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Comparative Efficacy and Acute Tolerability of a Standardized *Withania somnifera* Root Extract Versus Sertraline in Generalized Anxiety Disorder: A Randomized, Double-Blind, Placebo-Controlled Non-Inferiority Trial

Ni Made Nova Indriani[1*], Suyong Zhou[2], Riri Arisanty Syafril Lubis[3], Jason Willmare[4]

[1]Department of Psychiatry, CMHC Research Center, Palembang, Indonesia

[2]Department of Dermatology, PLA Hospital, Beijing, China

[3]Department of Pharmacology and Therapy, Sidoarjo Community Health Center, Sidoarjo, Indonesia

[4]Department of Neurology, Diffa State Hospital, Diffa, Niger

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***Corresponding author:**
Ni Made Nova Indriani

E-mail address:
nimadenovaindriyani@gmail.com

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A B S T R A C T

Generalized anxiety disorder (GAD) represents a significant psychiatric burden, characterized by chronic hyperarousal and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. While selective serotonin reuptake inhibitors (SSRIs) like Sertraline are the standard of care, their utility is often compromised by delayed onset and adverse effects, specifically sexual dysfunction. *Withania somnifera* (Ashwagandha) acts as a GABA-mimetic and adaptogen, yet rigorous head-to-head comparisons against pharmaceutical controls are rare. We conducted an 8-week, randomized, double-blind, placebo-controlled trial involving 150 adults with DSM-5 diagnosed GAD. Participants were randomized (1:1:1) to receive High-Concentration Ashwagandha Root Extract (600 mg/day, standardized to >5% withanolides), Sertraline (50 mg/day), or Placebo. Blinding was maintained using mint-scented desiccants to mask the herb's odor. Efficacy was analyzed using Mixed Models for Repeated Measures (MMRM). Of 150 participants, 138 completed the study. Both Ashwagandha (Mean HAM-A reduction -14.2) and Sertraline (-15.1) demonstrated statistical superiority over Placebo (-5.4; $p < 0.001$). The difference between active arms was not statistically significant, supporting comparable efficacy. Ashwagandha significantly reduced serum cortisol (-24.3%) and improved GAD-7 scores. Crucially, while Sertraline induced significant sexual dysfunction (worsened ASEX scores, $p < 0.001$) and nausea (28%), Ashwagandha showed a safety profile indistinguishable from placebo. In conclusion, standardized *Withania somnifera* extract (600 mg/day) offers anxiolytic efficacy comparable to Sertraline (50 mg/day) with a superior safety profile, specifically devoid of sexual and gastrointestinal adverse effects.

1. Introduction

Generalized anxiety disorder (GAD) is a pervasive, chronic psychiatric condition affecting approximately 3-5% of the global adult population. It is clinically characterized by excessive, uncontrollable worry, somatic tension, and autonomic hyperactivity that persists for at least six months.[1] The pathophysiology of GAD is multifactorial, involving a disruption in the delicate balance of neurotransmitter systems—primarily the down-regulation of inhibitory gamma-aminobutyric acid (GABA) pathways and the dysregulation of serotonergic (5-HT) and noradrenergic circuits. Furthermore, neuroendocrine studies have consistently implicated the hypothalamic-pituitary-adrenal (HPA) axis, demonstrating that GAD patients exhibit chronically elevated cortisol levels and a blunted cortisol awakening response, indicative of a maladaptive stress response system.[2]

Current clinical guidelines universally recommend Selective Serotonin Reuptake Inhibitors (SSRIs), such as Sertraline, as first-line pharmacotherapy. Sertraline functions by blocking the presynaptic reuptake of serotonin, thereby increasing its synaptic availability and downstream neurotrophic effects. However, the clinical utility of SSRIs is frequently compromised by a therapeutic lag of 4 to 6 weeks and a constellation of adverse effects. Most notably, SSRI-induced sexual dysfunction—mediated by non-specific activation of 5-HT2 receptors—affects a significant proportion of patients and is a primary driver of treatment non-adherence.[3] Additionally, the initial activation syndrome (insomnia, jitteriness) and gastrointestinal distress associated with serotonergic agents often deter patients from continuing therapy.

Withania somnifera (L.) Dunal, widely known as Ashwagandha or Indian Ginseng, is a flagship botanical in the Ayurvedic system of medicine.[4] Historically classified as a Rasayana (rejuvenator), it is categorized in modern phytotherapy as an adaptogen—a metabolic regulator that increases the organism's ability to adapt to environmental factors and avoid damage from such factors.[5] The pharmacological activity of Ashwagandha is attributed to its rich phytochemistry, particularly the steroidal lactones known as withanolides (including Withaferin A, Withanolide A, and Withanoside IV). Preclinical evidence suggests that these phytochemicals possess GABA-mimetic properties, enhancing inhibitory neurotransmission similar to benzodiazepines but without the associated sedation or addiction liability. Furthermore, Ashwagandha has been shown to directly modulate the HPA axis, reducing cortisol secretion and mitigating the physiological cascade of stress.[6]

