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REVIEW

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Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials

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Abstract

Clinical trial studies revealed conflicting results on the effect of Ashwagandha extract on anxiety and stress. Therefore, we aimed to evaluate the effect of Ashwagandha supplementation on anxiety as well as stress. A systematic search was performed in PubMed/Medline, Scopus, and Google Scholar from inception until December 2021. We included randomized clinical trials (RCTs) that investigate the effect of Ashwagandha extract on anxiety and stress. The overall effect size was pooled by random-effects model and the standardized mean difference (SMD) and 95% confidence interval (CIs) for outcomes were applied. Overall, 12 eligible papers with a total sample size of 1,002 participants and age range between 25 and 48 years were included in the current systematic review and meta-analysis. We found that Ashwagandha supplementation significantly reduced anxiety (SMD: −1.55, 95% CI: −2.37, −0.74; $p = .005$; $I^2 = 93.8\%$) and stress level (SMD: −1.75; 95% CI: −2.29, −1.22; $p = .005$; $I^2 = 83.1\%$) compared to the placebo. Additionally, the non-linear dose–response analysis indicated a favorable effect of Ashwagandha supplementation on anxiety until 12,000 mg/d and stress at dose of 300–600 mg/d. Finally, we identified that the certainty of the evidence was low for both outcomes. The current systematic review and dose–response meta-analysis of RCTs revealed a beneficial effect in both stress and anxiety following Ashwagandha supplementation. However, further high-quality studies are needed to firmly establish the clinical efficacy of the plant.

KEYWORDS
anxiety, Ashwagandha, meta-analysis, stress, systematic review

1 | INTRODUCTION

Stress is humans' natural reaction to physical and psychological threats that protects individuals from risky conditions (Selye, 1956). On the other hand, anxiety is a disorder characterized by tension, worries, and physical changes (Edition, 2013). Long-term stress could cause many health concerns and illnesses including cardiovascular diseases, depression, panic attack, cognitive impairment, and autoimmune diseases, some of them are among the most important cause of death (Chandrasekhar, Kapoor, & Anishetty, 2012). Moreover, stress is related to hormonal alteration such as cortisol (Salve, Pate, Debnath, & Langade, 2019). Therefore, the vast majority of people are looking for medical solution to get rid of stress (Choudhary, Bhattacharyya, & Joshi, 2017).

There are lots of drugs that are prescribed for the management of stress these days. Medications with harmful effects such as benzodiazepines and antidepressant including addiction have been indicated in some studies (Andrade, Aswath, Chaturvedi, Srinivasa, &

Raguram, 2000; Pratte, Nanavati, Young, & Morley, 2014). On the other hand, adaptogens are herbal solution for reducing stress and normalizing body's responses to cope with it (Provino, 2010; Salve et al., 2019). Ashwagandha (the botanical name is Withania somnifera Dunal) is a conventional Ayurvedic herb used for stress and anxiety treatment (Alramadhan et al., 2012; Panossian & Wikman, 2009; Provino, 2010). Ashwagandha has antiinflammatory, antioxidant, antitumor, hypotensive, immunomodulatory, and anxiolytic properties (Oliveira & Leitão, 2016; Singh, Sharma, Dudhe, & Singh, 2010). The anxiolytic effect of Ashwagandha and its similarity to medical drugs such as benzodiazepine has been reported without the side effects of harmful drugs (Bhattacharya, Bhattacharya, Sairam, & Ghosal, 2000; Pratte et al., 2014; Salve et al., 2019). There are some human trials that investigated the effect of Ashwagandha on stress and anxiety. In some trials, Ashwagandha's tendency to lower cortisol and stress level were shown (Andrade et al., 2000; Chandrasekhar et al., 2012). However, another randomized double-blind placebo-control study could not find a significant change between Ashwagandha and placebo group in stress scales (Chengappa, Brar, Gannon, & Schlicht, 2018). Furthermore, the duration and the dosage of Ashwagandha treatment varied among the trials.

Overall, based on these conflicting results, there is a need for a systematic review and meta-analysis to summarize the current findings in this area. Therefore, this recent systematic review and meta-analysis was performed to gather all the investigations on the effect of Ashwagandha on stress and anxiety in adults.

2 | METHOD

We reported this systematic review and meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (Moher, Liberati, Tetzlaff, & Altman, 2010). The protocol of our meta-analysis was not registered previously.

2.1 | Search strategy

A comprehensive computerized systematic search was conducted throughout PubMed/Medline, Scopus, and Google Scholar from inception until December 2021. The search terms were done by using the combination of MESH (Medical Subject Headings) and non-MESH terms as follow: ("Mood disorders") OR (Mood) OR (Psych*) OR (Moods) OR (Depress*) OR (Anxiety) OR (Affect*) OR (Stress*) OR (Fatigue) OR ("mood disorder") OR (Anxious) OR (Mental) OR (Emotion) AND (withania) OR (Ashwagandha) OR ("withania somnifera"). No date and language limitations were applied. In addition, to avoid missing any related study we hand-searched all reference lists in order to find out additional pertinent studies. Moreover, we active PubMed's e-mail alert service to find any new records publication that may have been looked on this after our primary search.

TABLE 1 The population, intervention, comparison, outcome, study design (PICO) criteria

Criteria	Description
Population	Adults (aged ≥18 years)
Intervention	Ashwaganha supplement
Comparison	Placebo or no intervention
Outcome	Changes in anxiety and stress score
Study design	Randomized controlled trials

2.2 | Inclusion criteria

The population, intervention, comparison, outcome, study design (PICOS) criteria used for the present meta-analysis are presented in Table 1.We included studies that met the following criteria: (a) randomized controlled trials with either parallel or crossover design; (b) studies were conducted on adult people (≥18 years old); (c) trials evaluated the effects of oral Ashwagandha supplementation on anxiety and/or stress; (d) reported sufficient data on pre- and post-supplementation for anxiety and stress in both intervention and control groups.

