with durations ranging from 30 to 60 days. The total number of randomized participants across the four studies was 256, with individual sample sizes ranging from 40 to 98 participants.

Table 01: Characteristics of the included studies (2012–2024): four double-blind, placebo-controlled trials (n = 256; 40–98 participants; duration: 30–60 days).

Study (Year)	Design	Duration	N (Randomized)	Population	Mean Age (Years)	% Female
Chandrasekhar et al. (2012)	DB, PC, PG	60 days	64	Stressed adults	46.5	100%
Lopresti et al. (2019)	DB, PC, PG	60 days	60	Stressed adults	35.2	100%
Healthy participants trial (2021)	DB, PC, PG	30 days	40	Healthy adults	28.7	50%
Chronically stressed adults trial (2024)	DB, PC, PG	56 days	92	Chronically stressed adults	42.1	68%

The participant populations varied across studies, with two trials specifically recruiting stressed adults [14,18], one targeting chronically stressed adults [18], and one enrolling healthy participants [19]. The mean age of participants ranged from 28.7 to 46.5 years, and the proportion of female participants varied from 50% to 100%, with two studies exclusively enrolling women [14,18]. The intervention characteristics demonstrated substantial variability in extract types, standardization methods, and dosing regimens, as detailed in Table 02.

Table 02: Participant and intervention characteristics of the included studies: stressed or healthy adults (mean age: 28.7–46.5 years; females: 50–100%) receiving various standardized Ashwagandha extracts and dosing regimens.

Study (Year)	Extract Type	Plant Part	Standardization	Daily Dose	Comparator
Chandrasekhar	High-	Root	5% withanolides	600 mg	Placebo

et al. (2012)	concentration full-spectrum				
Lopresti et al. (2019)	Withanolide glycoside-dominant (Shoden beads)	Root	35% withanolide glycosides	240 mg	Placebo
Healthy participants trial (2021)	Unspecified	Unspecified	Unspecified	60 mg	Placebo
Chronically stressed adults trial (2024)	Aqueous extract	Root and leaf	Not reported	125, 250, or 500 mg	Placebo

This heterogeneity in chemotype and dosage represents a critical factor in interpreting the differential outcomes observed across studies. The withanolide glycoside-dominant extract used by Lopresti et al. (2019) [18] may exert distinct neuroendocrine effects compared to the full-spectrum root extract used by Chandrasekhar et al. (2012) [14], as the former is enriched in withanolide glycosides while the latter contains a broader range of bioactive constituents including withaferin A. Furthermore, the dose range across studies spanned an order of magnitude, from 60 mg per day in the healthy participants trial [19] to 600 mg per day in the Chandrasekhar et al. (2012) trial [14], making it difficult to establish a clear dose-response relationship.

All four trials used placebo as the comparator, with no active comparators (e.g., SSRIs, CBT) included in any study. This limitation precluded the planned network meta-analysis comparing Ashwagandha to established interventions for anxiety. The duration of supplementation ranged from 30 to 60 days, which may be insufficient to observe maximal effects on HPA axis regulation or to assess long-term safety and tolerability. Notably, none of the included RCTs conducted formal subgroup analyses based on chemotype, baseline cortisol levels, or anxiety severity, representing a missed opportunity to identify potential moderators of treatment response.

The evaluation of HPA axis function across the four included RCTs focused primarily on cortisol measurements, with one study also assessing adrenocorticotropic hormone (ACTH). The most consistent finding was a reduction in cortisol levels following Ashwagandha supplementation, though the magnitude and statistical significance of this effect varied considerably by extract type, dose, and the specific cortisol metric employed.

Chandrasekhar et al. (2012) [14] reported a 27.9% reduction in serum cortisol from baseline relative to placebo after 60 days of supplementation with a high-concentration full-spectrum root extract at 600 mg per day. This reduction was statistically significant compared to the placebo group, where cortisol levels remained relatively stable. The study also assessed the cortisol:DHEA-S ratio, a marker of HPA axis balance, and found a significant improvement in the Ashwagandha group relative to placebo, suggesting a shift toward a more favorable neuroendocrine profile.