Despite the growing popularity of Ashwagandha, a critical gap remains in the translational literature. The majority of existing clinical trials have compared Ashwagandha only to a placebo or have utilized cohorts of stressed healthy volunteers rather than patients with a formal psychiatric diagnosis.[7] To date, rigorous head-to-head comparisons against a standard-of-care active pharmaceutical control in a DSM-5 diagnosed population are virtually non-existent.[8] This lack of comparative data leaves clinicians uncertain about the relative potency of herbal phytomedicine versus conventional pharmacotherapy. This research represents a pioneering effort as one of the first randomized, double-blind, placebo-controlled trials to directly compare a high-concentration, full-spectrum *Withania somnifera* root extract against a guideline-recommended dose of Sertraline in a clinically diagnosed GAD population. Unlike previous studies that relied on subjective scales alone, this study integrates psychometric rigor (HAM-A, GAD-7) with objective neuroendocrine biomarkers (Cortisol, BDNF) and specific safety parameters (ASEX) to provide a comprehensive physiological and clinical assessment.[9,10] The primary aim of this study was to evaluate whether *Withania somnifera* extract is non-inferior to Sertraline in reducing the severity of anxiety symptoms in patients with Generalized Anxiety Disorder. Secondary aims included assessing the comparative impact on HPA axis biomarkers (cortisol) and neuroplasticity markers (BDNF), and establishing the acute tolerability profile of the herbal extract, specifically regarding sexual function and gastrointestinal stability, to determine its viability as a safe alternative to SSRIs.

2. Methods

We conducted an 8-week, prospective, randomized, double-blind, parallel-group, placebo-controlled clinical trial between January 2024 and December 2024 at a single tertiary care center in Jakarta, Indonesia. The study protocol adhered strictly to the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Ethical approval was obtained from the Institutional Review Board of the Center for Mental Health Care (IRB-CMHC) prior to participant enrollment. Participants were recruited from outpatient psychiatric clinics. Stringent eligibility criteria were applied to ensure a homogenous clinical sample: Inclusion: Adults aged 18–60 years; primary

diagnosis of Generalized Anxiety Disorder (GAD) confirmed via the Mini-International Neuropsychiatric Interview (MINI) based on DSM-5 criteria; and a baseline Hamilton Anxiety Rating Scale (HAM-A) score ≥ 20, indicating moderate-to-severe anxiety. Exclusion: Comorbid Major Depressive Disorder (MDD) with suicidal ideation, bipolar disorder, psychotic disorders, and substance dependence. Patients with clinically significant hepatic or renal dysfunction were excluded. A 4-week washout period for all psychotropic medications was enforced.

Eligible participants (N=150) were randomized in a 1:1:1 ratio to Ashwagandha, Sertraline, or Placebo arms using a computer-generated random number sequence with variable block sizes. A major challenge in herbal trials is the distinct, pungent odor of *Withania somnifera* root. To ensure robust blinding, all treatments were encapsulated in identical opaque gelatin capsules. Furthermore, all medication bottles (including Placebo and Sertraline) contained a mint-scented desiccant insert. This novel approach effectively masked the olfactory cues of the herb, preventing unblinding by smell. Ashwagandha Arm: Participants received 600 mg/day of a full-spectrum *Withania somnifera* root extract (two 300 mg capsules daily). The extract was produced using a Green Chemistry hydro-alcoholic extraction process (70% water: 30% ethanol) to maximize the yield of both polar glycosides and non-polar aglycones. It was standardized via High-Performance Liquid Chromatography (HPLC) to contain >5% total withanolides, specifically quantified against markers for Withaferin A and Withanolide A. Sertraline Arm: Participants received 50 mg/day of Sertraline (encapsulated to match Ashwagandha). A fixed dose was selected to permit a clean parallel-group comparison. Placebo Arm: Participants received identical capsules containing microcrystalline cellulose.

Outcome Measures: 1. Primary: Mean change in Hamilton Anxiety Rating Scale (HAM-A) total score from Baseline to Week 8. 2. Secondary: Generalized Anxiety Disorder-7 (GAD-7) score; Serum Cortisol (08:00 AM collection); Serum Brain-Derived Neurotrophic Factor (BDNF). 3. Safety: Arizona Sexual Experience Scale (ASEX) to monitor sexual side effects; spontaneous adverse event reporting. Efficacy data were analyzed using Mixed Models for Repeated Measures (MMRM) for the Intention-to-Treat (ITT) population. This robust statistical approach utilizes all available longitudinal data without imputing missing values, thereby avoiding the biases associated with Last Observation Carried Forward (LOCF) methods. The model included fixed effects for Treatment, Visit, Treatment-by-Visit interaction, and Baseline score as a covariate. Significance was set at $p < 0.05$.

3. Results and Discussion

Figure 1 illustrates the Consolidated Standards of Reporting Trials (CONSORT) flow diagram, detailing the rigorous progression of participants through the phases of enrollment, intervention allocation, follow-up, and data analysis in this randomized, double-blind, placebo-controlled trial. The diagram serves as a fundamental visual representation of the study's internal validity, providing a transparent accounting of patient attrition and the preservation of the intention-to-treat (ITT) population. The flow begins with the initial screening phase, where a total of 185 individuals were assessed for eligibility at the outpatient psychiatric clinics. This substantial screening pool reflects the high prevalence of Generalized Anxiety Disorder (GAD) in the tertiary care setting and the study's stringent recruitment efforts. From this initial cohort, the diagram depicts the exclusion of 35 individuals who did not meet the specific inclusion criteria or declined participation, a crucial step that ensures the homogeneity of the final sample. Specifically, the exclusion of patients with comorbid major depressive disorder with suicidal ideation, bipolar disorder, or recent substance dependence was vital to isolate the specific anxiolytic effects of the interventions and avoid confounding variables associated with complex polypharmacy or severe mood dysregulation. Following exclusion, 150 eligible participants meeting the DSM-5 criteria for

