REVIEW ARTICLE

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Clinical evidence for the adaptogenic effects of *Withania somnifera* and *Rhodiola rosea* – A systematic review with molecular interpretation of psychometric outcomes

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Abstract

Introduction and Objective. Adaptogens are plant-derived substances that enhance the body's resilience to physical and psychological stress, with *Withania somnifera* and *Rhodiola rosea* being among the most studied representatives. The aim of this review is to evaluate the adaptogenic effects of *W. somnifera* and *R. rosea* based on randomized controlled trials (RCTs).

Review Methods. A systematic literature search was performed using the key words: 'ashwagandha', *'Withania somnifera'*, *'Rhodiola rosea'*, and 'plant adaptogen'. Twenty-four studies met the inclusion criteria – 19 on *W. somnifera* and 5 on *R. rosea*.

Brief description of the state of knowledge. The analyzed trials involved 10–590 participants, aged 18–75 years, both healthy individuals and patients with stress-related or functional disorders. Interventions included standardized extracts at daily doses of 120–1000 mg for *W. somnifera* and 290–1500 mg for *R. rosea*, with supplementation lasting 3–16 weeks. Reported benefits included reduction of stress and anxiety, alleviation of depressive symptoms, improved sleep quality, enhancement of cognitive functions, increased muscle strength and recovery, and favourable hormonal changes. Methodological heterogeneity, short intervention periods, and small sample sizes remain limitations.

Summary. Evidence from RCTs confirms that *W. somnifera* and *R. rosea* exert multi-dimensional adaptogenic effects, improving psychophysical health and supporting stress resilience. Their mechanisms involve regulation of the hypothalamic-pituitary-adrenal axis, neurotransmission, immune and hormonal pathways. Further long-term, high-quality clinical trials, supplemented with molecular and systemic approaches, are required to consolidate their role in integrative, evidence-based medicine.

Key words

randomized controlled trial, *Rhodiola rosea, Withania somnifera*, adaptogens

INTRODUCTION

Plant preparations in the form of drugs and dietary supplements are widely used worldwide, both in traditional medicine and as a complement to conventional medicine. Despite the growing popularity of plant extracts and a long history of their use, many of these preparations are still insufficiently studied from the perspective of modern scientific standards. This also applies to plants belonging to the so-called adaptogens – substances capable of modulating the body's response to stress and supporting its homeostasis, which are gaining increasing interest in scientific research and clinical medicine. Among the most commonly used and studied adaptogens are *Withania somnifera* (L.) Dunal (*Solanaceae*) (ashwagandha) and *Rhodiola rosea* L. (*Crassulaceae*). Both plants show significant therapeutic potential in the context of reducing stress symptoms, treating mental disorders, and improving the cognitive and physical functions of the body. In order to assess the effectiveness and safety of adaptogens and their use in modern medicine, scientists conduct high-quality randomized controlled trials (RCTs). However, the variety of methodologies and the small number of long-term studies constitute a significant limitation for determining the therapeutic applications of adaptogens in clinical practice [1–3].

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OBJECTIVE

The aim of review is to analyze randomized controlled trials on the effects of *Withania somnifera* and *Rhodiola rosea* on mental health, physical health, and general well-being. The collected data were used to assess the adaptogenic potential of the analyzed plants and to indicate key methodological advantages and limitations characteristic of randomized controlled trials in this area.

Plant adaptogens. The use of medicinal plants with stress-enhancing properties dates back to ancient times, but the definition of 'adaptogen' was not formulated until the 20th century, as a substance that increases the body's non-specific resistance to stress factors [4]. It was then clarified that

an adaptogen should be safe and effective and free from undesirable side-effects. According to the FDA (Food and Drug Administration) in the USA, adaptogens are metabolic regulators that improve the ability to adapt to environmental stress [5, 6]. At the same time, the complex interactions of these substances with the neuroendocrine and immune systems were indicated, with the central role assigned to the influence on the hypothalamic-pituitary-adrenal axis (HPA) [2, 7].

Plant adaptogens are distinguished by their rich phytochemical composition and synergistic mechanism of action – their properties are not the result of a single active substance, but the interaction of many biologically active compounds. Unlike synthetic adaptogens which are chemically uniform, herbal preparations are characterized by significant chemical diversity. This makes standardization difficult but can also contribute to their greater effectiveness and safety [4].

***Withania* somnifera** *(W.s.).* Belongs to plant adaptogens and is traditionally used in Ayurveda, an alternative Hindu medicine system, which is recognised as a rejuvenating and strengthening agent. It occurs naturally in India, Africa, Australia and southern Europe. All parts of the plant have medicinal potential, but the most commonly used pharmaceutical raw material is the root. Ashwagandha, an unusual adaptogenic plant from the nightshade family, also plays an important role in Ajurveda medicine. It has a broad spectrum of action, affecting the nervous, immune and hormonal systems, supporting the restoration of homeostasis, especially in states of increased mental and physical stress.