2.3 | Exclusion criteria

Publications were excluded if (a) were done on children and pregnant or lactating women; (b) had a non-RCT design like observational studies, in-vitro studies, letters, conference papers, dissertations, patents, and protocol studies; (c) trials without any placebo group; (d) studies contained deficit information about the selected results in the intervention group or the control.

2.4 | Data extraction

Two independent reviewers (C.A. and A.B.) extracted the following information from the approved publications: first author's name, year of publication, duration of intervention, mean age and the gender of subjects, study location, design of the study (parallel or crossover), participant's health condition, the dosage of the intervention, number of intervention and placebo, and mean ± standard deviation and/or changes of the outcomes including anxiety and stress, type of questionnaires that were used for assessing anxiety and stress. In the end, any disputes were resolved by the chief author (KD). If a study used several different doses, we brought it up as a separate trial. If a trial did not contain enough information, we emailed the author three times.

2.5 | Risk of bias assessment and GRADE of evidence

Two independent reviewers (C.A. and A.B.) assessed the risk of bias using the Cochrane Collaboration Risk of Bias guideline (Higgins

et al., 2011). This tool evaluates seven domains including random sequence generation, allocation concealment, blinding of participants, blinding of investigators who assess the outcomes, selective outcome reporting, attrition bias, and other bias sources. These items were categorized as low risk of bias, high risk of bias, or unclear. If all domains are low-risk, the study is classified as good, records with one high-risk domain or two unclear domains were categorized as fair, and studies with two or more high-risk or unclear criteria were ranked as poor quality. We also rated the certainty of evidence using the GRADE approach (Guyatt et al., 2008).

2.6 | Statistical analysis

The mean changes and standard deviations of anxiety and stress scores were used to calculate pooled effect size. The overall effect size was estimated using random-effects meta-analyses, and the standardized mean difference (SMD) and 95% confidence interval (CIs) for each outcome were determined. We used the following formula to calculate the mean change (SD) for studies that did not report it: SD_{change} = square root $[(SD_{baseline})^2 + (SD_{final})^2 - (2R \times SD_{baseline} \times SD_{final})]$, and mean change = final values − baseline values. The best correlation coefficient (R) was determined by examining studies that reported mean (SD) changes (Borenstein, Hedges, Higgins, & Rothstein, 2021). Furthermore, we extracted numerical estimates from graphs using Get. Data Graph Digitizer version 2.24 (Fedorov, 2002).

Subgroup analyses were performed on the basis of predefined variables including dosage, mean age, sample size, and health status of participants. To account for the obvious heterogeneity in study designs, we used random-effects models. The *I*-squared (I^2) index was used to assess study heterogeneity. If the I^2 was greater than 50%, there was heterogeneity between the included trials (Mousavi et al., 2021). A sensitivity analysis was carried out to assess the potential bias and robustness of the overall effect estimate (Mousavi et al., 2020). To determine the presence of publication bias, Egger's regression test as well as funnel plot were used (Mousavi et al., 2020). Additionally, non-linear associations were investigated using fractional polynomial models (polynomials) (Jie et al., 2018). Stata software (Stata Crop, College Station, TX) version 15 was applied for all statistical analyses. A significance level of p values < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study selection

A total of 325 articles were captured based on the initial search, including 85 records from PubMed, 238 from Scopus and two from other sources. After removing 69 duplicates, 256 records were screened for probably relevant RCTs. Then, 29 full-text articles were evaluated for their competency. Out of them, 17 records were excluded based on the following reasons: seven studies that evaluated the effect of Ashwagandha in combination with other components, two studies were conducted on children, five studies have not got sufficient information, and three of them were not RCT. Finally, 12 papers fulfilled the inclusion criteria and were included in this meta-analysis (Abedon, Auddy, Hazra, Mitra, & Ghosal, 2008; Andrade et al., 2000; Chandrasekhar et al., 2012; Chengappa et al., 2013; Chengappa et al., 2018; Choudhary et al., 2017; Khyati & Anup, 2013; Langade, Kanchi, Salve, Debnath, & Ambegaokar, 2019; Langade, Thakare, Kanchi, & Kelgane, 2021; Lopresti, Smith, Malvi, & Kodgule, 2019; Salve et al., 2019; Tiwari, Gupta, & Pathak, 2021). The exact steps of the selection process are shown in Figure 1. The study selection process was done separately by two authors (C.A. and A.M.) during the initial screening.

3.2 | Study characteristics

The detailed characteristics of the 12 included studies are summarized in Table 2. All trials had randomized controlled parallel trials design. Overall, 1,002 participants, including 555 in the intervention group and 447 in the control group had participated in these studies. These papers were published between 2000 and 2021. Duration of supplementation varied from 8 and 12 weeks, and the dosage of the Ashwagandha supplementation ranged from 240 to 1,000 mg/d; however, in one study the dosage of intervention was 12,000 mg/d (Khyati & Anup, 2013). The age range of participants was between 25 and 48 years. All studies were performed on both genders. Types and components of intervention are summarized in Table 2.

These 12 studies conducted on: healthy adults ($n = 3$) (Lopresti et al., 2019; Salve et al., 2019; Tiwari et al., 2021), adults with insomnia ($n = 2$) (Langade et al., 2019; Langade et al., 2021), adults with history of chronic stress ($n = 3$) (Abedon et al., 2008; Chandrasekhar et al., 2012; Choudhary et al., 2017), people with general anxiety disorders ($n = 2$) (Andrade et al., 2000; Khyati & Anup, 2013), subjects with schizophrenia or schizoaffective disorder ($n = 1$) (Chengappa et al., 2018), and bipolar adults ($n = 1$) (Chengappa et al., 2013). Type of questionnaires that were used to assess anxiety includes Hamilton Anxiety Rating Scale (HAM-A) and Depression Anxiety Stress Scale (DASS). Perceived Stress Scale (PSS), Recovery-Stress Questionnaire for Athletes (RESTQ), Depression, Anxiety, and Stress Scale −21 (DASS-21), modified Hamilton anxiety (mHAM-A) scale for stress were used to evaluate stress. Moreover, based on Cochrane Collaboration Risk of Bias guideline: six trials were good (Chengappa et al., 2018; Choudhary et al., 2017; Langade et al., 2019; Langade et al., 2021; Lopresti et al., 2019; Tiwari et al., 2021), five trials had a fair quality (Abedon et al., 2008; Chandrasekhar et al., 2012; Chengappa et al., 2013; Khyati & Anup, 2013; Salve et al., 2019), and one trial was poor (Andrade et al., 2000) (Table S1).