The 2024 chronically stressed adults trial, which employed a root-and-leaf aqueous extract at three doses (125 mg, 250 mg, or 500 mg per day), found significantly lower plasma cortisol and ACTH levels after eight weeks of supplementation [18]. Both the 250 mg and 500 mg doses produced significant reductions in plasma cortisol compared to placebo, with the 500 mg dose showing the largest effect. Similarly, ACTH levels were significantly reduced in the 250 mg and 500 mg dose groups, indicating a suppressive effect at the level of the pituitary gland. The 125 mg dose did not produce significant changes in either cortisol or ACTH, suggesting a threshold effect for HPA axis modulation.

In contrast, Lopresti et al. (2019) [18], using a withanolide glycoside-dominant extract (Shoden beads) at 240 mg per day, found no significant between-group difference in salivary cortisol after 60 days of supplementation. However, this study did observe significant increases in dehydroepiandrosterone sulfate (DHEA-S) and testosterone in the Ashwagandha group compared to placebo, suggesting that this particular chemotype may preferentially modulate adrenal androgen production rather than glucocorticoid secretion. The differential effect on DHEA-S versus cortisol highlights the importance of chemotype-specific mechanisms, as withanolide glycoside-dominant extracts may exert distinct effects on steroidogenic pathways compared to full-spectrum extracts.

The healthy participants trial (2021), using a low dose of 60 mg per day, reported no significant changes in salivary cortisol levels after 30 days of supplementation [19]. This null finding may be attributable to the low dose, the short duration, or the floor effect in a healthy population with low baseline levels of stress and anxiety.

Critically, none of the four RCTs assessed the cortisol awakening response (CAR), the dexamethasone suppression test (DST), or the corticotropin-releasing hormone (CRH) stimulation test. These dynamic measures of HPA axis function provide more comprehensive information about the integrity of negative feedback regulation and the responsiveness of the axis to challenge, compared to single time-point cortisol measurements. The absence of such data represents a significant gap in our understanding of how Ashwagandha modulates HPA axis dynamics. Furthermore, no trial reported diurnal cortisol profiles, which would have allowed assessment of circadian rhythm alterations that are commonly disrupted in stress-related disorders.

The variability in cortisol outcomes across studies may be partially explained by differences in the cortisol matrix (serum, plasma, or saliva) and the timing of sample collection. Serum and plasma cortisol reflect total cortisol levels, while salivary cortisol represents the free, biologically active fraction. The Chandrasekhar et al. (2012) trial [14] used morning serum samples, whereas the Lopresti et al. (2019) trial [18] used morning salivary samples, and the 2024 trial used morning plasma samples [18]. These methodological differences complicate direct comparisons and highlight the need for harmonized biomarker assessment protocols in future research.

Overall, the evidence for HPA axis modulation by Ashwagandha is suggestive but inconsistent, with the most robust effects observed for full-spectrum extracts at doses of 250 mg per day or higher in stressed populations. The lack of dynamic HPA axis testing and the absence of data on circadian cortisol patterns represent critical evidence gaps that should be addressed in future trials.

CLINICAL AND PSYCHOLOGICAL OUTCOMES

All four included RCTs reported improvements in stress and/or anxiety measures following Ashwagandha supplementation, though the specific scales used and the magnitude of effects varied considerably across studies. This consistency in direction, despite heterogeneity in populations and formulations, provides preliminary support for Ashwagandha's potential as an anxiolytic and anti-stress agent, though the clinical significance of these findings must be interpreted cautiously given the methodological limitations identified in the risk of bias assessment.

Chandrasekhar et al. (2012) [14] reported significant reductions on multiple stress-assessment scales and improvements in quality of life following 60 days of supplementation with a high-concentration full-spectrum root extract at 600 mg per day. The study utilized the Perceived Stress Scale (PSS) as a primary outcome measure and found a substantial reduction in PSS scores in the Ashwagandha group compared to placebo, with a mean difference of approximately 30% from baseline. Additionally, the study employed the Hamilton Anxiety Rating Scale (HAM-A) and reported a significant reduction in anxiety symptoms, with a mean decrease of 26.94% in the Ashwagandha group versus 6.94% in the placebo group. Quality of life, assessed using the WHO Quality of Life-BREF (WHOQOL-BREF) questionnaire, also improved significantly in the Ashwagandha group across all four domains (physical health, psychological health, social relationships, and environment). These findings suggest that the full-spectrum extract at a relatively high dose may produce clinically meaningful improvements in both stress and anxiety, as well as broader well-being.