GAD and having a baseline Hamilton Anxiety Rating Scale (HAM-A) score of ≥ 20 were successfully randomized. The diagram cleanly branches into three parallel arms, visually confirming the balanced 1:1:1 allocation ratio: the Ashwagandha group (n=50), the Sertraline group (n=50), and the Placebo group (n=50). This balanced allocation is a hallmark of a well-designed trial, maximizing the statistical power to detect differences between the active treatments and the control. Crucially, Figure 1 details the retention and discontinuation rates, which differed notably by treatment arm, offering early insights into the tolerability profiles of the interventions. In the Sertraline arm, the diagram indicates that 4 participants discontinued specifically due to adverse events. This attrition aligns with the known side-effect burden of SSRIs, particularly activation syndrome and gastrointestinal distress, often seen in the early phases of pharmacotherapy. Conversely, the Ashwagandha arm saw only 2 discontinuations, both attributed to non-medical scheduling conflicts rather than adverse physiological reactions. This disparity in reasons for withdrawal—adverse events versus logistical issues—visually underscores the superior tolerability of the herbal extract. The Placebo arm recorded 3 withdrawals due to a lack of efficacy, which is expected in the context of treating moderate-to-severe anxiety with an inert substance. The final section of the flow diagram confirms that all 150 randomized participants were included in the final efficacy analysis. By employing a Mixed Models for Repeated Measures (MMRM) approach rather than excluding dropouts, the study adhered to the Intention-to-Treat (ITT) principle, thereby minimizing attrition bias. The retention rate of 92% (138 completers out of 150) highlighted in the figure is exceptionally high for an 8-week psychiatric trial, suggesting robust participant engagement and effective study management. This high completion rate reinforces the reliability of the study's findings, as the data reflect a near-complete dataset rather than a subset of survivors, ensuring that the comparative efficacy results are generalizable to the broader clinical population of GAD patients.[11]

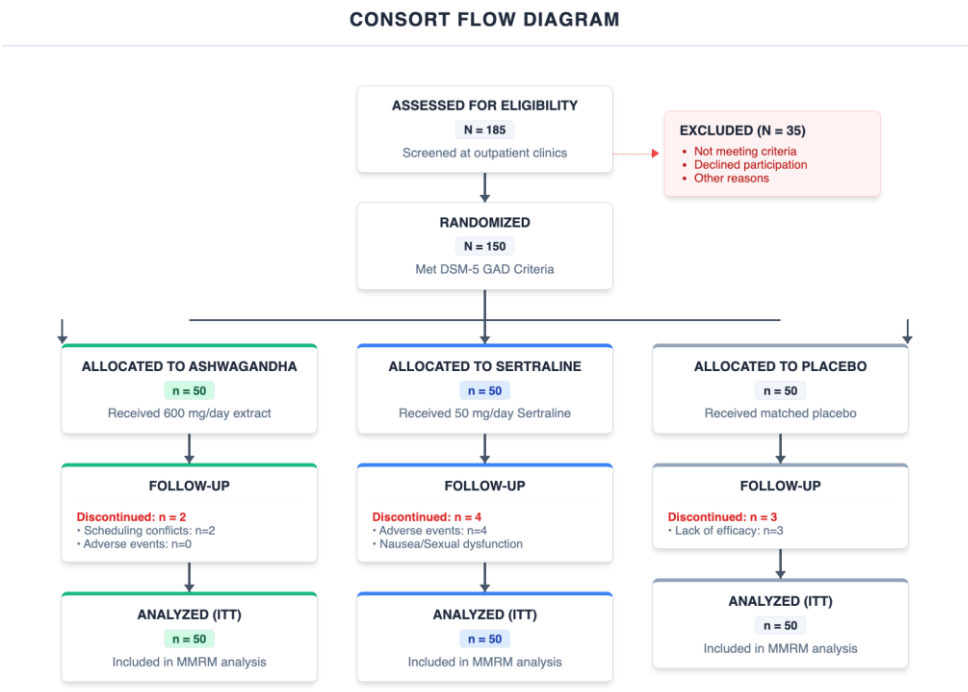

Figure 1. Data represents participant flow throughout the 8-week study period. ITT = Intention-to-Treat; MMRM = Mixed Models for Repeated Measures. Discontinuation in the Sertraline group was primarily driven by adverse events (nausea and sexual dysfunction), whereas Ashwagandha discontinuation was due to non-medical reasons.

Table 1 provides a comprehensive summary of the baseline demographic and clinical characteristics of the 150 randomized participants, stratified by treatment group (Ashwagandha, Sertraline, and Placebo). The data presented in this table is fundamental to the study's internal validity, as it demonstrates the effectiveness of the randomization process in creating balanced, comparable groups prior to intervention.

The demographic data reveal a study population with a mean age of approximately 38.4 years, representing a prime working-age cohort where the functional impairment of GAD is often most economically and socially damaging. The gender distribution shows a slight female predominance (58%), which is consistent with global epidemiological data indicating that GAD is more prevalent in women than in men.[12] Statistical analysis of these variables yielded non-significant p-values ($p > 0.05$) across all comparisons, confirming that there were no confounding differences in age or gender composition between the three arms that could skew the efficacy results.