3.3 | Effect of Ashwagandha supplementation on anxiety

Eight trials (containing 10 effect sizes), including a total 540 participants (289 subjects in the intervention group and 251 in the control group), examined the effect of Ashwagandha supplementation on anxiety. The pooled effect size using random-effects model indicated that

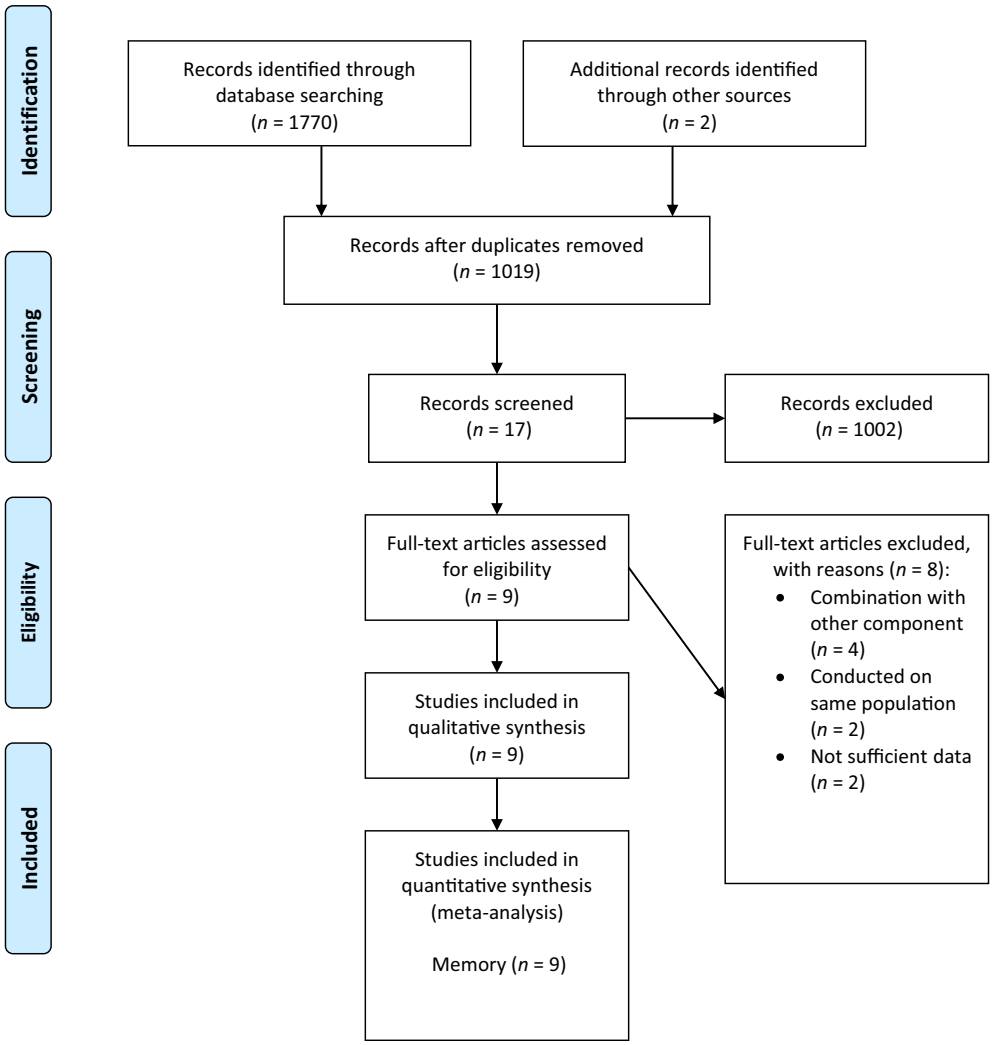

FIGURE 1 Flow diagram of study selection

Ashwagandha supplementation significantly reduced anxiety compared to the placebo (SMD: −1.55, 95% CI: −2.37, −0.74; $p = .005$), with a significant degree of heterogeneity between studies ($I^2 = 93.8\%$, $p < .001$) (Figure 2). To determine between-study heterogeneity, a subgroup analysis was performed based on supplementation dose, mean age, sample size, and health status of participants. The study's sample sizes and health status were two sources of heterogeneity. Moreover, healthy subjects (SMD: −0.82; 95% CI: −1.15, −0.48; $p < .001$), people with 40 years or older (SMD: −2.05; 95% CI: −3.14, −0.96; $p < .001$) and supplementation doses ≥600 mg/d (SMD: −2.30; 95% CI: −3.52 to −1.08; $p < .001$) had the greatest benefit from Ashwagandha supplementation. The detailed results for subgroup analyses are summarized in Table 3. Finally, sensitivity analysis showed that our results were not dependent on one study.

3.4 | Effect of Ashwagandha supplementation on stress

Overall, seven trials with 10 intervention arms including 286 subjects in the intervention group and 196 in the control group were analyzed. Combining effect sizes based on the random-effects model showed a significant reduction in the stress following Ashwagandha supplementation (SMD: −1.75; 95% CI −2.29, −1.22; $p = .005$) (Figure 3). A meaningful heterogeneity was observed across the studies ($I^2 = 83.1\%$, $p < .001$). The heterogeneity disappeared in studies performed on healthy subjects ($I^2 = 0.0$, $p = 52.4$), according to the subgroup analysis. Moreover, our finding confirmed on all of subgroup including doses of Ashwagandha supplementation (<600 mg/d and ≥600 mg/d), health status (healthy subjects/psychological disorders), mean age (<40 years/≥40 years), and sample size (<50/≥50). The detailed results for subgroup analyses are summarized in Table 3. Our findings were not reliant on a single study, according to a sensitivity analysis.