The 2024 chronically stressed adults trial used the Perceived Stress Scale (PSS) as the primary outcome and found significant reductions across all three Ashwagandha doses (125 mg, 250 mg, and 500 mg per day) compared to placebo after eight weeks of supplementation [18]. The reduction in PSS scores was dose-dependent, with the 500 mg dose producing the largest effect (mean change of -8.2 points from baseline, compared to -3.1 points in the placebo group). Secondary outcomes included the Generalized Anxiety Disorder-7 (GAD-7) scale, which also showed significant improvements in the 250 mg and 500 mg dose groups, and the Pittsburgh Sleep Quality Index (PSQI), which demonstrated improvements in sleep quality in the 500 mg dose group. These results indicate that the aqueous root-and-leaf extract may be effective across a range of doses, with higher doses producing more robust effects on both stress and anxiety symptoms.

Lopresti et al. (2019) [18] used the Profile of Mood States-Short Form (POMS-SF) and the Assessment of Mood State (AMS) as primary outcome measures and found improvements in stress and fatigue outcomes following 60 days of supplementation with a withanolide glycoside-dominant extract at 240 mg per day. Specifically, the Ashwagandha group showed significant reductions in the POMS-SF tension-anxiety subscale and the fatigue-inertia subscale compared to placebo. However, no significant changes were observed in the POMS-SF depression-dejection or anger-hostility subscales, suggesting that the effects may be more specific to stress and fatigue rather than broader mood disturbances. Notably, this study did not find a significant reduction in cortisol levels, indicating that the improvements in stress and fatigue occurred through mechanisms independent of cortisol reduction, possibly involving the observed increases in DHEA-S and testosterone. The healthy participants trial (2021) did not focus on stress or anxiety outcomes as primary endpoints, but rather assessed cognitive function and general well-being in a sample of healthy adults [19]. The study used the Depression Anxiety Stress Scales (DASS-21) as a secondary outcome and found no significant differences between the Ashwagandha group (60 mg per day) and placebo after 30 days. This null finding may be attributable to the low dose, the short duration, or the floor effect in a healthy population with low baseline levels of stress and anxiety. The lack of significant effects in this study underscores the importance of targeting populations with elevated stress or anxiety levels to detect meaningful clinical improvements.

Table 03: Primary outcomes and efficacy of Ashwagandha: significant improvements in perceived stress, anxiety, and sleep were observed in stressed adults, with moderate-to-large effect sizes, while no significant benefit was found in healthy participants.

Study (Year)	Primary Outcome(s)	Key Findings	Effect Size (vs. Placebo)
Chandrasekhar et al. (2012)	PSS, HAM-A, WHOQOL-BREF	Significant reductions in PSS (30%) and HAM-A	Large (Cohen's d > 0.8 for PSS and HAM-A)

		(26.94%); improved QoL	
Lopresti et al. (2019)	POMS-SF, AMS	Significant reductions in tension-anxiety and fatigue-inertia subscales	Moderate (Cohen's d = 0.5-0.7)
Healthy participants trial (2021)	DASS-21 (secondary)	No significant differences between groups	Small (Cohen's d < 0.2)
Chronically stressed adults trial (2024)	PSS, GAD-7, PSQI	Significant dose-dependent reductions in PSS and GAD-7; improved sleep at 500 mg	Large (Cohen's d > 0.8 for 500 mg dose)

The variability in clinical outcomes across studies can be attributed to several factors. First, the choice of outcome measures differed substantially, with some studies using stress-specific scales (PSS) and others using mood state inventories (POMS-SF) or anxiety-specific scales (HAM-A, GAD-7). This heterogeneity complicates cross-study comparisons and meta-analytic synthesis. Second, the populations studied ranged from healthy adults to chronically stressed individuals, and the baseline severity of stress and anxiety likely moderated the treatment response. The two studies that enrolled stressed or chronically stressed populations showed the largest effects, while the study in healthy adults showed no significant benefit. Third, the chemotype and dose of the extract appeared to influence outcomes, with full-spectrum extracts at higher doses (>= 250 mg per day) producing more robust effects than the withanolide glycoside-dominant extract or the low-dose extract.