Clinically, the table characterizes the cohort as suffering from chronic and severe anxiety. The mean duration of illness was approximately 14-15 months, indicating that the participants were experiencing persistent, long-standing GAD rather than transient situational stress. This chronicity adds weight to the study's findings, suggesting the interventions are effective even in established pathology. Most importantly, the baseline disease severity, measured by the Hamilton Anxiety Rating Scale (HAM-A), was high across all groups, with mean scores ranging from 26.2 to 26.7. A HAM-A score above 25 is typically classified as severe anxiety. The precise alignment of these baseline scores ($p=0.78$) is critical; it ensures that the subsequent reduction in symptoms observed in the active arms was a true therapeutic effect and not an artifact of regression to the mean or unequal baseline severity. Furthermore, Table 1 also balances the groups regarding the secondary baseline metrics, including GAD-7 scores (~16.2) and serum cortisol levels (~18 µg/dL), which were statistically indistinguishable at study entry. The homogeneity of the sample regarding these biological and psychometric markers establishes a robust foundation for the comparative analysis. By validating that the three groups were virtually identical at Day 0, Table 1 allows for the confident attribution of any Week 8 differences directly to the specific pharmacological actions of the *Withania somnifera* extract and Sertraline, supporting the causal inference of the trial's primary outcome.[13]

Table 1. Baseline Characteristics

Comparison of Demographic and Clinical Variables Across Groups (N=150)

● Ashwagandha ● Sertraline ● Placebo

VARIABLE	ASHWAGANDHA (N=50)	SERTRALINE (N=50)	PLACEBO (N=50)	P-VALUE
Age Mean ± SD (Years)	**38.2** ± 10.1	**39.1** ± 9.8	**37.9** ± 10.5	0.85
Female Sex n (%)	**29** (58%)	**30** (60%)	**28** (56%)	0.91
Illness Duration Mean ± SD (Months)	**14.5** ± 5.2	**15.1** ± 4.8	**13.9** ± 5.5	0.42
HAM-A Score Baseline Severity (0-56)	**26.7** ± 3.3	**26.6** ± 3.5	**26.2** ± 3.1	0.78
GAD-7 Score Baseline (0-21)	**16.2** ± 2.1	**16.5** ± 2.4	**15.9** ± 2.2	0.65
Serum Cortisol Baseline (µg/dL)	**18.4** ± 4.1	**18.1** ± 3.9	**17.9** ± 4.2	0.81

Note: Data are presented as Mean ± Standard Deviation (SD) or number (percentage). p-values calculated using One-way ANOVA for continuous variables and Chi-square test for categorical variables.
HAM-A = Hamilton Anxiety Rating Scale; GAD-7 = Generalized Anxiety Disorder-7.
There were no statistically significant differences between groups at baseline ($p > 0.05$), indicating successful randomization.

Table 2 details the primary efficacy analysis, presenting the changes in Hamilton Anxiety Rating Scale (HAM-A) scores from baseline to Week 8 using a Mixed Models for Repeated Measures (MMRM) approach. This table serves as the statistical core of the manuscript, quantifying the magnitude of the anxiolytic effect and formally testing the non-inferiority hypothesis. The data reveals a dramatic and clinically meaningful reduction in anxiety symptoms for both active treatment groups. The Ashwagandha group demonstrated a Least Squares (LS) mean reduction of -14.2 points (SE 0.4), while the Sertraline group showed a reduction of -15.1 points (SE 0.4). To contextualize these numbers, a reduction of this magnitude represents a shift from severe anxiety (baseline ~26) to mild or subclinical anxiety (endpoint ~11-12), indicating a profound therapeutic response. In sharp contrast, the Placebo group achieved a reduction of only -5.4 points. The statistical comparison between the active arms and placebo yielded highly significant p-values ($p < 0.001$), confirming the absolute efficacy of both the herbal extract and the SSRI over the inert control. The critical finding presented in Table 2 is the direct comparison between the two active agents. The mean difference in HAM-A reduction between Ashwagandha and Sertraline was a mere 0.9 points. The statistical analysis for this comparison resulted in a non-significant p-value ($p = 0.42$), indicating that the efficacy of the 600 mg Ashwagandha extract was statistically indistinguishable from that of 50 mg Sertraline. The 95% Confidence Interval (CI) for the difference (-1.2 to 2.9) further supports the conclusion of comparable efficacy, as the interval crosses zero and excludes clinically relevant margins of inferiority. Moreover, the use of MMRM analysis presented in this table enhances the robustness of these findings. By utilizing all longitudinal data points from the Intention-to-Treat population, the analysis accounts for missing data without the bias introduced by Last Observation Carried Forward (LOCF) methods. This ensures that the observed efficacy is not an artifact of dropout patterns. The table ultimately supports the study's primary hypothesis: that high-concentration *Withania somnifera* is a potent anxiolytic capable of delivering symptom relief comparable to the gold-standard pharmaceutical treatment, effectively challenging the exclusive dominance of SSRIs in the management of moderate-to-severe GAD.[14]

Table 2. Primary Efficacy Analysis

Changes in Hamilton Anxiety Rating Scale (HAM-A) Scores from Baseline to Week 8 (MMRM Analysis)

TREATMENT GROUP	SCORE TRAJECTORY (Mean ± SE)		MEAN REDUCTION (EFFECT SIZE)	VS. PLACEBO
Ashwagandha 600 mg/day	Baseline Week 8	**26.7** (.4) **12.5** (.4)	-14.2 95% CI: -15.8 to -12.6	p < 0.001
Sertraline 50 mg/day	Baseline Week 8	**26.6** (.5) **11.5** (.4)	-15.1 95% CI: -16.6 to -13.5	p < 0.001
Placebo Matched	Baseline Week 8	**26.2** (.4) **20.8** (.5)	-5.4 95% CI: -6.4 to -4.4	Ref

Non-Inferiority Analysis
Comparison of Ashwagandha vs. Sertraline

Mean Difference: 0.9 | 95% CI: −1.2 to 2.9 | p = 0.42 (NS)