3.5 | Dose–response analysis

The non-linear dose–response analysis indicated a linear reduction in anxiety until 12,000 mg/d of Ashwagandha dose (Figure 4). With regard to the dose–response effect of Ashwagandha on stress, a significant non-linear effect of Ashwagandha supplementation at dose of 300 until 600 mg/day on stress was observed (Figure 5).

TABLE 2 General characteristics of included randomized, double-blind, placebo-controlled parallel trial

References	Health status of subjects	Gender	Participants: Ashwagandha/ placebo	Duration (week)	Mean age (year)	Intervention treatment group	control group	Component of intervention (Capsul)	Questioner
Andrade et al. (2000)	Anxiety disorder	Both	20/19	6	41.9	500 (mg/d)	Placebo	Ashwagandha extract	Hamilton anxiety rating scale (HAM-A)
Abedon et al. (2008)	Chronic stress	Both	30/10 35/10 35/10	8	37.8 39.4 40	500 (mg/d) 250 (mg/d) 500 (mg/d)	Placebo	Withania somnifera extract (WSE)	Modified Hamilton anxiety rating scale (mHAM-A) for stress
Chandrasekhar et al. (2012)	Adult with a history of chronic stress	Both	32/32	8	25.8	600 (mg/d)	Placebo	Ashwagandha root extract	Depression anxiety stress scale (DASS) and perceived stress scale (PSS)
Chengappa et al. (2013)	Bipolar I, II, or NOS disorder	Both	24/29	8	46.9	500 (mg/d)	Placebo	Withania somnifera extract (WSE)	Hamilton anxiety rating scale (HAM-A)
Khyati and Anup (2013)	Generalized anxiety disorder	Both	44/42	8	NR	12,000 (mg/d)	Placebo	Ashwagandha root extract	Hamilton anxiety rating scale (HAM-A)
Choudhary et al. (2017)	Overweight adults under chronic stress	Both	25/25	8	NR	300 (mg/d)	Placebo	Ashwagandha root extract	Perceived stress scale (PSS)
Chengappa et al. (2018)	Schizophrenia or schizoaffective disorder	Both	34/34	12	48.2	1,000 (mg/d)	Placebo	Withania somnifera extract (WSE)	Perceived stress scale (PSS)
Salve et al. (2019)	Healthy adults	Both	20/10	8	29.7 29.7 30.3	250 (mg/d) 600 (mg/d) 250 (mg/d)	Placebo	Ashwagandha root extract	Hamilton anxiety rating scale (HAM-A)
Lopresti et al. (2019)	Healthy adults	Both	30/30	8	42.2	240 (mg/d)	Placebo	Withania somnifera extract (WSE)	Depression anxiety stress scale −21 (DASS-21) and Hamilton anxiety rating scale (HAM-A)
Langade et al. (2019)	Insomnia	Both	39/19	10	38.8	600 (mg/d)	Placebo	Ashwagandha root extract	Hamilton anxiety rating scale (HAM-A)
Langade et al. (2021)	Insomnia Healthy adults	Both	40/40 20/20	8	38.7 35.6	600 (mg/d)	Placebo	Ashwagandha root extract	Hamilton anxiety rating scale (HAM-A)
Tiwari et al. (2021)	Healthy athletic adults	Both	25/25	8	29.3	600 (mg/d)	Placebo	Ashwagandha extract	Recovery-stress questionnaire for athletes (RESTQ)

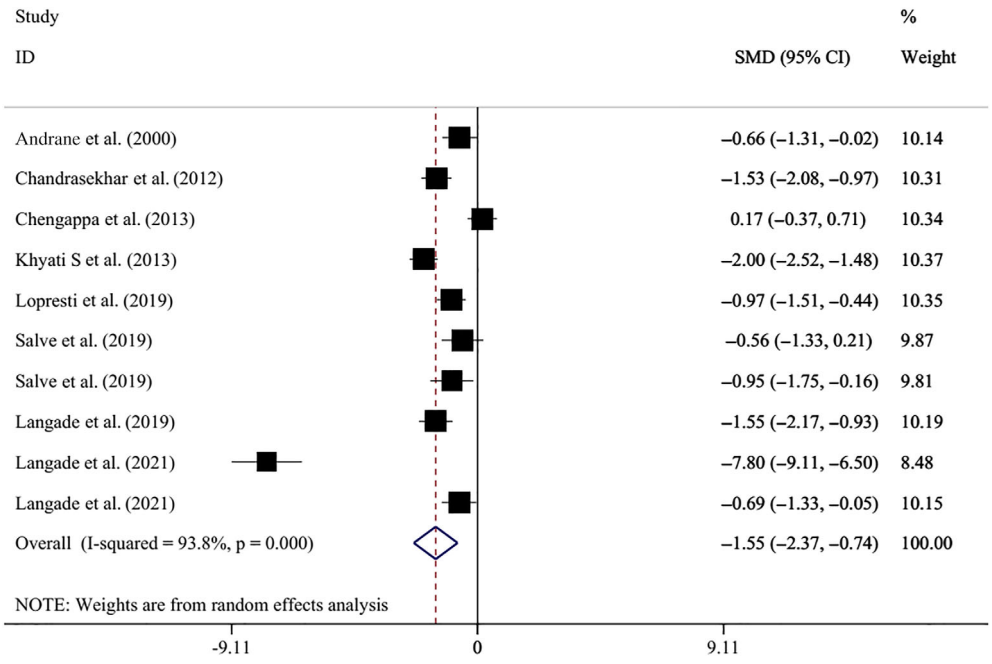

FIGURE 2 Forest plot for the effect of Ashwagandha supplementation on anxiety, expressed as standardized mean differences between intervention and control groups

TABLE 3 Pooled estimates of Ashwagandha supplementation on within different subgroups; using the random-effects model

