Journal of Functional Foods 108 (2023) 105695

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

# The effect of adaptogenic plants on stress: A systematic review and meta-analysis

Andrea Tóth-Mészáros [a], Gantsetseg Garmaa [a,b], Péter Hegyi [a,c,d], András Bánvölgyi [a,j], Bánk Fenyves [a,g,h], Péter Fehérvári [a,k], Andrea Harnos [a,k], Dorottya Gergő [a,i], Uyen Nguyen Do To [e], Dezső Csupor [a,c,f,*]

[a] Centre for Translational Medicine, Semmelweis University, H-1085 Budapest, Hungary
[b] Institute of Translational Medicine, Semmelweis University, H-1089 Budapest, Hungary
[c] Institute for Translational Medicine, Medical School, University of Pécs, H-7622 Pécs, Hungary
[d] Institute of Pancreatic Diseases, Semmelweis University, H-1085 Budapest, Hungary
[e] András Pető Faculty, Semmelweis University, H-1085 Budapest, Hungary
[f] Institute of Clinical Pharmacy, University of Szeged, H-6725 Szeged, Hungary
[g] Department of Emergency Medicine, Semmelweis University, H-1085 Budapest, Hungary
[h] Department of Molecular Biology, Semmelweis University, H-1085 Budapest, Hungary
[i] Department of Pharmacognosy, Semmelweis University, H-1085 Budapest, Hungary
[j] Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, H-1085 Budapest, Hungary
[k] Department of Biostatistics, University of Veterinary Medicine, H-1078 Budapest, Hungary

ARTICLE INFO

*Keywords:*
Stress
Adaptogens
Cortisol
*Withania somnifera*
Perceived Stress Scale
Stress management

ABSTRACT

Stress is a substantial part of life, however, persistent stress can disturb the hypothalamic–pituitary–adrenal axis leading to different diseases. Adaptogenic herbs are considered to have a stress-relieving effect via decreasing cortisol levels. We assessed the effect of adaptogenic plants on cortisol pathway (cortisol and ACTH levels) and on psychological stress levels of mentally stressed healthy adults, based on the results of randomized controlled trials published until June 25th, 2023. Twenty-five studies on nine adaptogenic herbs - *Bacopa monnieri, Eleutherococcus senticosus*, *Eurycoma longifolia*, *Gynostemma pentaphyllum*, *Lepidium peruvianum*, *Ocimum sanctum*, *Panax ginseng*, *Rhodiola rosea* and *Withania somnifera* - were processed in the systematic review. The results on *Withania somnifera* were meta-analyzed. Significant serum cortisol level decrease (MD = -3.27 ug/dL, 95% CI: −4.62—1.92, p = 0.003) and clinically relevant Perceived Stress Scale (PSS) score decrease were observed in the *Withania somnifera*-treated group compared to the placebo group after 56 or 60 days treatment.

## 1. Introduction

Stress is “the nonspecific response of the body to any demand”, as defined by Hans Selye, the founder of stress theory (Selye, 1956). In terms of the prevalence of stress, in 2021, four in 10 adults worldwide said they experienced a lot of worries (42%) or stress (41%) (gallup.com). Chronic stress can lead to the imbalance of the hypothalamic–pituitary–adrenal axis and to elevated cortisol levels. Chronic psychological stress can be the breeding ground for a variety of ailments and diseases, including cognitive impairment and mental disorders (Marin et al., 2011; Fiksdal et al., 2019), cardiovascular diseases (Iob and Steptoe, 2019) and reduced immune response (Dragoş and Tănăsescu, 2010).

Chronic psychological stress can be alleviated by using different psychological methods, such as mindfulness-based stress reduction (Janssen et al., 2018) or mindfulness-based cognitive therapy (Parsons et al., 2017). Pharmacotherapy for chronic stress-related complaints is a primarily symptomatic treatment with no significant effect on the underlying pathophysiological processes, and is associated with a risk of tolerance, dependence (Quagliato et al, 2018), relapse after cessation (Wildeboer et al., 2016) and adverse side effects (Anagha et al., 2021; Crowe and Stranks, 2018).

*Abbreviations:* **ACTH**, adrenocorticotropic hormone; **CI**, confidence interval; **HPA-axis**, hypothalamic–pituitary–adrenal axis; **MD**, mean difference; **PSS**, Perceived Stress Scale; **RCT**, randomized controlled trial.

* Corresponding author at: H-6725 Szeged, Szikra u. 8, Hungary.
*E-mail address:* csupor.dezso@szte.hu (D. Csupor).

https://doi.org/10.1016/j.jff.2023.105695
Received 18 May 2023; Received in revised form 6 July 2023; Accepted 18 July 2023
Available online 14 August 2023

Adaptogenic plants have been used in traditional medicine in India, China, Korea and Japan for thousands of years to improve resistance to stress through their normalizing effects, and to increase adaptability, resilience and survival, regardless of the nature of the stressor (Panossian et al., 2021). These plants, *Bacopa monnieri*, *Centella asiatica*, *Eleutherococcus senticosus, Lepidium meyenii, Panax ginseng*, *Panax notoginseng, Rhaponticum carthamoides, Rhodiola crenulata, Rhodiola rosea, Schisandra chinensis, Scutellaria baicalensis, Tribulus terrestris and Withania somnifera*, have attracted scientific interest since the 1940s (Panossian et al., 2021). Although, in our study we focus on the effect of adaptogens on mental stress of healthy individuals, these substances have been widely used and widely investigated as tonics (Liao, et al., 2018) administered to convalescent patients, and as medications in different diseases (Panossian et al., 2021; Kaur et al., 2017).

It has been shown that the stress-protective effect of adaptogens might be related to their effect on the hypothalamic–pituitary–adrenal (HPA) axis. Adaptogens might normalize chronically elevated cortisol/corticosterone levels, presumably through their interaction with the glucocorticoid receptors, helping to restore the balance of the HPA-axis (Panossian, 2017). Although some elements of the mechanism of action of certain adaptogens have been discovered, their clinical efficacy and mode of action are still not fully understood. The aim of our work was to perform a systematic review and meta-analysis to examine the effects of adaptogens on stress and hormone levels relating to cortisol pathway in order to better understand their function in stress management, including safety profiles, and to answer our clinical question whether adaptogens have an effect on the cortisol pathway and on the stress level. To assess stress level, we focused on studies using the Perceived Stress Scale (PSS), a self-rating 10-item questionnaire that assesses overall stress experienced in the past one month, with scores between 0 and 40; the higher the score, the higher the stress level (Cohen et al., 1983).

## 2. Methods

We reported our systematic review and meta-analysis based on the recommendations of the PRISMA 2020 guideline (see **Supplementary material Table 3**), while we followed the Cochrane Handbook. The study protocol was registered on PROSPERO (registration number CRD42022376109), and we fully adhered to it.

### 2.1. Search strategy

For the systematic search, we used the search key which can be found in the **Supplementary material in Table 1.**

Table 1 summarizes the population, intervention, comparison, and outcome (PICO) criteria for our investigation.

### 2.2. Selection

A systematic search was conducted in five databases: MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. References were downloaded into EndNote (Clarivate Analytics, Philadelphia, PA, USA) on June 25th, 2023 and, as a next step, duplicates were removed. Title-abstract selection, then the full-text selection were performed by two independent investigators using Rayyan.ai tool (Rayyan Systems, Inc., Cambridge MA, USA). For additional eligible articles, reference lists of already included studies were screened by one investigator, and an automated citation search program (https://estech.shinyapps.io/citationchaser/) was also applied. Disagreements during the selection process were resolved by means of reconciliation.

**Table 1**
Population, intervention, comparison, and outcome (PICO) criteria of the investigation.

| Criteria | Description |
|---|---|
| **Population1** | mentally stressed healthy adults (>18 years of age) |
| **Population 2** | mentally stressed healthy adults (>18 years of age) perceiving fatigue |
| **Intervention** | orally applied herbal adaptogens, single-substance preparations |
| **Comparison** | placebo or non-exposed control group |
| **Outcome 1** | changes in the concentration of cortisol pathway hormones and regulators; |
| **Outcome 2** | changes in stress level, as measured with the Perceived Stress Scale (PSS) score |
| **Study design** | randomized controlled trials |

### 2.3. Eligibility criteria

Studies reporting on randomized controlled trials in English were eligible if they assessed the effect of an extract or dried powder of any part of a single adaptogenic plant, compared with placebo or no treatment, and if the study population consisted of mentally stressed healthy adults (age 18–65 years old); further, if the assessed outcomes were cortisol pathway hormones and regulators and/or scores of questionnaires evaluating mental stress level; moreover, if data on the outcomes being studied were provided at no less than baseline and the end of the trial.

### 2.4. Exclusion criteria

Studies applying study designs other than randomized controlled trials, studies assessing the effect of adaptogens on physical stress, studies involving populations other than adults or those with chronic diseases, or studies using differing populations as control groups, using combined product intervention, or applying active substances as control treatments, were excluded.

### 2.5. Data collection process

The following data were collected for each publication: study design, main population characteristics (i.e., age (range or mean and SD), and relevant stress-related symptoms and/or complaints), number of subjects per group, geographical location, dose and type of intervention, duration of treatment, baseline values of cortisol pathway hormones and regulators and/or PSS scores and the values after any duration of treatment, time of sample taking (for cortisol level). Data were verified by a second independent investigator.

### 2.6. Assessment of the risk of bias

The risk of bias was assessed using the Cochrane Risk of Bias tool (Sterne et al., 2019). The assessment was conducted by two independent reviewers, and disagreements were resolved by means of reconciliation.

### 2.7. Synthesis methods and statistical analysis

Because of a priori presumed considerable between-study heterogeneity, random-effect models were used to pool effect sizes following the recommendations of Harrer et al. (Harrer et al., 2021).