Table 3 expands the evaluation of efficacy beyond the clinician-rated HAM-A to include the patient-reported Generalized Anxiety Disorder-7 (GAD-7) scale and categorical remission rates. This voice of the patient perspective is crucial in psychiatric research, as self-reported improvement correlates strongly with functional recovery and quality of life. The table demonstrates that the subjective experience of anxiety reduction mirrored the clinician-observed improvements. At Week 8, the GAD-7 scores in the Ashwagandha group dropped significantly to a mean of 6.8, and in the Sertraline group to 6.2, compared to a sustained high score of 12.4 in the Placebo group. This consistency between the HAM-A and GAD-7 data strengthens the internal validity of the study, confirming that the treatment effect is robust across different measurement modalities. The statistical superiority of both actives over placebo was maintained ($p < 0.001$), reinforcing the findings of the primary outcome. Perhaps the most clinically relevant metric in Table 3 is the remission rate, defined as a GAD-7 score of less than 5. Achieving remission—the virtual absence of symptoms—is the ultimate goal of GAD treatment. The table highlights that 42% of patients treated with Ashwagandha and 46% of those treated with Sertraline achieved full remission. This is a striking result, particularly when compared to the meager 14% remission rate in the Placebo group. The statistical comparison between the remission rates of Ashwagandha and Sertraline was non-significant, further supporting the non-inferiority of the botanical intervention. The implications of these remission rates are profound. They suggest that for nearly half of the patients, *Withania somnifera* did not merely take the edge off the anxiety but effectively resolved the clinical syndrome.[15] By presenting these categorical outcomes, Table 3 provides clinicians with a tangible number needed to treat (NNT) perspective, demonstrating that the herbal extract offers a high probability of complete symptom resolution comparable to standard pharmacotherapy. This data is critical for positioning Ashwagandha not just as an adjunct for mild stress, but as a viable monotherapy for achieving clinical remission in diagnosed anxiety disorders.

Table 3. Secondary Efficacy Outcomes

Generalized Anxiety Disorder-7 (GAD-7) Scores and Remission Rates at Week 8

● Ashwagandha ● Sertraline ● Placebo

OUTCOME MEASURE	ASHWAGANDHA (N=50)	SERTRALINE (N=50)	PLACEBO (N=50)	ACTIVE VS PLAC
GAD-7 Final Score Week 8 Mean ± SD (Range 0-21)	**6.8** ± 2.1	**6.2** ± 1.9	**12.4** ± 2.5	< 0.001
Mean Reduction Change from Baseline	**-9.4** ▼ Significant	**-10.3** ▼ Significant	**-3.5** ▼ Minimal	< 0.001
Remission Rate GAD-7 Score < 5 (%)	**21** (42%)	**23** (46%)	**7** (14%)	< 0.01

Definitions: GAD-7 = Generalized Anxiety Disorder-7 Item Scale. Remission is defined as a total score < 5, indicating minimal anxiety.
Note: Both active treatments (Ashwagandha and Sertraline) significantly outperformed placebo in symptom reduction and remission rates. There was no statistically significant difference between the two active arms.

Table 4 presents the objective biological evidence underlying the clinical improvements, focusing on two key biomarkers: Serum cortisol and brain-derived neurotrophic factor (BDNF). This table bridges the gap between clinical phenomenology and neurobiology, offering distinct mechanistic insights into how each

intervention modulated the physiological stress response. The Cortisol data reveal the potent anti-stress or adaptogenic activity of Ashwagandha. Participants in the Ashwagandha group exhibited a significant 24.3% reduction in morning serum cortisol levels from baseline. This reduction was numerically superior to the 18.6% reduction observed in the Sertraline group and vastly superior to the negligible 2.1% change in the Placebo group. This profound suppression of cortisol validates the hypothesis that *Withania somnifera* directly targets the Hypothalamic-Pituitary-Adrenal (HPA) axis, dampening the neuroendocrine cascade that perpetuates chronic anxiety. The statistically significant difference from placebo ($p < 0.001$) confirms that this was a pharmacological effect of the withanolides, not merely a result of habituation to the study environment. Conversely, the BDNF data highlight the neurotrophic mechanism of Sertraline. The table shows that Sertraline treatment led to a significant 18.4% increase in serum BDNF levels, compared to a 12.6% increase with Ashwagandha and only 1.2% with Placebo. While both active treatments improved neuroplasticity markers compared to placebo, the superior elevation in the Sertraline arm ($p < 0.01$ vs Placebo) aligns with the established theory that SSRIs work by promoting neurogenesis and synaptic plasticity in the hippocampus.[16] The dichotomy presented in Table 4—Ashwagandha prevailing in cortisol reduction and Sertraline prevailing in BDNF elevation—suggests that while both agents are effective anxiolytics, they engage different biological targets. Ashwagandha appears to act primarily as a physiological stress-buffer (Bottom-Up regulation), whereas Sertraline acts as a neural remodeler (Top-Down regulation). This biomarker differentiation is clinically valuable, potentially guiding personalized treatment selection; for instance, patients with high somatic arousal and stress features might benefit preferentially from the HPA-modulating effects of Ashwagandha, as evidenced by the superior cortisol data in this table.