Group	Number of trials	SMD (95% CI)	*p*-effect	I^2 (%)	*p*-heterogeneity
Anxiety					
Ashwagandha dosage					
<600 mg/d	4	−0.49 (−1.03, 0.03)	.07	67.3	.03
≥600 mg/d	6	−2.30 (−3.52, −1.08)	<.001	95.0	<.001
Mean age					
<40 years	7	−0.48 (−1.192, 0.22)	.18	94.4	<.001
≥40 years	3	−2.05 (−3.14, −0.96)	<.001	78.1	.01
Sample size					
<50	4	−0.70 (−1.05, −0.35)	<.001	0.0	.91
≥50	6	−2.16 (−3.44, −0.88)	.01	96.3	<.001
Health status					
Healthy	4	−0.82 (−1.15, −0.48)	<.001	0.0	79.0
Psychological disorders	6	−2.12 (−3.46, −0.78)	.002	96.3	<.001
Stress					
Ashwagandha dosage					
<600 mg/d	4	−2.050 (−2.916, −1.184)	<.001	86.7	<.001
≥600 mg/d	6	−1.366 (−1.980, −0.751)	<.001	74.0	.01
Mean age					
<40 years	7	−1.795 (−2.419, −1.172)	<.001	80.3	<.001
≥40 years	3	−1.693 (−2.927, −0.459)	.01	90.4	<.001
Sample size					
<50	5	−2.388 (−3.333, −1.443)	<.001	81.1	<.001
≥50	5	−1.204 (−1.628, −0.780)	<.001	64.3	<.001
Health status					
Healthy	3	−1.130 (−1.527, −0.733)	<.001	0.0	52.4
Psychological disorders	7	−2.024 (−2.773, −1.276)	<.001	87.6	<.001

Abbreviation: SMD, standardized mean difference.

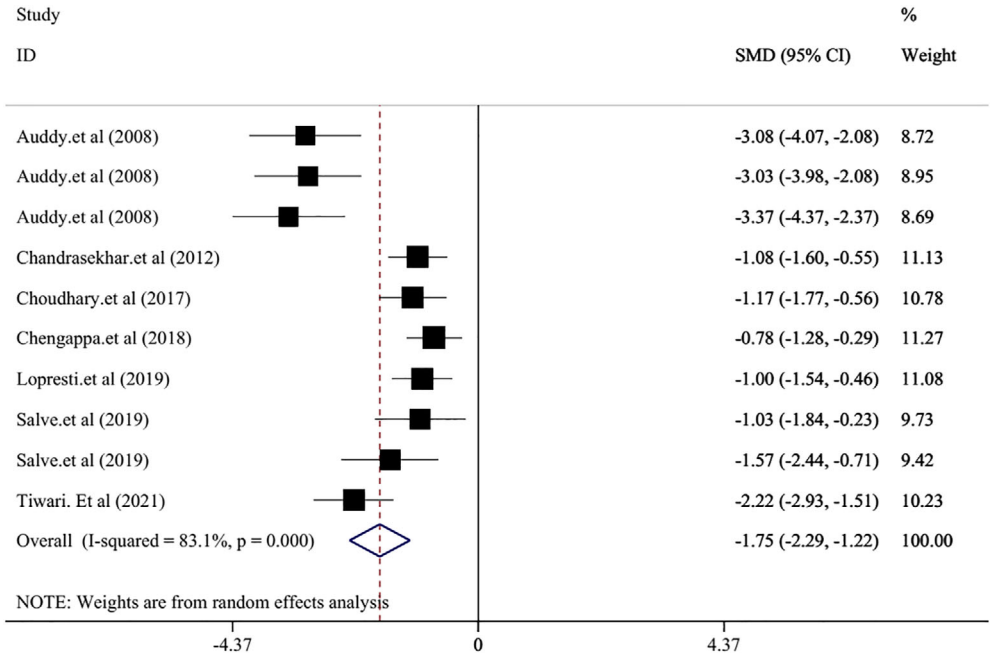

FIGURE 3 Forest plot for the effect of Ashwagandha supplementation on stress, expressed as standardized mean differences between intervention and control groups

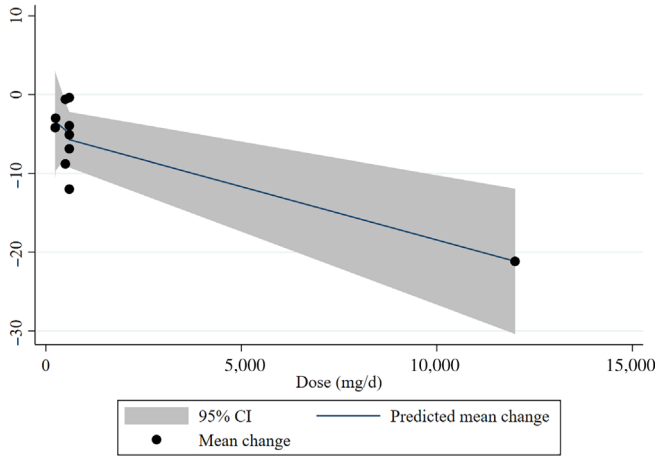

FIGURE 4 Non-linear dose–response relations between Ashwagandha dosage (mg/d) and anxiety. The 95% CI is revealed in the shaded regions

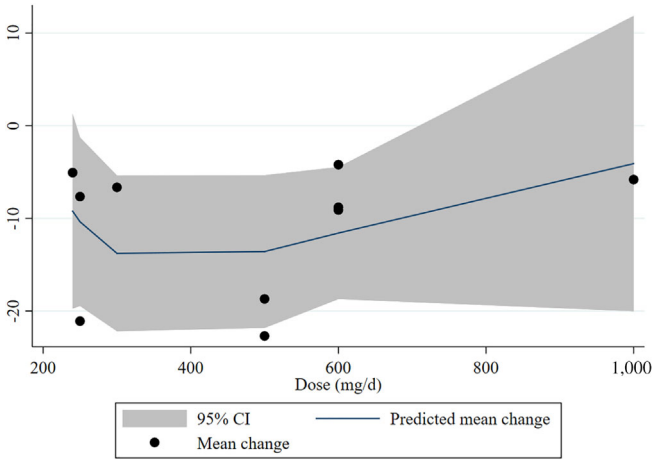

FIGURE 5 Non-linear dose–response relations between Ashwagandha dosage (mg/d) and stress. The 95% CI is revealed in the shaded regions

3.6 | Grading the evidence

The certainty of evidence was rated using the GRADE approach. The certainty of evidence was rated low for both outcomes due to downgrades for serious imprecision (n < 800) and inconsistency (Table 4).