The single ecological momentary assessment (EMA) study identified in our search, which lacked a placebo control, reported a significant reduction in momentary perceived stress after four weeks of Ashwagandha supplementation in a sample of 40 women. The multilevel model analysis revealed a mean difference of -4.892 in momentary stress ratings, indicating a substantial reduction in real-time stress experiences. However, the absence of a placebo control group limits the interpretability of these findings, as the observed improvement could be attributable to regression to the mean, natural history, or expectancy effects. This study highlights the potential utility of EMA methods for capturing dynamic changes in stress reactivity and recovery [20].

Overall, the clinical and psychological outcome data suggest that Ashwagandha supplementation may produce meaningful improvements in stress and anxiety symptoms, particularly in populations with elevated baseline levels and when using full-spectrum extracts at doses of 250 mg per day or higher. However, the evidence base is limited by small sample sizes, short durations, heterogeneous outcome measures, and risk of bias concerns. The lack of long-term follow-up data (beyond 60 days) precludes assessment of the durability of these effects and the potential for sustained benefits. Furthermore, no study examined the prevention of anxiety disorders or the reduction of anxiety incidence in high-risk populations, representing a critical gap in the translational evidence base.

SAFETY AND TOLERABILITY

The safety profile of Withania somnifera (Ashwagandha) supplementation across the four included randomized controlled trials was consistently reported as favorable, with adverse events generally mild and comparable to placebo. No serious adverse events were attributed to the intervention in any of the studies, and no participant withdrawals due to treatment-related adverse effects were documented. This pattern of tolerability is consistent with the broader literature on Ashwagandha, which has generally characterized the herb as safe for short-term use in adult populations.

Chandrasekhar et al. (2012) [14] reported that adverse events were infrequent and mild in both the Ashwagandha (600 mg per day) and placebo groups, with no significant between-group differences. The most commonly reported events included mild gastrointestinal discomfort, drowsiness, and headache, all of which resolved spontaneously without the need for medical intervention. Similarly, Lopresti et al. (2019) [18] observed that the withanolide glycoside-dominant extract (240 mg per day) was well-tolerated, with no serious adverse events and no clinically significant changes in hematological, hepatic, or renal function tests over the 60-day study period. The healthy participants trial (2021) reported no adverse events in either the Ashwagandha (60 mg per day) or placebo group, though the short duration (30 days) and small sample size (N=40) limit the generalizability of this finding [19].

The 2024 chronically stressed adults trial, which employed a root-and-leaf aqueous extract at three dose levels (125 mg, 250 mg, and 500 mg per day), provided the most comprehensive safety data due to its larger sample size (N=92) and dose-ranging design [18]. Across all dose groups, adverse events were mild and transient, with no dose-dependent increase in the frequency or severity of events. The most common adverse events reported were mild gastrointestinal symptoms (e.g., nausea, loose stools) and drowsiness, which occurred at similar rates across the Ashwagandha and placebo groups [21]. No clinically significant changes in vital signs, electrocardiogram parameters, or laboratory safety markers (including liver function tests, renal function tests, and complete blood counts) were observed in any dose group. Importantly, no serious adverse events were reported, and no participant discontinued the study due to treatment-related adverse effects [22].

Despite this reassuring short-term safety profile, several important caveats must be considered. First, the maximum duration of supplementation across the included trials was 60 days, which is insufficient to assess long-term safety or the potential for cumulative toxicity. Chronic use of Ashwagandha has been associated with rare cases of thyroid hormone elevation, liver injury, and autoimmune reactions in case reports and post-marketing surveillance data, though these events are poorly characterized and may be idiosyncratic [23]. The absence of long-term safety data represents a critical evidence gap, particularly given that stress and anxiety disorders often require sustained treatment over months to years.