Both for serum cortisol level and Perceived Stress Scale score, mean difference (MD) was used for the effect size measure with a 95% confidence interval (CI). The sample size, mean, and corresponding standard deviation (SD) were extracted from each study to calculate the pooled difference. Typically, analyzed studies have reported baseline and post treatment measurements of target variables. We reported both baseline and post-treatment between group pooled mean differences (MDs) to allow readers to evaluate treatment efficacy transparently. If the SD was not given, but standard error (SE), we calculated the SD based on it (e.g., multiplying by the square root of the sample size for SE or using the t-distribution value for confidence interval based on the

given confidence level).

The inverse variance weighting method was used to calculate the pooled MDs. We used a Hartung-Knapp adjustment, resulting in a more conservative estimation than without adjustment (IntHout, Ioannidis, and Borm, 2014). To estimate the heterogeneity variance measure (τ2), the restricted maximum-likelihood estimator was used with the Q profile method for the confidence interval.

We summarized the meta-analysis findings on forest plots. Where applicable, we report the prediction intervals (i.e., the expected range of effects of future studies) of results. Higgins and Thompson I2 statistics assessed heterogeneity (Higgins and Thompson, 2002). Fitted model parameters and potential outlier publications were explored using different influence measures and plots. Sensitivity analysis was carried out via leave-one-out analyses for all models. Small study publication bias was assessed by visual inspection of Funnel-plots and Egger's test (modified Egger's test depends on the type of effect size measures) with a 10% significance level. The statistical analysis of the data was conducted using the R software (R Core Team, 2021, Vienna, Austria).

## 3. Results

### 3.1. Search and selection process

The systematic search provided 6293 articles. The selection flowchart is summarized in Fig. 1. At the end of the selection process, 25 studies remained included in the systematic review (Auddy et al., 2008; Baek et al., 2019; Benson et al., 2014; Chandrasekhar et al., 2012; Choi et al., 2019; Choudhary et al., 2017; Cropley, et al., 2015; Gopukumar et al., 2021; Jòwko et al., 2018; Hartz, et al., 2004; Lee et al., 2017; Lopresti, Smith, Malvi and Kodgule, 2019; Lopresti, Drummond, Smith, 2019; Lopresti et al., 2021; Lopresti et al., 2022; Meissner et al., 2001; Olsson et al., 2009; Pingali et al., 2013; Remenapp et al., 2022; Salve et al., 2019; Sampath et al., 2015; Saxena et al., 2012; Schaffler et al., 2013; Sung et al., 2020; Talbott et al., 2013), and 5 of them were eligible for the meta-analysis to assess the effects on the predefined outcomes (Auddy et al., 2008; Chandrasekhar et al., 2012; Choudhary et al., 2017; Lopresti, Smith, Malvi and Kodgule, 2019; Salve et al., 2019). All articles in our meta-analysis reported clinical trials performed with *Withania somnifera*. For the other studies on *Withania somnifera*, and other herbs, the measured outcomes and/or the duration of treatment were too diverse to make them applicable to a meta-analysis.

### 3.2. Baseline characteristics of the included studies

The baseline characteristics of the five studies (Auddy et al, 2008; Chandrasekhar et al, 2012; Choudhary et al., 2017; Lopresti, Smith, Malvi and Kodgule, 2019; Salve et al., 2019) included in the meta-analysis are detailed in Table 2. Further, in **Supplementary material Table 2**, we detailed the type and composition of each intervention product, all of which were extracts made of various parts of the *Withania somnifera* plant. *Also,* our calculations on the withanolide content of each intervention product, which we made to find the comparable groups of interventions, can be found in **Supplementary material Table 2.** Withanolides are active compounds of *Withania somnifera* with adaptogenic effects (Panossian, 2017; Panossian et al., 2021). Three of the five studies (Chandrasekhar et al., 2012; Choudhary et al., 2017,

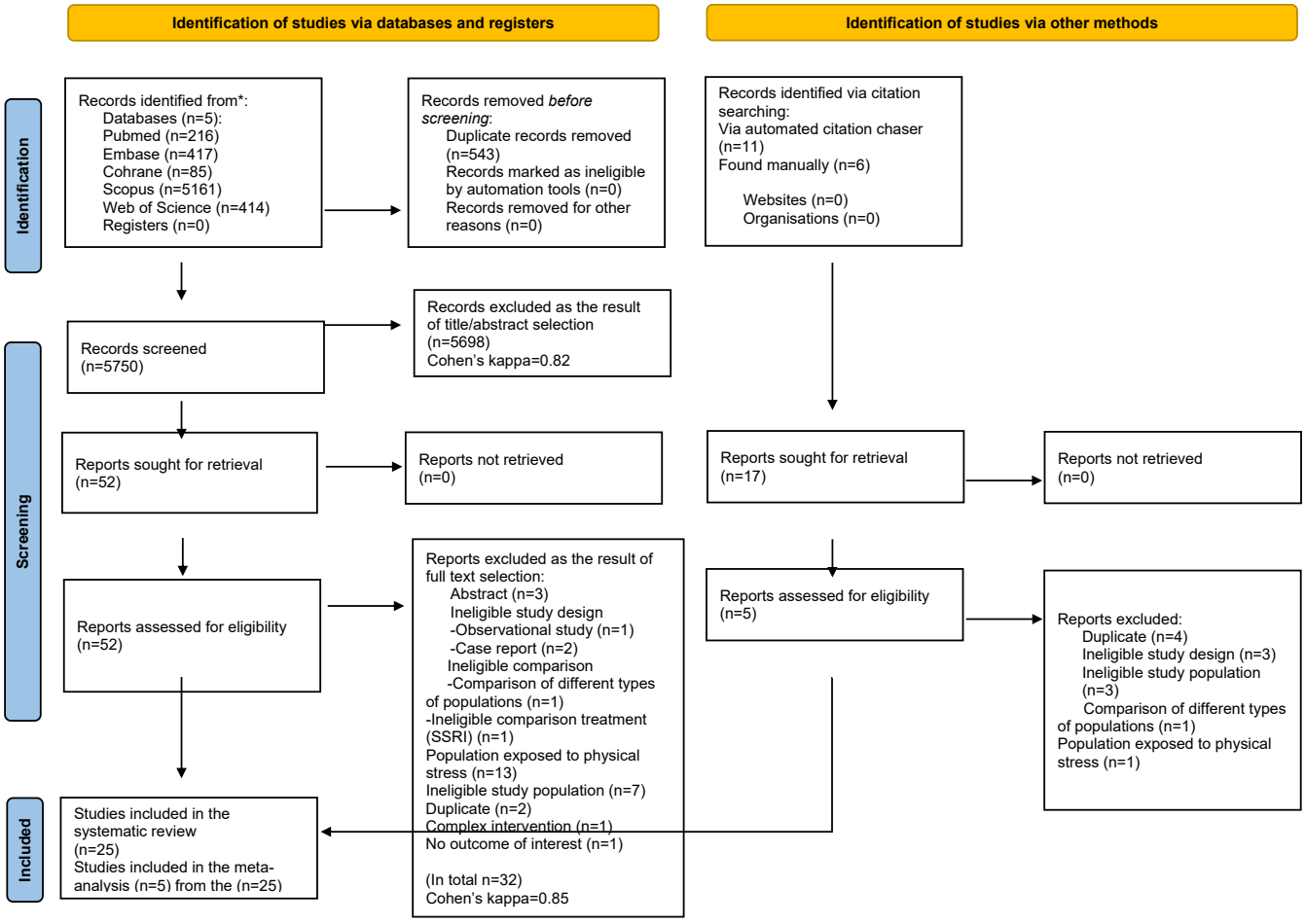



**Fig. 1.** Study selection flow-chart, *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For.

**Table 2**
Baseline characteristics of the RCTs investigated in the meta-analysis.

| Reference | Study design | Population | | | Intervention | | | Comparison | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | Characteristics | Age | Geographical location | Type of intervention | Dose (number of subjects in the group) | Duration of treatment | Comparison (number of subjects in the group) | Outcome processed in the meta-analysis (Time of sample taking with respect to SC) |
| Auddy et al., 2008 | double-blind RCT | Men and women with a HAM-A score between 24 and 42 | 18–60 years | Kolkata, India | *Withania somnifera extract* | 500 mg/day (34) | 60 days | Placebo (15) | SC (between 9AM and 11AM) |
| Chandrasekhar et al., 2012 | double-blind RCT | Adults with the history of chronic stress, with a PSS score of at least 14 | 18–54 years | Hyderabad, India | *Withania somnifera extract* | 600 mg/day (30) | 60 days | Placebo (31) | SC ('in the morning') PSS |
| Choudhary et al., 2017 | double-blind RCT | Adults with the symptoms of chronic routine work stress, PSS 20 or above, BMI between 25 and 39.9 kg/m2 | 18–60 years | Pune, India | *Withania somnifera extract* | 600 mg/day (25) | 56 days | Placebo (25) | SC (no information on time) PSS |
| Lopresti, Smith, Malvi and Kodgule, 2019 | double-blind RCT | Healthy adults with a HAM-A score between 6 and 17 | 18–65 years | India | *Withania somnifera extract* | 240 mg/day (30) | 60 days | Placebo (30) | SC (approximately at 8AM) |
| J. Salve et al., 2019 | double-blind RCT | Healthy adults with a PSS score above 20 | 18–55 years | Maharashtra, India | *Withania somnifera extract* | 600 mg/day (20) | 56 days | Placebo (19) | SC ('in the morning') PSS |

**Legend: BMI** – body mass index; **HAM-A –** Hamilton Anxiety Rating Scale; **PSS** – Perceived Stress Scale; **RCT**-randomized controlled trial; **SC** – serum cortisol.