4 | DISCUSSION

In the present systematic review and dose–response meta-analysis, we pooled the findings of 12 available RCTs published between 2000 and 2021, examined the effects of Ashwagandha on stress and anxiety in adults. Our results showed that Ashwagandha supplementation significantly reduced anxiety as well as stress in adult population. In the subgroup analysis, significant reduction in anxiety was considerable at higher dose of Ashwagandha (≥600 mg/d), and studies were conducted on those who were healthy as well as those who had psychological disorders. With regards to stress, subgroup analysis indicated supplementation was effective at both doses of Ashwagandha (<600 mg/d and ≥600 mg/d), and in healthy as well as subjects with psychological disorders. In dose–response analysis, we observed a linear reduction in anxiety until 12,000 mg/d of Ashwagandha supplementation. In addition, a significant non-linear association was detected between Ashwagandha dosage and stress. The effect was more considerable when Ashwagandha was administered between 300 and 500 mg/d.

Previous in-vivo and in-vitro studies found beneficial effects of Ashwagandha extract and its phytochemicals on cancer, inflammatory disease, cardiovascular disease, and diabetes (Paul et al., 2021). They also suggested that Ashwagandha supplementation could be considered as complementary medicine in treatment of neurological and

TABLE 4 GRADE evidence table for the effect of Ashwaganda supplementation on anxiety and stress

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Intervention]	[Comparison]	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Anxiety												
8	Randomized trials	Not serious	Serious[a]	Not serious	Serious[b]	None	298	251	–	SMD 1.55 SD lower (2.37 lower to 0.74 lower)	⨁⨁◯◯ low	Important
Stress												
7	Randomized trials	Not serious	Serious[c]	Not serious	Serious[b]	None	286	196	–	SMD 1.75 SD lower (2.29 lower to 1.22 lower)	⨁⨁◯◯ low	Important

Abbreviations: CI, confidence interval; SMD, standardized mean difference.
[a]Serious inconsistency since $I^2 = 93\%$. Downgraded.
[b]Serious imprecision since optimal information size was not met ($n < 800$). Downgraded.
[c]Serious inconsistency since $I^2 = 83\%$. Downgraded.

psychological disorders such as sleep deprivation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, anxiety, as well as depression (Paul et al., 2021; Zahiruddin et al., 2020). Mostly root extract of Ashwagandha might have anxiolytic and anti-stress properties (Chandrasekhar et al., 2012; Paul et al., 2021).

We evaluated the effect of Ashwagandha supplementation on anxiety and stress whether there is a strong relationship between them. In the present study, we showed that Ashwagandha supplementation had a significant improvement in anxiety as well as stress. In line with our study, Cheah et al. in a recent meta-analysis of RCTs, found a beneficial effect of Ashwagandha extract on anxiety level (Cheah, Norhayati, Yaacob, & Rahman, 2021), while they missed some eligible studies (Andrade et al., 2000; Chandrasekhar et al., 2012; Lopresti et al., 2019). Furthermore, they showed a significant effect of Ashwagandha extract on overall sleep, especially in dosage more than 600 mg/d, and duration of ≥8 weeks (Cheah et al., 2021). A recent systematic review of human trials conducted by Lopresti et al., suggested that Ashwagandha supplementation resulted in the reduction of anxiety and stress symptoms (Lopresti & Smith, 2021). The ameliorative effect of Ashwagandha on another psychological disorder such as depression has been reported previously (Zahiruddin et al., 2020). Depression usually is accompanied by sleep disruption, and disturbance in daily activities along with degrees of anxiety (Ahmed, Khan, Waseem, & Khan, 2017). Gannon et al, in a randomized placebo-controlled clinical trial on persons with schizophrenia, suggested a favorable effect of Ashwagandha supplementation on depression and anxiety symptoms (Gannon, Brar, Rai, & Chengappa, 2019). With regards to animal studies, Bhattacharya et al. in an animal study conducted on rats, showed antidepressant and anxiolytic effect of Ashwagandha (Bhattacharya et al., 2000). The results of these previous studies indicate that Ashwagandha supplementation is effective in the management of anxiety as well as stress.

It has been shown that root extract of Ashwagandha is able to alleviate unfavorable changes which occurs as a result of stress in neuronal cell bodies (Jain, Shukla, Sharma, & Bhatnagar, 2001). Indeed, it has anti-anxiety properties by having gamma aminobutyric acid (GABA) activity (Mehta, Binkley, Gandhi, & Ticku, 1991). The pivotal effect of GABA on anxiety, stress, and sleep regulation has been examined previously (Jie et al., 2018; Nemeroff, 2003). Furthermore, it has been investigated that Ashwagandha extract constitutes various components which have neuroprotective properties via inhibition of lipid peroxidation (Kumar, Dey, Hadimani, Marcovic, & Emerald, 2015). The root extract has been reported to activate choline acetyltransferase and inhibit the release of corticosterone while finally reducing nitric oxide production in the brain (Bhatnagar, Sharma, & Salvi, 2009). Nitric oxide production may be further associated with neurological disease like stress and anxiety (A. Kumar & Chanana, 2017). Another important chemical that help to reduce stress and improve mental health are antioxidants (Gautam et al., 2012). Studies found that phenolic compounds in Ashwagandha extracts have potent antioxidant activities and attenuate oxidative stress as a hallmark for neurodegenerative disorders (Paul et al., 2021).