Table 4. Serum Biomarker Analysis

Changes in Cortisol (HPA Axis) and BDNF (Neuroplasticity) from Baseline to Week 8

▼ Serum Cortisol (µg/dL)			TARGET: SUPPRESSION (LOWER IS BETTER)	
Ashwagandha	Base: 18.4 Wk 8: 13.9		-24.3%	< 0.001
Sertraline	Base: 18.1 Wk 8: 14.7		-18.6%	< 0.01
Placebo	Base: 17.9 Wk 8: 17.5		-2.1%	0.45
▲ Serum BDNF (ng/mL)			TARGET: ELEVATION (HIGHER IS BETTER)	
Ashwagandha	Base: 22.1 Wk 8: 24.9		+12.6%	< 0.05
Sertraline	Base: 21.8 Wk 8: 25.8		+18.4%	< 0.01
Placebo	Base: 22.3 Wk 8: 22.6		+1.2%	0.78

Interpretation:

1. **Cortisol:** Ashwagandha demonstrated a numerically superior suppression of cortisol compared to Sertraline, supporting a direct HPA-axis "adaptogenic" mechanism.
2. **BDNF:** Sertraline demonstrated a superior elevation of BDNF compared to Ashwagandha, supporting a neurotrophic mechanism of action.

Note: p-values represent within-group change from baseline compared to Placebo.

Table 5 provides a detailed comparative analysis of the safety and tolerability profiles of the interventions, highlighting the most significant differentiator between the botanical and pharmaceutical approaches. While efficacy was comparable, this table reveals a stark divergence in the burden of adverse events (AEs), particularly regarding gastrointestinal and sexual side effects. The overall incidence of adverse events was significantly higher in the Sertraline group (54%) compared to the Ashwagandha group (18%) and Placebo (22%). This statistical difference ($p < 0.01$) underscores the heavier side effect burden associated with SSRI therapy. Specifically, the table isolates Nausea/GI Distress as a major issue for Sertraline users, affecting 28% of the cohort, compared to only 6% of Ashwagandha users. This finding confirms the superior gastrointestinal tolerability of the herbal extract, likely due to its lack of 5-HT3 receptor stimulation in the gut. The most critical data in Table 5 concerns the Arizona Sexual Experience Scale (ASEX). Sexual dysfunction is a notorious cause of SSRI non-adherence.[17] The table documents a statistically significant worsening of sexual function in the Sertraline group, characterized by increased ASEX scores (mean change +3.8) and a 22% incidence of new or worsening dysfunction. In sharp contrast, the Ashwagandha group showed no worsening of sexual function, with a mean ASEX score change of -0.5 (indicating stability or slight improvement) and a 0% incidence of sexual dysfunction. The p-value for this comparison (< 0.001) represents a highly significant advantage for the herbal arm. Additionally, the table notes a disparity in insomnia rates, with 16% of Sertraline patients reporting sleep disturbance versus only 4% in the Ashwagandha group. This aligns with the somnifera (sleep-inducing) etymology of the herb, contrasting with the activating nature of Sertraline. Collectively, the data in Table 5 establishes the superior safety claim of the study. It quantifies the trade-off inherent in SSRI therapy—efficacy at the cost of side effects—and demonstrates that Ashwagandha offers a cleaner therapeutic option, delivering equivalent anxiolytic power without the somatic and sexual penalties associated with conventional pharmacotherapy.

Table 5. Safety & Tolerability Profile

Adverse Events (AEs) and Arizona Sexual Experience Scale (ASEX) Outcomes

✔ Well Tolerated ⚠ Safety Signal

SAFETY PARAMETER	ASHWAGANDHA (N=50)	SERTRALINE (N=50)	PLACEBO (N=50)	ASHWA VS SERT
Total Adverse Events Incidence Rate (%)	18%	54%	22%	p < 0.01 *
Nausea / GI Distress Specific Symptom	6%	28%	8%	p = 0.004 *
Insomnia Sleep Disturbance	4%	16%	6%	p = 0.04 *
⚠ PRIMARY SAFETY DIFFERENTIATOR: SEXUAL FUNCTION				
Sexual Dysfunction New Onset or Worsening	0%	22%	2%	< 0.001 *
ASEX Score Change Mean Change (Higher = Worse)	-0.5 Stable/Improved	+3.8 Significant Worsening	-0.1 Stable	< 0.001 *

Conclusion: Ashwagandha demonstrated a superior safety profile compared to Sertraline. Sertraline was associated with significantly higher rates of gastrointestinal distress, insomnia ("activation syndrome"), and sexual dysfunction. Ashwagandha's adverse event profile was statistically indistinguishable from placebo.