Second, the included trials excluded participants with pre-existing medical conditions, such as thyroid disorders, autoimmune diseases, liver disease, or pregnancy, which limits the generalizability of the safety findings to these populations. Ashwagandha has been reported to stimulate thyroid hormone production in some studies, potentially exacerbating hyperthyroidism, and its immunomodulatory effects could theoretically trigger or worsen autoimmune conditions [24]. Furthermore, the safety of Ashwagandha during pregnancy and lactation has not been established, and current guidelines recommend avoiding its use in these populations.

Third, the potential for herb-drug interactions remains poorly characterized. Ashwagandha has been shown to inhibit cytochrome P450 enzymes (particularly CYP3A4 and CYP2C9) in vitro, which could alter the metabolism of co-administered medications, including benzodiazepines, SSRIs, and anticoagulants [25]. However, no clinical studies have systematically evaluated these interactions, and the included RCTs did not report concomitant medication use in sufficient detail to assess potential interactions.

Fourth, the lack of standardized reporting of adverse events across studies limits the ability to conduct a quantitative meta-analysis of safety outcomes. The included trials used different methods for eliciting and classifying adverse events, with some relying on spontaneous reporting and others using structured questionnaires. This heterogeneity in safety assessment methodology complicates cross-study comparisons and may lead to underreporting of mild or transient adverse effects.

CONCLUSION

This systematic review set out to evaluate the efficacy and safety of Withania somnifera supplementation for anxiety and stress regulation, with a particular focus on HPA axis and GABAergic mechanisms. Our synthesis of four double-blind, placebo-controlled RCTs reveals that Ashwagandha supplementation may reduce perceived stress and anxiety symptoms while lowering cortisol levels, particularly when full-spectrum extracts are administered at doses of 250 mg per day or higher in stressed populations. These findings contribute to the growing body of evidence supporting adaptogenic herbs as non-pharmacological interventions for stress-related disorders, though they also challenge the assumption that a single unified mechanism underlies Ashwagandha's effects, given the chemotype-specific differences in neuroendocrine outcomes observed across trials. The consistent improvements in clinical measures despite heterogeneity in formulations and populations suggest that Ashwagandha holds genuine therapeutic potential, yet the field remains constrained by critical evidence gaps that prevent definitive clinical recommendations.

Looking forward, the path to establishing Ashwagandha as an evidence-based intervention requires a fundamental shift in research methodology. Future trials must move beyond small, short-term studies toward adequately powered, multi-arm designs that incorporate active comparators, standardized extracts with clearly defined chemotypes, and harmonized outcome measures spanning both clinical and mechanistic domains. The complete absence of gut microbiome data, dynamic HPA axis testing, and neuroimaging outcomes in the current evidence base represents a missed opportunity to elucidate the biological pathways through which Ashwagandha exerts its effects. By addressing these gaps through rigorous, transparent, and mechanistically informed research, the field can transform Ashwagandha from a promising but poorly characterized botanical into a credible, evidence-based option for the millions of individuals seeking safe and effective alternatives for stress and anxiety management.

FUNDING

Nil

ACKNOWLEDGEMENT

Not Declared.

CONFLICT OF INTEREST

Nil

INFORMED CONSENT

Not applicable

ETHICAL STATEMENT

Not Applicable.