It is worth mentioning that, herbal supplementation with Ashwagandha has been indicated to have similar effects to benzodiazepines,

but without the harmful adverse effects. Bhattacharya et al. in an experimental study on rats showed analogous effect of Ashwagandha extract in comparison lorazepam (Bhattacharya et al., 2000). Benzodiazepines are commonly used as the sedative, anti-stress, and anxiolytic drugs (Griffin, Kaye, Bueno, & Kaye, 2013; Mediratta, Sharma, & Rana, 2001). Overall, previous studies have been proved safety and efficacy of Ashwagandha supplementation on stress and anxiety. Indeed, it should be considered that, the need for the production of the herbal nutraceutical to prove safety and efficacy of a marketed product is less strongly enforced than in the pharmaceutical sector due to lack of rigorous regulation. Therefore, many available products might be ineffective (Williamson, Liu, & Izzo, 2020).

4.1 | Strengths and limitations

To the best of our knowledge, this is the first systematic review and dose–response meta-analysis which evaluated the effect of Ashwagandha extract on stress and anxiety. Systematic reviews and meta-analyses come in the top tier of the clinical evidence (Gopalakrishnan & Ganeshkumar, 2013). Although between study heterogeneity was observed among included studies, potential source of heterogeneity was found by subgroup analysis. On the other hand, the present study has some limitations. The studies were conducted on individuals with various health conditions which could affect our findings. Moreover, Ashwagandha supplementation was administered in different dosages and different age groups. Although we considered these factors in subgroup analyses, this should be noted in the interpretation of results. Although we did a dose–response meta-analysis, most of the articles used similar dosage and only two or three articles had used different doses. Therefore, we should have interpreted the dose–response meta-analysis results carefully.

5 | CONCLUSION

The current systematic review and dose–response meta-analysis of RCTs, found a significant reduction in both stress as well as anxiety following Ashwagandha supplementation. Dose–response analysis indicated that lower doses of Ashwagandha supplementation were more effective on stress while the results with doses around 600 mg/day was consistent for both anxiety and stress. More clinical trial studies are needed to support our findings and indicate the efficacy of Ashwagandha supplementation on the management of anxiety and stress.

AUTHOR CONTRIBUTIONS

Kurosh Djafarian is the guarantor; Camellia Akhgarjand and Amir Bagheri wrote the manuscript. Farzaneh Asoudeh, Zahra Kalantar, and Zahra Vahabi conducted the literature search and performed data extraction and quality assessment. Sakineh Shab-bidar and Camellia Akhgarjand developed the search strategy. KD conceived the study and performed the statistical analysis. All authors (Camellia Akhgarjand, Farzaneh Asoudeh, Amir Bagheri, Zahra Kalantar, Zahra Vahabi, Sakineh Shab-bidar, Hamid Rezvani, and Kurosh Djafarian) read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Abedon, B., Auddy, B., Hazra, J., Mitra, A., & Ghosal, S. (2008). A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: A double-blind, randomized, placebo-controlled study. *Jana*, *11*, 51.

Ahmed, R., Khan, N. A., Waseem, M., & Khan, Z. J. (2017). Holistic approach in the management of depression: A review. *Journal of Integrated Community Health*, *6*, 10–14.

Alramadhan, E., Hanna, M. S., Hanna, M. S., Goldstein, T. A., Avila, S. M., & Weeks, B. S. (2012). Dietary and botanical anxiolytics. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *18*(4), RA40–RA48.

Andrade, C., Aswath, A., Chaturvedi, S., Srinivasa, M., & Raguram, R. (2000). A double-blind, placebo-controlled evaluation of the anxiolytic efficacy ff an ethanolic extract of Withania somnifera. *Indian Journal of Psychiatry*, *42*(3), 295–301.

Bhatnagar, M., Sharma, D., & Salvi, M. (2009). Neuroprotective effects of Withania somnifera dunal: A possible mechanism. *Neurochemical Research*, *34*(11), 1975–1983.

Bhattacharya, S., Bhattacharya, A., Sairam, K., & Ghosal, S. (2000). Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: An experimental study. *Phytomedicine*, *7*(6), 463–469.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2021). *Introduction to meta-analysis*. Padstow, UK: John Wiley & Sons.

Chandrasekhar, K., Kapoor, J., & Anishetty, S. (2012). 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 Journal of Psychological Medicine*, *34*(3), 255–262.

Cheah, K. L., Norhayati, M. N., Yaacob, L. H., & Rahman, R. A. (2021). Effect of Ashwagandha (Withania somnifera) extract on sleep: A systematic review and meta-analysis. *PLoS One*, *16*(9), e0257843.

Chengappa, K. R., Bowie, C. R., Schlicht, P. J., Fleet, D., Brar, J. S., & Jindal, R. (2013). Randomized placebo-controlled adjunctive study of an extract of Withania somnifera for cognitive dysfunction in bipolar disorder. *The Journal of Clinical Psychiatry*, *74*(11), 16816–11083.

Chengappa, K. R., Brar, J. S., Gannon, J. M., & Schlicht, P. J. (2018). Adjunctive use of a standardized extract of Withania somnifera (Ashwagandha) to treat symptom exacerbation in schizophrenia: A randomized, double-blind, placebo-controlled study. *The Journal of Clinical Psychiatry*, *79*(5), 22496.

Choudhary, D., Bhattacharyya, S., & Joshi, K. (2017). Body weight management in adults under chronic stress through treatment with ashwagandha root extract: A double-blind, randomized, placebo-controlled trial. *Journal of Evidence-Based Complementary & Alternative Medicine*, *22*(1), 96–106.

Edition, F. (2013). Diagnostic and statistical manual of mental disorders. *American Psychiatric Association*, *21*(21), 591–643.

Fedorov, S. (2002). GetData graph digitizer version 2.24. Retrieved from www.getdata-graph-digitizer.com

Gannon, J. M., Brar, J., Rai, A., & Chengappa, K. R. (2019). 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. *Annals of Clinical Psychiatry*, *31*(2), 123–129.

Gautam, M., Agrawal, M., Gautam, M., Sharma, P., Gautam, A. S., & Gautam, S. (2012). Role of antioxidants in generalised anxiety disorder and depression. *Indian Journal of Psychiatry*, *54*(3), 244–247.