Salve et al., 2019) applied the same intervention, namely, 600 mg/day *Withania somnifera* root extract (KSM-66) containing 30 mg/day withanolides, however, in the other two studies (Auddy et al, 2008, Lopresti, Smith, Malvi and Kodgule, 2019) different extracts were used. Sensitivity analysis was conducted to assess heterogeneity among the studies. **Supplementary material Fig. 1. a., b., c., d., e. and f.**

In Table 3**,** we provide a comprehensive overview of the 25 studies that assessed the effects of a total of 9 adaptogenic herbs (*Bacopa monnieri, Eleutherococcus senticosus, Eurycoma longifolia, Gynostemma pentaphyllum, Lepidium peruvianum, Ocimum sanctum, Panax ginseng, Rhodiola rosea,* and *Withania somnifera*) on salivary or serum cortisol levels and stress-related outcomes of healthy, stressed adults.

### *3.3. The effect of Withania somnifera supplementation on the serum cortisol level*

In our meta-analysis, five studies investigated the effect of *Withania somnifera* supplementation on serum cortisol level after 56 or 60 days of treatment (Auddy et al, 2008; Chandrasekhar et al, 2012; Choudhary et al., 2017; Lopresti, Smith, Malvi and Kodgule, 2019; Salve et al., 2019), whereas in three studies this effect was assessed also after 28 or 30 days (Choudhary et al., 2017; Lopresti, Smith, Malvi and Kodgule, 2019; Salve et al., 2019) **(**Table 2**.).** Intervention groups and control groups were found to be similar at baseline **(**Fig. 2**.a).** After 28 or 30 days of intervention, pooled MDs with a total of 149 participants showed a statistically significant mean decrease in serum cortisol levels in the *Withania somnifera* groups (N = 75) compared tom the placebo groups (N = 74) (MD = − 1.29; 95%CI: −1.90 –0.68, $p = 0.012$) **(**Fig. 2**.b).** After 56 or 60 days of treatment, the pooled MDs with a total of 259 participants showed a statistically significant 3.27ug/dL mean decrease of serum cortisol level in the intervention group (n = 139) compared to the placebo group (n = 120); (MD = − 3.27; 95%CI: −4.62 –1.92, p = 0.003) **(**Fig. 2**.c).** This is a clinically relevant improvement, as the normal range of serum cortisol levels is between 5 and 25 ug/dL (McPherson and Henry's, 2017). The study populations were found to be homogenous.

Some studies with *Withania somnifera* were omitted from the meta-analysis (Gopukumar et al., 2021; Lopresti, Drummond, Smith, 2019; Pingali et al., 2013; Remenapp et al., 2022) because the duration of the studies varied (Gopukumar et al., 2021; Pingali et al., 2013) or the assessed outcome was not serum cortisol but saliva cortisol level (Lopresti, Drummond, Smith, 2019; Remenapp et al., 2022). A 90-day study found a non-relevant cortisol level lowering effect in stressed adults (Gopukumar et al., 2021); in a 56-day trial, *Withania* treatment showed no appreciable effect on saliva cortisol concentration in overweight, aging men suffering from mild fatigue (Lopresti, Drummond, Smith, 2019); a 14-day trial showed a significant serum cortisol level decreasing effect in adults exposed to mental stress prior to sample taking (Pingali et al., 2013); a 30-day study showed a time- and dose-dependent cortisol level decreasing effect in stressed adults (Remenapp et al., 2022). In all cases, efficacy was compared to placebo.

### *3.4. The effect of other adaptogens on the serum cortisol level*

The effect of adaptogens other than *Withania somnifera* on cortisol levels could not be meta-analyzed because of insufficient data. The results of available clinical trials identified during our systematic review are presented below. The effects of different adaptogenic plants are controversial, making it impossible to draw broad conclusions on the effect of adaptogens on cortisol levels. This is partly due to the diversity of trial designs and the heterogeneity of the populations examined.

*Bacopa monnieri* showed a cortisol level lowering effect in single dose (Benson et al., 2014), and after 28 days of administration (Lopresti et al., 2021). *Eleutherococcus senticosus* significantly reduced cortisol awakening response in a 56-day trial in subjects with asthenia (Schaffler et al., 2013). *Eurycoma longifolia* showed significant cortisol level lowering effect after 28 days of treatment (Talbott et al., 2013). *Gynostemma pentaphyllum,* however, did not change salivary cortisol levels or plasma ACTH levels in chronically stressed subjects after 56 days of intervention (Choi et al., 2019). *Lepidium peruvianum,* administered for 60 days, increased serum cortisol and the ACTH levels in healthy perimenopausal women (Meissner et al., 2001). *Ocimum tenuiflorum* significantly reduced saliva cortisol levels in a 30-day trial (Sampath et al., 2015). In fatigued healthy adults, 56 days of *Panax ginseng* treatment showed no significant effect (Lee et al., 2017); in a 42-day trial, however, it showed a non-significant cortisol-increasing effect (Sung et al., 2020). A 28-day treatment with *Rhodiola rosea* showed no effect on the cortisol levels in stressed young adults (Jòwko et al., 2018), while it showed morning

**Table 3**
Trials on the effect of adaptogens on serum or saliva cortisol levels and different stress-related outcomes. – Table of systematic review.

| Reference | Study characteristics | Participants | | | Supplementation | | | Outcome | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Study design | Participants' characteristics | Age | Geographical location | Adaptogenic substance | Groups (number of subjects in the group) | Length of treatment | Outcome of interest | Time of blood or saliva sampling (if applicable) | Conclusion regarding the outcome of interest |
| Benson et al., 2013 | double-blind, crossover RCT | Healthy adults exposed to multitasking stress. | 18–44 years | Melbourne, Australia | *Bacopa monnieri extract (BME)* | 1. *BME* 320 mg (17) 2. *BME* 640 mg (17) 3. Placebo (17) | single dose, 1 week of wash-out period | △SaC, BL-VAS, STAI | probably before noon | The 640 mg treatment decreased cortisol level significantly. |
| Lopresti et al., 2021 | double-blind RCT | Healthy adults with self-reported poor sleep. | 18–70 years | Perth, Australia | *Bacopa monnieri extract (BME)* | 1. *BME* 300 mg/day (44) 2. Placebo (45) | 28 days | SaC, DASS | in the morning and in the evening | Emotional well-being improved, saliva cortisol level increased. |
| Schaffler et al., 2013 | open-label RCT | Healthy adults with the symptoms of asthenia such as fatigue or weakness. | 30–50 years | Germany | *Eleutherococcus senticosus* root extract (ESE) | 1. *ESE* 120 mg/day (49) 2. 2-day professional stress management training (40) | 56 days | SaC, TICS, MFI-20, BDI | within 30 and 45 min after awakening and at 9AM, at 3PM and at 9PM | No beneficial effects on stress markers and fatigue. |
| Hartz et al., 2004 | double-blind RCT | Adults with chronic, unexplained fatigue. | 21–65 years | Iowa, USA | *Eleutherococcus senticosus* root extract (ESE) | 1. *ESE* 2000 mg/day (41) 2. Placebo (36) | 60 days | Rand Vitality Index | not applicable | Possible efficacy in moderate fatigue suggests the need for further research. |
| Talbott et al., 2013 | subjects blinded RCT | Healthy adults experiencing moderate level of stress. | no information | Utah, USA | *Eurycoma longifolia extract (ELE)* | 1. *ELE* 200 mg/day (35) 2. Placebo (35) | 28 days | SaC, POMS | in the morning, in the afternoon, in the evening | Stress hormone profile and certain mood state parameters improved. |
| Choi et al., 2019 | double-blind RCT | Healthy adults perceiving stress and anxiety. | 20–64 years | Republic of Korea | *Gynostemmapentaphyllum extract (GPE)* | 1. *GPE* 400 mg/day (31) 2. Placebo (35) | 56 days | SaC, saACTH, STAI-T, STAI-S, HAM-A, BAI | 'in the morning' | Chronic psychological stress induced anxiety decreased. No effect on cortisol and on ACTH level. |
| Meissner et al., 2001 | double-blind, crossover RCT | Healthy perimenopausal women. | 41–50 years | Poznan, Poland | pre-gelatinized dried and pulverized hypocotyls of *Lepidium peruvianum (PG-LP)* | 1. *PG-LP* 2000 mg/day (9) 2. Placebo (9) | 60 days | SC, sACTH | no information | ACTH level increased substantially, cortisol level increased non-substantially. |
| Lopresti et al., 2022 | double-blind RCT | Healthy adults experiencing stress for longer than a month, and currently experiencing sleep problems. | 18–65 years | Perth, Australia | *Ocimum tenuiflorum extract (OTE)* | 1. *OTE* 350 mg/day (43) 2. Placebo (38) | 56 days | HC, PSS, MAST | not applicable | Self-report measures of subjective stress perception improved, chronic cortisol excretion was decreased. |
| Sampath et al., 2015 | double-blind RCT | Healthy male subjects. | 18–30 years | New Delhi, India | *Ocimum tenuiflorum extract (OTE)* | 1. *OTE* 300 mg/day (20) 2. Placebo (20) | 30 days | SaC, STAI | no information | Saliva cortisol levels significantly decreased. |
| Saxena et al., 2012 | double-blind RCT | Healthy adults suffering from at least 3 symptoms of stress. | 18–65 years | Lucknow, India | *Ocimum tenuiflorum whole plant extract (OTE)* | 1. *OTE* 1200 mg/day (71) 2. Placebo (79) | 42 days | Symptom scores of stress | not applicable | 1.6 times or 39 % more efficacy in the management of stress symptoms was |

(*continued on next page*)