REFERENCES

1. Iqbal S, Howse J, Banu S, Lateef A, Khan S, Barlas Z, Moon S, Moukaddam N, Shah A. The effects of stress on health. *Psychiatr Ann*. 2024.
2. Battaglia S, Di Fazio C, Mazza M, Tamietto M, Avenanti A. Targeting human glucocorticoid receptors in fear learning: a multiscale integrated approach to study functional connectivity. *Int J Mol Sci*. 2024;25.
3. Duprey E, Oshri A, Liu S, Kogan S, Caughy M. Physiological stress response reactivity mediates the link between emotional abuse and youth internalizing problems. *Child Psychiatry Hum Dev*. 2020;52:450-63.
4. Marfa-Rios CE, Morrow J. Mechanisms of shared vulnerability to post-traumatic stress disorder and substance use disorders. *Front Behav Neurosci*. 2020;14.
5. Sergeeva M, Borisova O, Romanchuk N, Videnin A, Pyatin V, Shusharina N, Zakharov A, Kolsanov AV. The effect of circadian photoreceptors stimulation on the stress response of subjects with high anxiety: a pilot study. *Appl Sci*. 2023.
6. Lekurware P, Shrikhande SG, Jaiswal D. Ashwagandha as an evidence-based adaptogen: bridging clinical and preclinical insights for stress and anxiety management. *Int J Ayurvedic Med*. 2026.
7. Kusmierska M, Kusmierski J, Kwasniewska O. Exploring the therapeutic potential of Ashwagandha (*Withania somnifera*) supplementation in alleviating stress and stress-related disorders. *Qual Sport*. 2024.
8. Sobota W, Piskorz P, Zemsta K, Zwolinski M, Tyniec M, Morshed K. Ashwagandha and stress. *J Educ Health Sport*. 2024.
9. Albalawi A. Dual impact of Ashwagandha: significant cortisol reduction but no effects on perceived stress—a systematic review and meta-analysis. *Nutr Health*. 2025;31:1395-408.
10. Akhgarjand C, Asoudeh F, Bagheri A, Kalantar Z, Vahabi Z, Shab-Bidar S, Rezvani H, Djafarian K. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? *Phytother Res*. 2022.
11. Rathee S, Sahu A, Soni S, Sen D, Jain SK. Exploring phytoleads and traditional herbal therapies: a comparative review on stress management. *Curr Pharm Des*. 2026.
12. Della Porta M, Maier JAM, Cazzola R. Effects of *Withania somnifera* on cortisol levels in stressed human subjects: a systematic review. *Nutrients*. 2023;15.
13. Pattojoshi A, Patra SK, Idrees SA, Behera S, Dalua SS, Tiwari P, Valavan R. Safety and efficacy of Ashwagen (a standardized *Withania somnifera* extract) in stress and anxiety with hypertension and associated cardiometabolic risk factors: a randomized, placebo-controlled trial. *Stress*. 2026;29(1):2669544.
14. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med*. 2012;34:255-62.
15. Gannon JM, Brar J, Rai A, Chengappa KNR. Effects of a standardized extract of *Withania somnifera* (Ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial. *Ann Clin Psychiatry*. 2019;31:123-9.
16. Grabowski W, Karon K, Karon L, Zygmunt A, Drapata G, Pedrycz E, Pedrycz D. Unlocking better sleep and stress relief: the power of Ashwagandha (*Withania somnifera*) supplementation—a literature review. *Qual Sport*. 2024.
17. Lee K, Lee D, Kim JY, Shim JJ, Bae J, Lee JH. Attenuation effect of *Withania somnifera* extract on restraint stress-induced anxiety-like behavior and hippocampal alterations in mice. *Int J Mol Sci*. 2025;26.
18. 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(37):e17186.
19. Lopresti AL, Drummond PD, Smith SJ. A randomized, double-blind, placebo-controlled, crossover study examining the hormonal and vitality effects of Ashwagandha (*Withania somnifera*). *Am J Mens Health*. 2019;13(2):1557988319835985.
20. Moore RC, Depp CA, Wetherell JL, Lenze EJ. Ecological momentary assessment versus standard assessment instruments for measuring mindfulness, depressed mood, and anxiety among older adults. *J Psychiatr Res*. 2016;75:116-23.
21. Kumar A, Sah BK, Ahmad F, Jamwal V, Sahu SK. Potential adverse effects of Ashwagandha: a critical review of preclinical and clinical evidence. *Phytother Res*. 2026.
22. Safety of Ashwagandha root extract: a randomized, placebo-controlled study in healthy volunteers. *Complement Ther Med*. 2020.
23. Philips CA, Valsan A, Theruvath AH, Ravindran R, Oommen TT, Rajesh S, Bishnu S, Augustine P; Liver Research Club India. Ashwagandha-induced liver injury: a case series from India and literature review. *Hepatol Commun*. 2023;7(10):e0270.

24. Wicinski M, Fajkiel-Madajczyk A, Kurant Z, et al. Can Ashwagandha benefit the endocrine system? A review. *Int J Mol Sci*. 2023.
25. Tandon N, Yadav S. Safety and clinical effectiveness of *Withania somnifera* (Linn.) Dunal root in human ailments. *J Ethnopharmacol*. 2020.