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic reviews and meta-analysis: Understanding the best evidence in primary healthcare. *Journal of Family Medicine and Primary Care*, *2*(1), 9–14.

Griffin, C. E., Kaye, A. M., Bueno, F. R., & Kaye, A. D. (2013). Benzodiazepine pharmacology and central nervous system–mediated effects. *The Ochsner Journal*, *13*(2), 214–223.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, *336*(7650), 924–926.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., … Sterne, J. A. (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*, d5928.

Jain, S., Shukla, S. D., Sharma, K., & Bhatnagar, M. (2001). Neuroprotective effects of Withania somnifera Dunn. in hippocampal sub-regions of female albino rat. *Phytotherapy Research*, *15*(6), 544–548.

Jie, F., Yin, G., Yang, W., Yang, M., Gao, S., Lv, J., & Li, B. (2018). Stress in regulation of GABA amygdala system and relevance to neuropsychiatric diseases. *Frontiers in Neuroscience*, *12*, 562.

Khyati, S., & Anup, B. (2013). A randomized double blind placebo controlled study of ashwagandha on generalized anxiety disorder. *International Ayurvedic Medical Journal*, *1*, 1–7.

Kumar, A., & Chanana, P. (2017). Role of nitric oxide in stress-induced anxiety: From pathophysiology to therapeutic target. *Vitamins and Hormones*, *103*, 147–167.

Kumar, V., Dey, A., Hadimani, M. B., Marcovic, T., & Emerald, M. (2015). Chemistry and pharmacology of Withania somnifera: An update. *CELLMED*, *5*(1), 1.1–1.13.

Langade, D., Kanchi, S., Salve, J., Debnath, K., & Ambegaokar, D. (2019). Efficacy and safety of Ashwagandha (Withania somnifera) root extract in insomnia and anxiety: A double-blind, randomized, placebo-controlled study. *Cureus*, *11*(9), e5797.

Langade, D., Thakare, V., Kanchi, S., & Kelgane, S. (2021). Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. *Journal of Ethnopharmacology*, *264*, 113276.

Lopresti, A. L., & Smith, S. J. (2021). Ashwagandha (Withania somnifera) for the treatment and enhancement of mental and physical conditions: A systematic review of human trials. *Journal of Herbal Medicine*, *28*, 100434.

Lopresti, A. L., Smith, S. J., Malvi, H., & Kodgule, R. (2019). An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. *Medicine*, *98*(37), e17186.

Mediratta, P., Sharma, K., & Rana, J. (2001). Development of differential tolerance to the sedative and anti-stress effects on benzodiazepines. *Indian Journal of Physiology and Pharmacology*, *45*(1), 111–115.

Mehta, A., Binkley, P., Gandhi, S., & Ticku, M. (1991). Pharmacological effects of Withania somnifera root extract on GABAA receptor complex. *The Indian Journal of Medical Research*, *94*, 312–315.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *International Journal of Surgery*, *8*(5), 336–341.

Mousavi, S. M., Jayedi, A., Bagheri, A., Zargarzadeh, N., Wong, A., Persad, E., … Koohdani, F. (2021). What is the influence of cinnamon supplementation on liver enzymes? A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*, *35*(10), 5634–5646.

Mousavi, S. M., Karimi, E., Hajishafiee, M., Milajerdi, A., Amini, M. R., & Esmaillzadeh, A. (2020). Anti-hypertensive effects of cinnamon supplementation in adults: A systematic review and dose-response meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition*, *60*(18), 3144–3154.

Mousavi, S. M., Mofrad, M. D., do Nascimento, I. J. B., Milajerdi, A., Mokhtari, T., & Esmaillzadeh, A. (2020). The effect of zinc supplementation on blood pressure: A systematic review and dose–response meta-analysis of randomized-controlled trials. *European Journal of Nutrition*, *59*(5), 1815–1827.

Nemeroff, C. B. (2003). The role of GABA in the pathophysiology and treatment of anxiety disorders. *Psychopharmacology Bulletin*, *37*(4), 133–146.

Oliveira, D. R.d., & Leitão, S. G. (2016). Fortifier, tonic, and rejuvenating plants and the adaptogen concept. In *Introduction to ethnobiology* (pp. 151–161). Berlin, Switzerland: Springer.

Panossian, A., & Wikman, G. (2009). Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. *Current Clinical Pharmacology*, *4*(3), 198–219.

Paul, S., Chakraborty, S., Anand, U., Dey, S., Nandy, S., Ghorai, M., … Proćków, J. (2021). Withania somnifera (L.) Dunal (Ashwagandha): A comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. *Biomedicine & Pharmacotherapy*, *143*, 112175.

Pratte, M. A., Nanavati, K. B., Young, V., & Morley, C. P. (2014). An alternative treatment for anxiety: A systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera). *The Journal of Alternative and Complementary Medicine*, *20*(12), 901–908.

Provino, R. (2010). The role of adaptogens in stress management. *Australian Journal of Medical Herbalism*, *22*(2), 41–49.

Salve, J., Pate, S., Debnath, K., & Langade, D. (2019). Adaptogenic and anxiolytic effects of ashwagandha root extract in healthy adults: A double-blind, randomized, placebo-controlled clinical study. *Cureus*, *11*(12), e6466.

Selye, H. (1956). *The stress of life*. New York City, NY.

Singh, G., Sharma, P., Dudhe, R., & Singh, S. (2010). Biological activities of Withania somnifera. *Annals of Biological Research*, *1*(3), 56–63.

Tiwari, S., Gupta, S. K., & Pathak, A. K. (2021). 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. *Journal of Ethnopharmacology*, *272*, 113929.

Williamson, E. M., Liu, X., & Izzo, A. A. (2020). Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *British Journal of Pharmacology*, *177*(6), 1227–1240.

Zahiruddin, S., Basist, P., Parveen, A., Parveen, R., Khan, W., & Ahmad, S. (2020). Ashwagandha in brain disorders: A review of recent developments. *Journal of Ethnopharmacology*, *257*, 112876.

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