**Table 3** (*continued*)

| Reference | Study characteristics | Participants | | | Supplementation | | | Outcome | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Study design** | **Participants' characteristics** | **Age** | **Geographical location** | **Adaptogenic substance** | **Groups (number of subjects in the group)** | **Length of treatment** | **Outcome of interest** | **Time of blood or saliva sampling (if applicable)** | **Conclusion regarding the outcome of interest** |
| | | | | | | | | | | found with respect to placebo. |
| Baek et al., 2019 | double-blind RCT | Nurses and fire fighters i.e., adults with high occupational stress. | 20–60 years | Republic of Korea | *Panax ginseng powder (PGP)* | 1. *PGP* 2.0 g/day (28) 2. Placebo (27) | 42 days | PSS, POMS | not applicable | No significant differences were observed regarding psychological measures (PSS, POMS). |
| Lee et al., 2017 | double-blind RCT | Healthy adults with fatigue and decreased vigor. | 30–60 years | Tokyo, Japan | *Panax ginseng as Puffed Fermented Red Ginseng (FRG)* | 1. *FRG* 76 mg/day (19) 2. Placebo (19) | 56 days | SC, POMS-revised | no information | Fatigue improved, no remarkable effect on cortisol level. |
| Sung et al., 2020 | double-blind RCT | Adults with chronic fatigue. | 19–65 years | Republic of Korea | *Panax ginseng powder (PGP)* | 1. *PGP* 3.0/day (24) 2. Placebo (23) | 42 days | SaC - AUC, F-VAS, BDI, CFSQ, FSI, SRI | 4 times during the day from within 30 min after awakening till 12AM | Fatigue-related symptoms improved, cortisol level increased. |
| Cropley et al., 2015 | open-label RCT | Healthy young adults with a STAI (State Trait Anxiety Inventory) score 30 or above. | 18–35 years | Brighton, UK | *Rhodiola rosea extract (RRE)* | 1. *RRE* 400 mg/day (40) 2. Placebo (41) | 14 days | PSS, POMS | not applicable | Efficacy was found in mild anxiety and stress. |
| Jòwko et al., 2018 | double-blind RCT | Physical education student during exam period. | Mean age RR group: 20.9 +/- 0.2; mean age Placebo group: 20.5 +/- 0.3 years | Warsaw, Poland | *Rhodiola rosea extract (RRE)* | 1. *RRE* 600 mg/day (13) 2. Placebo (13) | 28 days | SC | 'in the morning' | No significant changes in cortisol level were found. |
| Olsson et al., 2009 | double-blind RCT | Healthy adults perceiving stress-related fatigue. | 20–55 years | Uppsala, Sweden | *Rhodiola rosea extract (RRE)* | 1. *RRE* 576 mg/day (30) 2. Placebo (30) | 28 days | SaC, PBS, MADRS | within 0 to 60 min after awakening | Cortisol level decreased, fatigue improved. |
| Auddy et al., 2008 | double-blind RCT | Men and women with a HAM-A score between 24 and 42. | 18–60 years | Kolkata, India | *Withania somnifera extract (WSE)* | 1.*WSE* 125 mg/day (19) 2. *WSE* 250 mg/day (30) 3. *WSE* 500 mg/day (34) 4. Placebo (15) | 60 days | SC, mHAM-A | between 9AM and 11AM | Cortisol level decreased significantly, stress and anxiety improved. |
| Chandrasekhar et al., 2012 | double-blind RCT | Adults with the history of chronic stress, with a score of at least 14 on the Perceived Stress Scale (PSS). | 18–54 years | Hyderabad, India | *Withania somnifera extract (WSE)* | 1. *WSE* 600 mg/day (30) 2. Placebo (31) | 60 days | SC, PSS, DASS-S | 'in the morning' | Cortisol level decreased significantly, stress perception improved. |
| Choudhary et al., 2017 | double-blind RCT | Adults with the symptoms of chronic routine work stress, PSS 20 or above, BMI between 25 and 39.9 kg/m2. | 18–60 years | Pune, India | *Withania somnifera extract (WSE)* | 1. *WSE* 600 mg/day (25) 2. Placebo (25) | 56 days | SC, PSS, OHQ | no information | Cortisol level decreased significantly, stress perception improved. |
| Gopukumar et al., 2021 | double-blind RCT | Healthy, cognitively sound adults with a PSS score between 14 and 24. | 20–55 years | Bengaluru, India; Mandya, India | *Withania somnifera extract (WSE)* | 1. *WSE* in Sustained Release (SR) capsule 300 | 90 days | SC, PSS, OHQ | between 9 and 11AM | Significant cortisol level and PSS score lowering effect was observed. |

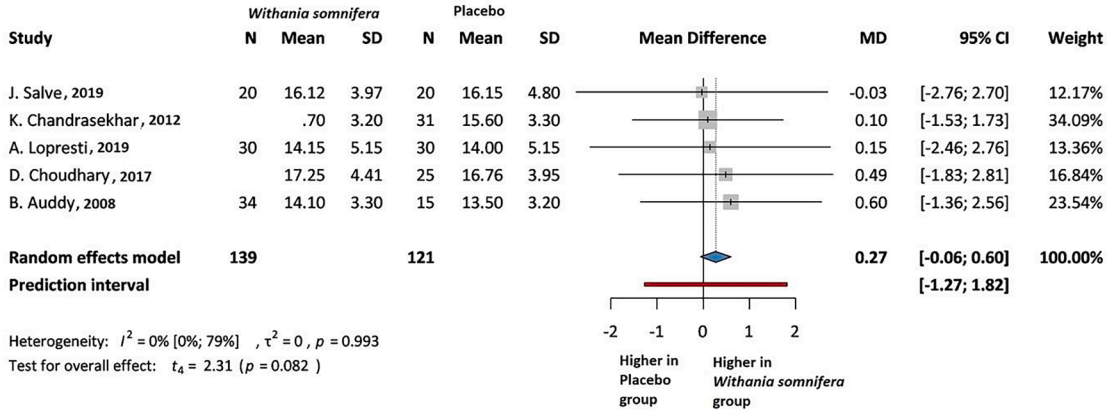
(*continued on next page*)

**Table 3** (*continued*)

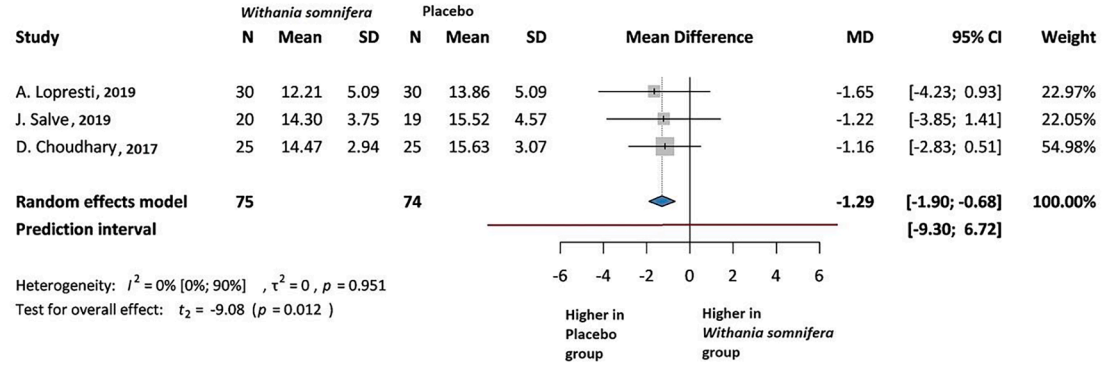
| Reference | Study characteristics | Participants | | | Supplementation | | | Outcome | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Study design** | **Participants' characteristics** | **Age** | **Geographical location** | **Adaptogenic substance** | **Groups (number of subjects in the group)** | **Length of treatment** | **Outcome of interest** | **Time of blood or saliva sampling (if applicable)** | **Conclusion regarding the outcome of interest** |
| | | | | | | mg/day (62) 2. Placebo (63) | | | | |
| Lopresti, Smith, Malvi and Kodgule, 2019 | double-blind RCT | Healthy adults with a HAM-A score between 6 and 17. | 18–65 years | India | *Withania somnifera extract (WSE)* | 1. *WSE* 240 mg/day (30) 2. Placebo (30) | 60 days | SC, HAM-A, DASS | ~at 8AM | Cortisol level decreased significantly, anxiety improved. |
| Lopresti, Drummond, Smith, 2019 | double-blind, crossover RCT | Healthy males with mild-to-moderate symptoms of fatigue or reduced vitality, with a BMI between 25 and 35 kg/m2. | 40–70 years | Perth, Australia | *Withania somnifera extract (WSE)* | 1. *WSE* 600 mg/day (23) 2. Placebo (20) | 56 days | SaC, POMS | between 6AM and 8AM or within 30 min of rising | No appreciable effect on cortisol level, no significant effect on symptoms of fatigue and psychological well-being. |
| Pingali et al., 2013 | double-blind, crossover RCT | Healthy male individuals exposed to experimental mental stress directly prior to sample taking. | Mean age: 25.10 ± 2.29 years | Haiderabad, India | *Withania somnifera extract (WSE)* | 1. *WSE* 1000 mg/day (10) 2. Placebo (10) | 14 days | SC | no information | Serum cortisol decreased significantly. |
| Remenapp et al., 2022 | double-blind RCT | Healthy adults with a PSS score of 14 or more. | 18–54 years | Florida, USA | *Withania somnifera extract (WSE)* | 1. *WSE* 225 mg/day (19) 2. *WSE* 400 mg/day (19) 3. Placebo (19) | 30 days | SaC | at 8AM | Significant reduction in cortisol levels. |
| Salve et al., 2019 | double-blind RCT | Healthy adults with a PSS score above 20. | 18–55 years | Maharashtra, India | *Withania somnifera extract (WSE)* | 1. *WSE* 250 mg/day (19) 2. WSE 600 mg/day (20) 3. Placebo (19) | 56 days | SC, PSS, HAM-A | 'in the morning' | Cortisol level decreased significantly, subjective stress perception improved. |