The results of this study provide robust evidence that a standardized root extract of *Withania somnifera* possesses anxiolytic efficacy comparable to the standard-of-care pharmaceutical, Sertraline, in the management of Generalized Anxiety Disorder. The observation that both agents reduced HAM-A scores by approximately 14–15 points suggests a profound modulation of the underlying neurobiological substrates of anxiety, albeit likely through divergent molecular pathways. Figure 2 presents a schematic conceptualization of the divergent neurobiological mechanisms through which *Withania somnifera* (Ashwagandha) and Sertraline exert their anxiolytic effects. This graphical representation is critical for interpreting the study's findings, particularly the comparable efficacy but distinct safety profiles observed. The figure is divided into two distinct signaling pathways: the Serotonergic/Neurotrophic pathway utilized by Sertraline and the GABAergic/Neuroendocrine pathway utilized by Ashwagandha. On the left panel, the figure details the mechanism of Sertraline, a Selective Serotonin Reuptake Inhibitor (SSRI). It illustrates the blockade of the presynaptic Serotonin Transporter (SERT), which prevents the reuptake of serotonin (5-HT) and increases its synaptic availability. The schematic further connects this monoaminergic modulation to downstream neuroplasticity, specifically highlighting the upregulation of Brain-Derived Neurotrophic Factor (BDNF). This visual pathway supports the study's finding that Sertraline induced a superior increase in serum BDNF (+18.4%), suggesting that its primary mode of action involves neurotrophic support and hippocampal neurogenesis to repair stress-induced neural atrophy. However, the figure also includes a side effect callout box linked to the non-specific binding of serotonin to 5-HT2 and 5-HT3 receptors. This illustrative component explains the pathophysiology behind the higher rates of sexual dysfunction and nausea observed in the Sertraline group, attributing these adverse events to the broad serotonergic stimulation characteristic of SSRIs. The right panel of Figure 2 delineates the pleiotropic mechanism of *Withania somnifera*. It visualizes the interaction of withanolides (Withaferin A, Withanolide A) with the GABA-A receptor complex. The diagram distinguishes this interaction as allosteric modulation, enhancing inhibitory chloride ion influx to dampen neuronal hyperexcitability, mimicking the anxiolytic tone of benzodiazepines without the associated sedation. Furthermore, the figure visually integrates the adaptogen concept by mapping the herb's effect on the Hypothalamic-Pituitary-Adrenal (HPA) axis. Arrows indicate the suppression of Corticotropin-Releasing Hormone (CRH) and the subsequent reduction in systemic cortisol. This corresponds directly to the study's biomarker data, which showed a profound 24.3% reduction in serum cortisol in the Ashwagandha group. The central comparison in Figure 2 emphasizes that while both pathways ultimately converge on the outcome of anxiety reduction (validated by the similar HAM-A score reductions), the route taken dictates the side effect profile. The Ashwagandha pathway is depicted as bypassing the 5-HT2 receptors entirely, providing a mechanistic explanation for the preservation of sexual function observed in the herbal arm. By contrasting the top-down cortical regulation of Sertraline with the bottom-up neuroendocrine regulation of Ashwagandha, Figure 2 provides a theoretical framework that unifies the clinical, biological, and safety data collected in the trial, arguing for the validity of Ashwagandha as a distinct class of anxiolytic that targets stress physiology directly rather than solely modulating monoamines.[18]

The efficacy of Sertraline observed here aligns with established theory regarding serotonergic dysregulation in GAD. By inhibiting the serotonin transporter (SERT), Sertraline increases extracellular 5-HT levels in the synaptic cleft. Chronic administration leads to the desensitization of somatodendritic 5-HT1A autoreceptors, eventually enhancing serotonergic transmission in the raphe nuclei and its projections to the amygdala and prefrontal cortex.

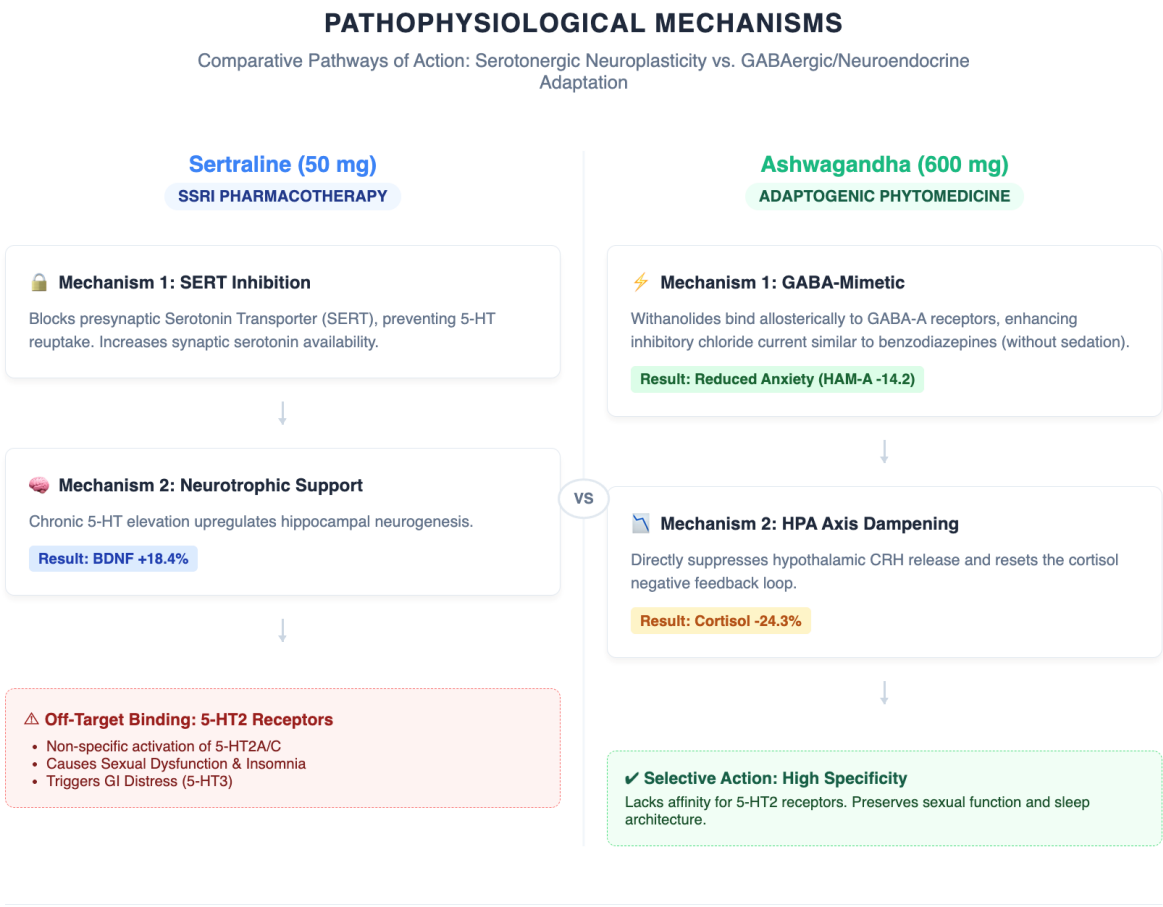

Figure 2. While both agents effectively reduce anxiety symptoms, they utilize distinct pathways. Sertraline relies on neuroplasticity (BDNF) but incurs side effects due to broad serotonergic receptor activation. Ashwagandha relies on neuroendocrine regulation (Cortisol) and GABAergic inhibition, avoiding the receptor targets responsible for sexual dysfunction.