**Legend: AUC** - Area Under the Curve; **BAI** - Beck Anxiety Inventory; **BDI** -Beck depression inventory; **BL-VAS** - Bond-Lader -VAS mood rating scale; **BMI**- Body Mass Index; **CFSQ** - Chalder fatigue severity questionnaire; **DASS** - Depression-Anxiety-Stress Scale; **DASS-S** - Depression-Anxiety-Stress Scale - Stress subpart; **F-VAS** - Fatigue Visual Analogue Scale, **FSI** - Fatigue Severity Index; **HAM-A** - Hamilton Anxiety Inventory; **mHAM-A** - mean Hamilton Anxiety Inventory Score; **HC** - Hair cortisol; **MAST** - Maastricht Acute Stress Test; **MADRS** - Montgomery-Asberg Depression Rating Scale; **MBI** - Maslach Burnout inventory; **MDMQ** - Multidimensional Mood State Questionnaire; **MFI-20** - Muntidimensional Fatigue Inventory-20; **OHQ** - Oxford Happiness Questionnaire; **PBS** - Pines' Burnout Scale; **POMS** - Profile of Mood States; **PSS** - Perceived Stress Scale; **sa-ACTH** - Saliva ACTH; **SaC** - Saliva Cortisol; **△SaC** - Change of Saliva cortisol level; **sACTH** - serum ACTH; **SC** - Serum cortisol; **SRI** - Stress Response Inventory; **STAI** - State Trait Anxiety Inventory; **STAI-S** - State version of State-Trait Anxiety Inventory, STAI-T - Trait version of State-Trait Anxiety Inventory, TICS - Trier Inventory for Chronic Stress.

## a. at baseline




## b. after 28 or 30 days of treatment




## c. after 56 or 60 days of treatment

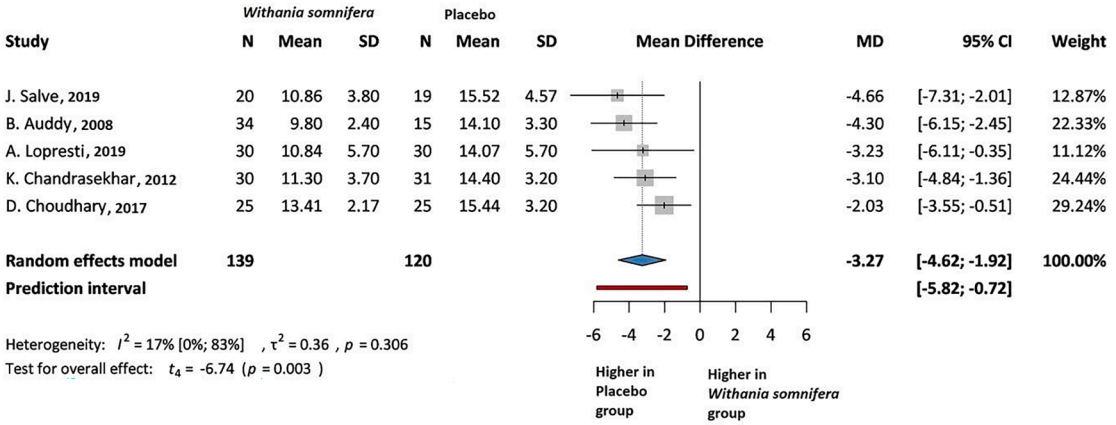



**Fig. 2.** The effect of *Withania somnifera (WS)* treatment on the serum cortisol level (ug/dL).

cortisol-lowering effect in healthy adults experiencing stress-related fatigue (Olsson et al., 2009).

### 3.5. The effect of Withania somnifera supplementation on the Perceived Stress Scale (PSS) score

The effect on PSS scores was measured in three studies that could be meta-analyzed (N = 150). Seventy-five participants were assigned to intervention groups, who were treated with 600 mg/day KSM-66 *Withania somnifera* extract for 56 or 60 days, and 75 participants were assigned to placebo groups (Chandrasekhar et al., 2012; Choudhary et al., 2017; Salve et al., 2019). The intervention and control groups were compared at baseline **(**Fig. 3**a)**. However, the population of the study by Chandrasekhar et al. (2012) was somewhat out of line, probably because the randomization process ended with suboptimal results and because a broader range of PSS scores was given as eligibility criterion than in the other two studies (Choudhary et al., 2017; Salve et al., 2019), ranging from 14 to 40 and 20 to 40, respectively **(**Fig. 3**a)**. After 28 days of treatment, results from only two studies (Choudhary et al., 2017; Salve et al., 2019), showed an average reduction of 1.50 points in the Perceived Stress Scale score of the intervention group (MD = −1.5, 95%CI: −11,18 8,19, $p$ = 0.300) **(**Fig. 3**b)** compared to the placebo group, showing a tendency of reduction, but no conclusions could be drawn. However, after 56 or 60 days of treatment, the mean reduction in the Perceived Stress Scale score was 6.01 points (MD = −6.01, 96%CI: −18,20 6,19, $p$ = 0.168) **(**Fig. 3**c)** in the intervention group compared to the placebo group. This represents a clinically relevant improvement in stress level; however, this result was not statistically significant, and also, there was a substantial heterogeneity among the study populations.

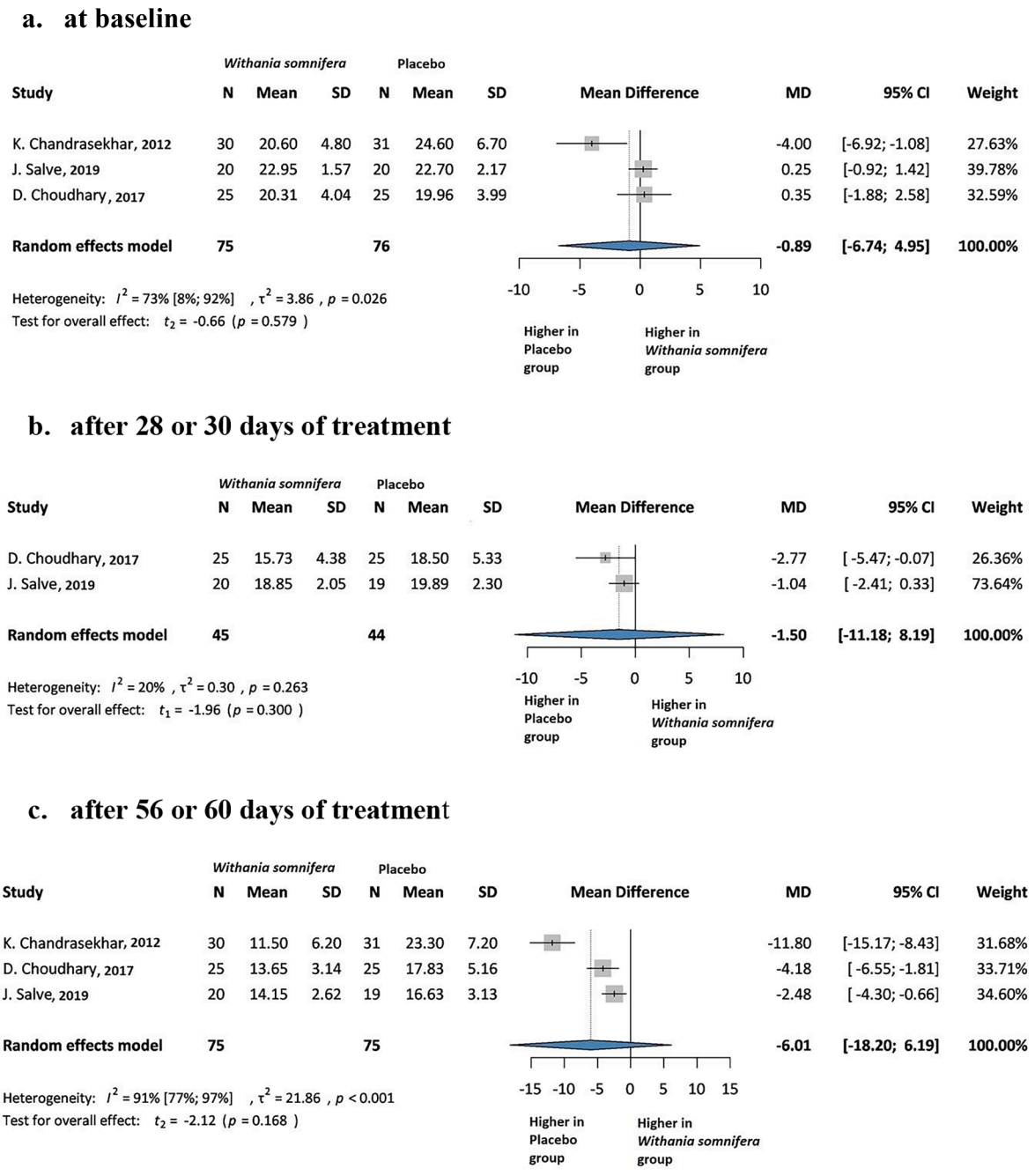



**Fig. 3.** The effect of *Withania somnifera (WS)* treatment on the Perceived Stress Scale (PSS) score.

### 3.6. The effect of other adaptogens on the Perceived Stress Scale score

The effects of other adaptogenic herbs on PSS score were assessed in some trials identified during the systematic search. In a 56-day study, *Ocimum tenuiflorum* showed a statistically significant PSS score-reducing effect. (Lopresti et al., 2022). In a 42-day study, *Panax ginseng* did not significantly reduce the PSS score (Baek et al., 2019). In a 14-day study, *Rhodiola rosea* showed the tendency of PSS score-reducing effect from day 0, 4 hours after administration of the first dose, through day 7 to day 14, when this effect was statistically significant compared to placebo (Cropley et al., 2015). A sustained-release formulation of *Withania somnifera* root extract significantly reduced the PSS scores from baseline to day 90 compared to placebo (Gopukumar et al., 2021).

### 3.7. Safety

On the basis of studies included in the systematic review, adaptogens can be considered generally safe. In the case of *Withania somnifera*, this statement is based on nine trials. In four studies, *Withania somnifera* was well tolerated, and participants reported no adverse effects (Chandrasekar et al., 2012; Lopresti, Drummond, Smith, 2019; Salve et al., 2019; Remenapp et al., 2022;) In one study (Choudhary et al., 2017), two subjects (4%) reported effects such as giddiness, heaviness of head, blurred vision, and/or hyperacidity; the severity of these adverse events was mild and temporary. In four studies (Auddy et al., 2008; Gopukumar et al., 2021; Lopresti, Smith, Malvi and Kodgule, 2019; Pingali et al., 2013), safety laboratory parameters were within the normal range and were not affected by the treatment. The safety of the treatment was further supported by the absence of adverse events and high compliance of patients.

In a study on *Bacopa monnieri*, no adverse effects were reported throughout the study (Benson et al., 2014). In a subsequent study, there were no significant differences in the reports of adverse effects (mainly gastrointestinal disturbances) between the treated and placebo groups, and the participants reported no significant adverse events. However, one participant in the placebo group withdrew from the study (Lopresti et al., 2021) due to reports of increased skin itching.

For *Eleutherococcus senticosus*, one trial reported no severe or serious adverse events or changes in clinically relevant laboratory parameters (Schaffler et al., 2013). In another trial, higher (but not significantly different) breast tenderness and uterine bleeding rates were observed in the intervention group compared to the placebo group (Hartz et al., 2004).

No adverse events were recorded for *Ocimum tenuiflorum* in two trials (Saxena et al., 2012; Sampath et al., 2015). In one further trial (Lopresti et al., 2022), no serious adverse events were reported by participants, and the frequency of adverse effects (mainly indigestion and headache) was similar in both groups, however, one person in the *Ocimum* group withdrew from the study due to increased agitation, and one in the placebo group withdrew due to persistent nausea.

No adverse events were reported in two trials on *Panax ginseng* (Sung et al., 2020; Baek et al., 2019). In one study (Lee et al., 2017), 19 adverse events were reported in 8 of the 19 subjects in the intervention group; however, all these adverse effects were mild and not considered to be related to the intervention.

For *Rhodiola rosea*, no adverse effects were reported in two clinical trials (Olsson et al., 2009; Jòwko et al., 2018). In one trial (Cropley et al., 2015), 4 of the 40 participants receiving *Rhodiola rosea,* reported adverse events either related to the condition under investigation (forgetfulness, loss of appetite, metabolic and nutritional disturbences) or related to independent concomitant conditions (food poisoning and pelvic infection).

No adverse events were reported in the case of *Lepidium meyenii* (Talbott et al., 2013) and *Eurycoma longifolia* (Meissner et al., 2001). No serious adverse events were noted for *Gynostemma pentaphyllum* (Choi et al., 2019). In the Gynostemma group, 14 mild adverse events of 7 subjects; in the placebo group, 8 events of 6 subjects were reported; however, none of these were related to the treatment. Safety laboratory parameters did not change throughout the study (Choi et al., 2019).

### 3.8. Risk of bias assessment

The risk of bias assessment was completed on June 25th, 2023. We conducted the risk of bias assessment regarding the two outcomes, serum cortisol level and Perceived Stress Scale score, apart. The study by Lopresti et al., (Lopresti, Smith, Malvi and Kodgule, 2019) used the intention-to-treat datasets of the effectiveness analysis. In contrast, all the other studies (Auddy et al., 2008; Chandrasekhar et al., 2012; Choudhary et al., 2017; Salve et al., 2019) used the efficacy analysis of per-protocol datasets. We evaluated the overall risk of bias high for both outcomes, as we had some concerns regarding the baseline differences among the intervention groups and the control groups in most of the studies, and because we could not exclude the possible deviation from the intended intervention as a result of the method of follow up of the adherence. Further, we found no information regarding the pre-specified analysis plan and the unblindedness of them, and regarding serum cortisol level measurements, we saw high risk of the occurrence of the confounding effect of the diurnal variation of serum cortisol level as a result of the time range given in the studies for sample taking. Table 4**.** presents the results of the risk of bias assessment.

### 3.9. Quality of evidence

Certainty of evidence regarding three outcomes, namely serum cortisol level, Perceived Stress Scale score and safety (occurrence and severity of adverse events), were rated using the GRADE Pro software tool (Copyright 2021, McMaster University and Evidence Prime Inc.) (Cochrane Handbook). The evidence was rated low for the PSS score and for the safety because of the low number of participants included in the assessment, and because of the imprecise verification of possible non-adherence. The certainty of evidence was rated very low for serum cortisol level because of the low number of participants included in the assessment, because of the imprecise verification of possible non-adherence, and because of the possible confounding effect of the diurnal variation of cortisol level as a result of inaccurate timing of sample taking. Table 5**.** details the results.

## 4. Discussion

Our systematic review summarizes the results of 25 studies published between 2001 and 2022, whereas our meta-analysis is based on the results of 5 studies. The meta-analysis showed an apparent beneficial effect of 56 days or 60 days *Withania somnifera* treatment (containing a calculated amount of 30 to 47 mg active withanolide) on serum cortisol and on stress level. Most of the studies included in the systematic review also showed an improving effect of the investigated adaptogenic plants on different stress-related outcomes; however, the results were somewhat controversial. The use of adaptogens seems to be safe based on the included trials.

Several systematic reviews and meta-analyses have been conducted to find evidence and the prospects for using adaptogens in various therapeutic indications. A systematic review of the efficacy of *Eleutherococcus senticosus* revealed its beneficial effect on cognitive functions and on physical and mental endurance (Gerontakos et al., 2021). A systematic review on the efficacy of *Panax ginseng* on semen quality (Lee et al., 2020), a systematic review on the efficacy of *Lepidium peruvianum* on menopausal symptoms (Lee et al., 2011), and a systematic review and meta-analysis on the efficacy of *Withania somnifera* on male infertility (Durg et al., 2018) concluded with limited evidence. A systematic review and meta-analysis on the efficacy of *Withania somnifera* on sleep quality revealed positive results; however, the investigators pointed out the lack of evidence regarding safety (Cheah et al., 2021).

**Table 4**
Risk of bias assessment.

Table 4.**a** Risk of bias assessment regarding the study of Lopresti, Smith, Malvi, and Kodgule, 2019

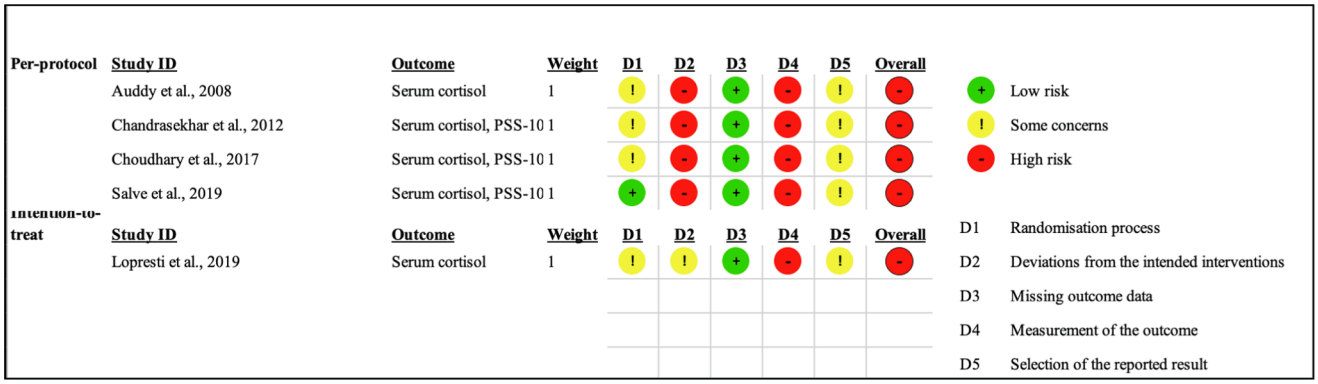



Table 4.**b** Risk of bias assessment regarding the studies of Auddy et al., 2008, Chandrasekhar et al., 2012, Choudhary et al., 2017 and Salve et al., 2019