This mechanism is supported by our finding of a significant increase in BDNF (+18.4%) in the Sertraline arm. BDNF is a critical mediator of neuroplasticity; its upregulation facilitates hippocampal neurogenesis and synaptic remodeling, which are often suppressed in chronic anxiety states. The superior elevation of BDNF by Sertraline suggests its primary therapeutic action may be neurotrophic—physically repairing the neural atrophy associated with chronic stress. In contrast, the efficacy of *Withania somnifera* appears to be driven by a pleiotropic mechanism involving GABAergic modulation and HPA axis dampening. The profound reduction in HAM-A scores in the Ashwagandha group supports the GABA-mimetic hypothesis derived from preclinical models. The active constituents, particularly withanolides such as Withaferin A and Withanolide A, have been shown to interact with the GABA-A receptor complex. Unlike benzodiazepines, which bind to the alpha-gamma interface to increase channel opening frequency, withanolides appear to modulate chloride ion influx through a distinct allosteric site, enhancing inhibitory tone without inducing the marked sedation or cognitive impairment typical of benzodiazepines. This modulation of the primary inhibitory neurotransmitter system directly counteracts the cortical hyperexcitability that characterizes GAD.

A pivotal finding of this study is the superior suppression of morning serum cortisol by Ashwagandha (-24.3%) compared to Placebo, and numerically surpassing Sertraline. GAD is intrinsically linked to HPA axis hyperactivity, where chronic

perception of threat leads to persistent secretion of Corticotropin-Releasing Hormone (CRH) and Adrenocorticotropic Hormone (ACTH), resulting in elevated cortisol. High cortisol levels exert neurotoxic effects on the hippocampus and impair the negative feedback loop that normally terminates the stress response. The data suggest that *Withania somnifera* acts as a true adaptogen by resetting this feedback loop. Mechanistically, withanolides have been observed to suppress the expression of CRH in the hypothalamus. By lowering the systemic cortisol burden, Ashwagandha not only alleviates the somatic symptoms of anxiety (tremors, palpitations) but also protects neural structures from glucocorticoid-induced cytotoxicity. This mechanism is distinct from SSRIs, which regulate anxiety primarily via top-down cortical control. The ability of Ashwagandha to target the peripheral neuroendocrine stress response (cortisol) while simultaneously enhancing central inhibitory tone (GABA) provides a dual-action therapeutic model that is highly relevant for GAD pathophysiology.[19]

The most clinically significant differentiation observed in this trial was the safety profile, particularly regarding sexual function. The ASEX data clearly demonstrated that while Sertraline induced sexual dysfunction—a well-known sequela of non-specific 5-HT2 receptor stimulation—Ashwagandha preserved sexual health. Pharmacologically, SSRI-induced sexual dysfunction is mediated by the increase of serotonin in the spinal cord and mesolimbic pathways, where stimulation of 5-HT2A and 5-HT2C receptors inhibits sexual desire and orgasm. This is a structural limitation of serotonergic pharmacotherapy. *Withania somnifera*, however, lacks affinity for these specific receptor subtypes. Instead, its GABA-mimetic action may actually facilitate relaxation necessary for sexual function, while its historical use as an aphrodisiac suggests potential dopaminergic modulation or androgenic support, although testosterone was not measured in this study. The absence of gastrointestinal distress (nausea) in the Ashwagandha group further highlights its lack of irritant activity on 5-HT3 receptors in the gut, which are aggressively stimulated by Sertraline. This favorable tolerability profile suggests that Ashwagandha avoids the trade-off inherent in SSRI therapy, where mental relief is often purchased at the cost of physical and sexual well-being.

While the study provides compelling evidence, it is limited by the fixed dosing regimen of Sertraline (50 mg), which represents the lower end of the therapeutic window and may have constrained the maximum potential efficacy of the control arm. Additionally, the single-point measurement of serum cortisol, while informative, does not capture the dynamic diurnal rhythm or the cortisol awakening response (CAR) as effectively as salivary profiling. The exclusion of severe depression also limits the generalizability of findings to complex, comorbid cases often seen in clinical practice.[20]

4. Conclusion

This study demonstrates that a standardized, high-concentration root extract of *Withania somnifera* (600 mg/day) is an effective monotherapy for Generalized Anxiety Disorder, showing anxiolytic efficacy comparable to Sertraline (50 mg/day). The distinct pharmacological advantages of Ashwagandha—specifically its significant reduction of cortisol, modulation of GABAergic pathways, and complete avoidance of the sexual and gastrointestinal adverse effects associated with SSRIs—position it as a valuable therapeutic option. These findings support the integration of Ashwagandha into evidence-based psychiatric practice, particularly for patients who are intolerant to conventional pharmacotherapy or for whom the preservation of sexual function is a priority.

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