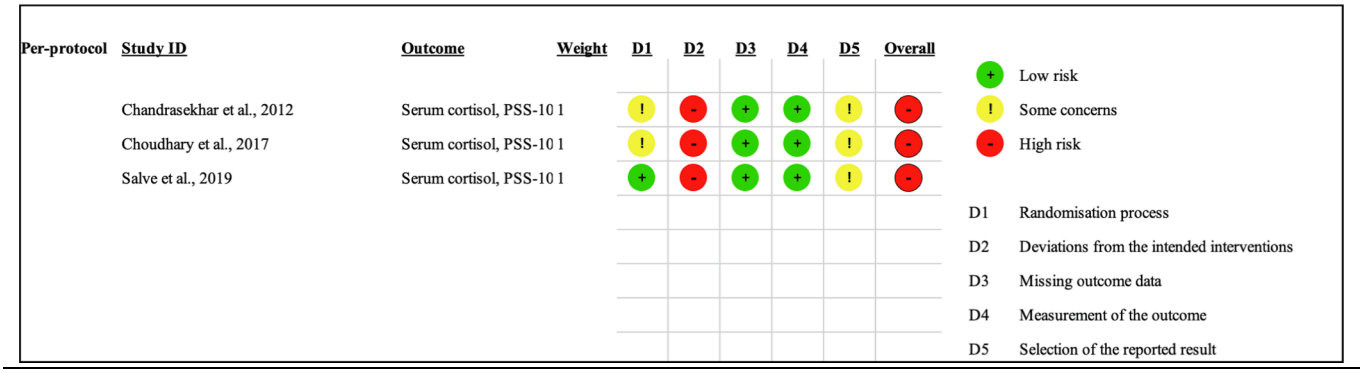



**Table 5**
Table of certainty of evidence – GRADE.

**Patient or population:** stress
**Setting:** randomized controlled trials
**Intervention:** Withania somnifera extract
**Comparison:** Placebo

| Outcome<br>№ of participants(studies) | Relative effect(95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | | | **Difference** | | |
| Perceived Stress Scale (PSS)<br>№ of participants: 151 (3 RCTs) | – | The mean perceived Stress Scale was **0** | – | MD **6.01 lower** (18.2 lower to 6.19 higher) | ⊕⊕○○ Low[a,b,c] | We decreased the level of evidence (1) because of the low number of patients included in the assessment, and (2) because of the imprecise verification of possible non-adherence. |
| Serum cortisol<br>№ of participants: 278 (5 RCTs) | – | The mean serum cortisol was **0** | – | MD **3.27 lower** (4.62 lower to 1.92 lower) | ⊕○○○ Very low[a,b] | We decreased the level of evidence (1) because of the low number of participants included in the assessment, (2) because of the imprecise verification of possible non-adherence, and (3) because of the possible confounding effect of the diurnal variation of cortisol level as a result of a inaccurate timing of sample taking. |
| Safety<br>assessed with: Adverse events reported by the participants<br>№ of participants: (5 RCTs) | not estimable | 0.0% | **0.0%** (0 to 0) | **0.0% fewer** (0 fewer to 0 fewer) | ⊕⊕○○ Low[d] | We decreased the level of evidence because of the (1) low number of participants included in the assessment, and (2) because of the imprecise verification of possible non-adherence. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference
**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

To the best of our knowledge, our systematic review and meta-analysis is the first one to assess adaptogens' effect on cortisol levels. A recently published systematic review and meta-analysis (Akhgarjand et al., 2022) assessed the effect of *Withania somnifera* supplementation on the Perceived Stress Scale score; however, our analysis addressed this effect on a uniformized study population, namely on healthy, mentally stressed adults, and also, data uniformization, to a certain extent, was conducted regarding daily dose and length of treatment.

Our study has some limitations. First of all, the meta-analysis covers only studies performed with *Withania somnifera*. The meta-analysis is based only on 5 clinical trials, and the number of involved subjects is limited. The effect on cortisol pathway-related hormone levels could be assessed only for cortisol. The effects of other adaptogens on stress level and hormone levels could not be meta-analyzed, hence we could not make comprehensive statements regarding the effect of adaptogens in general. In our meta-analysis, we did not conduct a dose–response analysis, and although we assessed time-response analysis, the optimal length of treatment could still not be determined. Among the limitations of our study, we also have to mention the heterogeneity among the study populations regarding the outcome of Perceived Stress Scale score and the overall high risk of bias regarding both outcomes (PSS score and serum cortisol level).

The clinical implication of our research is that *Withania somnifera* might be used as a rational tool to reduce cortisol levels in stressed healthy adults, and this intervention might also be clinically relevant. However, further studies are needed to determine the optimal dosage and duration of treatment. The same applies to other adaptogens as well. Due to a lack of data, no generalized statements could be made on the effects of adaptogens on cortisol pathway-related hormone levels. Their stress-relieving effects could not be compared since there is a lack of studies using widely accepted scales such as PSS.

## 5. Conclusion

According to our meta-analysis, *Withania somnifera* treatment of at least 56 or 60 days results in a clinically relevant improvement of stress level and serum cortisol level of stressed healthy adults (the latter result being also statistically significant), thus, this treatment might be used in stress management. However, more trials would be needed to elucidate the mechanism of action of adaptogens on the HPA-axis, and their clinical efficacy in mental stress.

## Funding

The research was funded by ITM NKFIA TKP2021-EGA-32.

## Ethical approval

No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of the study.

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

## CRediT authorship contribution statement

**Andrea Tóth-Mészáros:** Conceptualization, Project administration, Methodology, Formal analysis, Writing – original draft. **Gantsetseg Garmaa:** Conceptualization, Formal analysis, Visualization, Writing – review & editing. **Péter Hegyi:** Conceptualization, Funding acquisition, Writing – review & editing. **András Bánvölgyi:** Conceptualization, Writing – review & editing. **Bánk Fenyves:** Conceptualization, Writing – review & editing. **Péter Fehérvári:** Conceptualization, Data curation, Statistical analysis. **Andrea Harnos:** Conceptualization, Statistical analysis. **Dorottya Gergő:** Conceptualization, Data curation. **Uyen Nguyen Do To:** Conceptualization, Data curation. **Dezső Csupor:** Conceptualization, Supervision, Writing – original draft. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

All the data can be found either in the paper or as supplementary material.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2023.105695.

## References

Akhgarjand, C., Asoudeh, F., Bagheri, A., Kalantar, Z., Vahabi, Z., Shab-bidar, S., et al. (2022). Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research, 1–10*. https://doi.org/10.1002/ptr.7598

Anagha, K., Shafeena, T., Shihabudheen, P., Uvais, N. A., 2021. Side Effect Profiles of Selective Serotonin Reuptake Inhibitors: A Cross-Sectional Study in a Naturalistic Setting. The Primary Care Companion for CNS Disorders (PCC) 23(4), 20m02747. https://doi.org/10.4088/PCC.20m02747.

Auddy, B., Hazra, J., Mitra, A., Abedon, B., & 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*(1).

Baek, J. H., Heo, J.-Y., Fava, M., Mischoulon, D., Choi, K. W., Na, E. J., et al. (2019). Effect of Korean Red Ginseng in individuals exposed to high stress levels: A 6-week, double-blind, randomized, placebo-controlled trial. *Journal of Ginseng Research, 43*, 402e407. https://doi.org/10.1016/j.jgr.2018.03.001

Benson, S., Downey, L. A., Stough, C., Wetherell, M., Zangara, A., Scholey, A., 2014. An Acute, Double-Blind, Placebo-Controlled Cross-over Study of 320 mg and 640 mg Doses of *Bacopa monnieri* (CDRI 08) on Multitasking Stress Reactivity and Mood. *Phytotherapy Research 28*: 551–559 (2014), DOI: 10.1002/ptr.5029.

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. *J Psychol Med., 34*(3). https://doi.org/10.4103/0253-7176.106022

Cheah, K. L., Norhayati, M. N., Husniati Yaacob, L., & Abdul, R. R. (2021). Effect of Ashwagandha (Withania somnifera) extract on sleep: A systematic review and meta-analysis. *PLoS One1, 16*(9), e0257843.

Choi, E.-K., Won, Y. H., Kim, S.-Y., Noh, S.-O., Park, S.-H., Jung, S.-J., et al. (2019). Supplementation with extract of *Gynostemma pentaphyllum* leaves reduces anxiety in healthy subjects with chronic psychological stress: A randomized, double-blind, placebo-controlled clinical trial. *Phytomedicine, 52*, 198–205. https://doi.org/10.1016/j.phymed.2018.05.002

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. *Evidence-Based Complementary and Alternative Medicine, 22*(1), 96–106. https://doi.org/10.1177/2156587216641830

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. *Journal of Health and Social Behavior, 24*(4), 385–396. https://doi.org/10.2307/2136404

Cropley, M., Banks, A. P., & Boyle, J. (2015). The Effects of Rhodiola rosea L. Extract on Anxiety, Stress, Cognition and Other Mood Symptoms. *Phytotherapy Research, 29*, 1934–1939. https://doi.org/10.1002/ptr.5486

Crowe, S. F., & Stranks, E. K. (2018). The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. *Archives of Clinical Neuropsychology, 33*, 901–911. https://doi.org/10.1093/arclin/acx120

Dragoş, D., Tănăsescu, M.D., 2010. The effect of stress on the defense systems. Journal of Medicine and Life. Vol. 3. No.1, January-March, pp.10-18.

Durg, S., Shivaram, S. B., & Bavage, S. (2018). *Withania somnifera* (Indian ginseng) in male infertility: An evidence-based systematic review and meta-analysis. *Phytomedicine, 50*, 247–256. https://doi.org/10.1016/j.phymed.2017.11.011

Fiksdal, A., Hanlin, L., Kuras, Y., Gianferante, D., Chen, X., Thoma, M. V., et al. (2019). Associations between symptoms of depression and anxiety and cortisol responses to

and recovery from acute stress. *Psychoneuroendocrinology, 102*, 44–52. https://doi.org/10.1016/j.psyneuen.2018.11.035

Gallup.com, https://news.gallup.com/poll/394025/world-unhappier-stressed-ever.aspx, date of downloading: April 11th, 2023.

Gerontakos, S., Taylor, A., Avdeeva, A. Y., Shikova, V. A., Pozharitskaya, O. N., Casteleijn, D., Wardle, J., Shiko, A. N., 2021. Findings of Russian literature on the clinical application of *Eleutherococcus senticosus* (Rupr. & Maxim.): A narrative review. *Journal of Ethnopharmacology 278*, 114274. https://doi.org/10.1016/j.jep.2021.114274.

Gopukumar, K., Thanawala, S., Somepalli, V., Rao, T. S. S., Thamatam, V. B., & Chauhan, S. (2021). Efficacy and Safety of Ashwagandha Root Extract on Cognitive Functions in Healthy, Stressed Adults: A Randomized, Double-Blind, Placebo-Controlled Study. *Evidence-Based Complementary and Alternative Medicine*. https://doi.org/10.1155/2021/8254344. Article ID 8254344.

Harrer, M., Cuijpers, P., Furukawa Toshi, A., & Ebert, D. D. (2021). *Doing Meta-Analysis With R: A Hands-On Guide* (1st ed). Boca Raton, FL and London: Chapman & Hall/CRC Press.

Hartz, A. J., Bentler, S., Noyes, R., Hoehns, J., Logemann, C., Sinift, S., Butani, Y., Wang, W., Brake, K., Ernst, M., Kautzman, H., 2004. Randomized controlled trial of Siberian ginseng for chronic fatigue. *Psychological Medicine 34*, 51–61. http://doi.org/10.1017/S0033291703008791.

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying Heterogeneity in a Meta-Analysis. *Statistics in Medicine, 21*(11), 1539–1558. https://doi.org/10.1002/sim.1186

IntHout, J., Ioannidis, J. PA., & Borm, G. F. (2014). The Hartung-Knapp-Sidik-Jonkman Method for Random Effects Meta-Analysis Is Straightforward and Considerably Outperforms the Standard DerSimonian-Laird Method. *BMC Medical Research Methodology, 14*(1), 25. https://doi.org/10.1186/1471-2288-14-25

Iob, E., & Steptoe, A. (2019). Cardiovascular Disease and Hair Cortisol: A Novel Biomarker of Chronic Stress. *Current Cardiology Reports, 21*, 116. https://doi.org/10.1007/s11886-019-1208-7

Janssen, M., Heerkens, Y., Kuijer, W., van der Heijden, B., & Engels, J. (2018). Effects of Mindfulness- Based Stress Reduction on employees' mental health: A systematic review. *PLoS One1, 13*(1), e0191332.

Jòwko, E., Sadowski, J., Dlugolecka, B., Gierczuk, D., Opaszovski, B., & Cieslinski, I. (2018). Effects of *Rhodiola rosea* supplementation on mental performance, physical capacity, and oxidative stress biomarkers in healthy men. *Journal of Sport and Health Science, 7*, Article 473480. https://doi.org/10.1016/j.jshs.2016.05.005

Kaur, P., et al. (2017). Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes. *Biomedicine & Pharmacotherapy, 95*(2017), 1815–1829. https://doi.org/10.1016/j.biopha.2017.09.081

Lee, H. W., Kil, K.-J., & Lee, M. S. (2020). Ginseng for Improving Semen Quality Parameters: A Systematic Review. *The World Journal of Men's Health, 38*(3), 377–384. https://doi.org/10.5534/wjmh.190125

Lee, J. J., Pyo, H. J., Kim, H. J., & Fukuda, R. (2017). Effects of intake of puffed fermented Korean ginseng extract-containing drink on the status of stress, fatigue, and sleep. *Japanese Pharmacology & Therapeutics, 45*(9).

Lee, M. S., Shin, B.-C., Yang, E. J., Lim, H.-J., & Ernst, E. (2011). Maca (*Lepidium meyenii*) for treatment of menopausal symptoms: A systematic review. *Maturitas, 70*(2011), 227–323. https://doi.org/10.1016/j.maturitas.2011.07.017

Liao, L.-Y. et al., 2018. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. *Chinese Medicine* (2018) 13:57. https://doi.org/10.1186/s13020-018-0214-9.

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. *Medicine, 98*(37), e17186. https://doi.org/10.1097/MD.0000000000017186

Lopresti, A. L., Smith, S. J., Ali, S., Metse, A. P., Kalns, J., & Drummond, P. D. (2021). Effects of a *Bacopa monnieri* extract (Bacognize®) on stress, fatigue, quality of life and sleep in adults with self-reported poor sleep: A randomised, double-blind, placebo-controlled study. *Journal of Functional Foods, 85*, 10467. https://doi.org/10.1016/j.jff.2021.104671

Lopresti, A. L., Smith, S. J., Metse, A. P., & Drummond, P. D. (2022). A randomized, double-blind, placebo-controlled trial investigating the effects of an *Ocimum tenuiflorum* (Holy Basil) extract (Holixer™) on stress, mood, and sleep in adults experiencing stress. *Frontiers in Nutrition, 9*, Article 965130. https://doi.org/10.3389/fnut.2022.965130

Lopresti, A.L., Drummond, P.D., Smith, S.J., 2019. A Randomized, Double-Blind, Placebo-Controlled, Crossover Study Examining the Hormonal and Vitality Effects of Ashwagandha (*Withania somnifera*) in Aging, Overweight Males. American Journal of Men's Health (AJMH). March-April 2019, 1-15. doi10.1177/1557988319598.

Marin, M.-F., Lord, C., Andrews, J., Juster, R.-P., Sindi, S., Arsenault-Lapierre, G., et al. (2011). Chronic stress, cognitive functioning and mental health. *Neurobiology of Learning and Memory, 96*(2011), 583–595. https://doi.org/10.1016/j.nlm.2011.02.016

McPherson, R.A., Henry's Clinical Diagnosis and Management by Laboratory Methods, 23rd edition, 2017. ISBN: 978-0-323-29568-0.

Meissner, H. O., Reich-Bilinska, H., Mscisz, A., & Kedzia, B. (2001). Therapeutic Effects of Pre-Gelatinized Maca (*Lepidium Peruvianum* Chacon) used as a Non-Hormonal Alternative to HRT in Perimenopausal Women - Clinical Pilot Study. *International Journal of Biomedical Science: IJBS*.

Olsson, E. M. G., Von Schéele, B., & Panossian, A. G. (2009). A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Standardized Extract SHR-5 of the Roots of *Rhodiola rosea* in the Treatment of Subjects with Stress-Related Fatigue. *Planta Medica, 2009*(75), 105–112. https://doi.org/10.1055/s-0028-1088346

Panossian, A. (2017). Understanding adaptogenic activity: Specificity of the pharmacological action of adaptogens and other phytochemicals. *Annals of the New York Academy of Sciences, 1401*, 49–64. https://doi.org/10.1111/nyas.13399

Panossian, A. G., Thomas, E., Shikov, A. N., Pozharitskaya, O. N., Kuchta, K., Mukherjee, P. K., et al. (2021). Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. *Medicinal Research Reviews, 41*, 630–703. https://doi.org/10.1002/med.21743

Parsons, C. E., Crane, C., Parsons, L. J., Fjorback, L. O., & Kuyken, W. (2017). Home practice in Mindfulness-Based Cognitive Therapy and Mindfulness-Based Stress Reduction: A systematic review and meta- analysis of participants' mindfulness practice and its association with outcomes. *Behaviour Research and Therapy, 95*, 29e41. https://doi.org/10.1016/j.brat.2017.05.004

Pingali, U. R., Raveendranadh, P., & Nishat, F. (2013). Effect of *Withania somnifera* extract on mental stress induced changes in hemodynamic properties and arterial wave reflections in healthy subjects. *Current Topics in Nutraceutical Research, 11*(4), 151–158. https://doi.org/10.4103/0974-8490.122912

Quagliato, L. A., Freire, R. C., & Nardi, A. E. (2018). Risks and benefits of medications for panic disorder: A comparison of SSRIs and benzodiazepines. *Expert Opinion on Drug Safety*. https://doi.org/10.1080/14740338.2018.1429403

R Core Team. 2021. "R: A Language and Environment for Statistical Computing." https://www.R-project.org/.

Remenapp, A., Coyle, K., Orange, T., Lynch, T., Hooper, D., Hooper, S., et al. (2022). Efficacy of *Withania somnifera* supplementation on adult's cognition and mood. *Journal of Ayurveda and Integrative Medicine, 13*, Article 100510. https://doi.org/10.1016/j.jaim.2021.08.003

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.

Sampath, S., Mahapatra, S. C., Padhi, M. M., Sharma, R., & Talwar, A. (2015). Holy basil (*Ocimum sanctum* Linn.) leaf extract enhances specific cognitive parameters in healthy adult volunteers: A placebo controlled study. *Indian The Journal of Physiology, 59*(1), 69–77.

Saxena, R. C., Singh, R., Kumar, P., Singh Negi, M. P., Saxena, V. S., Geetharani, P., et al. (2012). Efficacy of an Extract of *Ocimum tenuiflorum* (OciBest) in the Management of General Stress: A Double-Blind, Placebo-Controlled Study. *Evidence-Based Complementary and Alternative Medicine, 894509*, 7. https://doi.org/10.1155/2012/894509

Schaffler, K., Wolf, O. T., Burkart, M., 2013. No Benefit Adding *Eleutherococcus senticosus* to Stress Management Training in Stress-Related Fatigue/ Weakness, Impaired Work or Concentration, A Randomized Controlled Study. *Pharmacopsychiatry. 46*: 181–190. https://doi.org/10.1055/s-0033-1347178.

Selye, H. (1956). *The stress of life*. McGraw-Hill.

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). 2: A revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, Article l4898.

Sung, W.-S., Kang, H.-R., Jung, C.-Y., Park, S.-S., Lee, S.-H., & Kim, E.-J. (2020). Efficacy of Korean red ginseng (*Panax ginseng*) for middle-aged and moderate level of chronic fatigue patients: A randomized, double-blind, placebo-controlled trial. *Complementary Therapies in Medicine, 48*, Article 102246. https://doi.org/10.1016/j.ctim.2019.102246

Talbott, S. M., Talbott, J. A., George, A., & Pugh, M. (2013). Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. *Journal of the International Society of Sports Nutrition, 10*, 28. http://www.jissn.com/content/10/1/28.

Wildeboer, R. M., Van der Hoek, L., & Verhaak, P. F. M. (2016). Use of general practice services 5 years after an episode of mental illness: Case-control study using electronic records. *The British Journal of General Practice*. https://doi.org/10.3399/bjgp16X684973