W.s. has gained interest as a dietary supplement supporting the body in adapting to stress, improving the quality of sleep and influencing cognitive, hormonal, metabolic and physical functions. In animal model studies, *W.s.* has been observed to have properties modulating the body's response to stress and neuro-protective, cardio-protective, hypoglycaemic, antimicrobial and anticancer activity [8–12]. *In vitro* studies have also shown the anti-oxidant and anti-inflammatory potential of ashwagandha. Depending on the place of origin of the raw material, *Withania somnifera* has a diverse hytochemical composition [6, 13–17]. The main active ingredients of ashwagandha are withanolides, alkaloids, sitoindosides, flavonoids and other secondary metabolites. The key pharmacological role is played by withanolides, which exhibit, among others, anti-inflammatory, antioxidant and immunomodulatory effects [6, 14, 18].

Rhodiola rosea (R.r.). A plant found in cool and mountainous areas of Eurasia and North America, and particularly used in Siberian folk medicine to improve mental and physical abilities. It includes many varieties that differ in their phytochemical profile, which is important for their biological effects and potential therapeutic applications [19–21]. The most important raw material is the root, which is the main source of bioactive substances. The main groups of components are: phenolic glycosides, organic acids, sterols, flavonoids, alkaloids, coumarins, essential oils. Among them, salidroside and rosavin play a special role, which are often the basis for standardization of pharmaceutical preparations and dietary supplements containing *Rhodiola rosea* [21–23]. Adaptogenic properties of *R.r.* are related to its ability to support the physiological adaptation of the body to stress factors – both psychological and environmental. It affects the functioning of the HPA (hypothalmic-pituitary-somatotropic) axis, regulates the activity of monoaminergic neurotransmitters (including serotonin and dopamine), and modulates the level of β-endorphins [22]. It has been shown to have a strong antioxidant effect, consisting in the effective removal of free radicals. The plant has an anti-fatigue effect and reduces muscle damage, which may be related to the improved use of energy substrates and antioxidant activity. It also has anti-cancer and immunomodulatory effects in autoimmune diseases.

Studies on animal models have observed a reduction in lipid levels, including visceral fat mass and lipid indices, with simultaneous regulation of genes related to adipogenesis. *Rhodiola rosea* reduces pain caused by cold and increases cell resistance to radiation. In addition, its beneficial effect has been noted in Alzheimer's disease, pulmonary fibrosis and osteoarthritis [24–26]. At the molecular level, anti-oxidant, anti-inflammatory, neuroprotective, and immunomodulatory properties of *Rhodiola rosea* and its active metabolites have been documented. These mechanisms are responsible for its potential use in the treatment or support of anxiety disorders, depression, chronic fatigue syndrome, mild cognitive dysfunction, cardiovascular diseases, type 2 diabetes, inflammation and neurodegenerative diseases [19, 21, 27, 28]. Moreover, there are indications that *Rhodiola rosea* has a beneficial effect on the homeostasis of the intestinal microbiome and on the alleviation of vascular endothelial dysfunction [23].

Randomized controlled trials (RCTs). Are trials which the foundation of evidence-based medicine (EBM), and are a recognized standard for assessing the effectiveness of therapeutic interventions. Their main methodological advantage is their prospective nature and the random assignment of participants to treatment and control groups. This helps limit the influence of both known and unknown confounding factors. This study design allows for a reliable assessment of the causal relationship between the intervention and the observed clinical outcomes. A key element of RCTs is the randomization process, which serves to ensure an even distribution of participant characteristics between the comparison groups. This procedure minimizes the risk of systematic selection bias and strengthens the internal validity of the study. Randomization should be performed using appropriate tools, most often automated systems that generate random sequences, a solution that limits the ability of researchers to influence participant group assignment [29–31]. An additional mechanism increasing the reliability of results is the use of blinded groups, which is intended to reduce observational errors and the placebo effect. In the ideal case, double blinding is used, covering both participants and researchers, which allows the avoidance of subjective influences on the assessment of the effectiveness of the intervention. To ensure adequate statistical power and reliable interpretation of results, RCTs must have a precisely defined sample size and primary endpoints. The studies should also be registered in public databases, in accordance with applicable guidelines and principles of clinical research ethics [31–33].

REVIEW METHODS

A detailed search of scientific literature was conducted in the PubMed database which covered papers published between January 2015 – March 2025. Articles published in English and available in open access mode were included in the analysis, which allowed for a full insight into the content of the publications and a reliable assessment of the methodological quality of the included studies. The search strategy was developed based on the key words: 'plant adaptogen', 'ashwagandha', '*Withania somnifera*' and '*Rhodiola rosea*'. This enabled the identification of studies focused on selected plant adaptogens that are the subject of this study. As a result of the initial search stage, a total of 101 scientific articles were identified. Subsequently, according to the established inclusion criteria, a selection of publications was carried out, selecting only randomized clinical trials. After full-text analysis, 24 articles meeting all the adopted criteria were qualified for further review. Among them, 19 studies concerned *Withania somnifera* and 5 concerned *Rhodiola rosea*.

Inclusion and exclusion criteria. Studies that met the following criteria were included in the review: randomized controlled trials (RCTs) published in English, available in open access mode, covering interventions using plant adaptogens – *Withania somnifera* or *Rhodiola rosea*. Further analysis excluded papers published in languages other than English, book chapters, review articles and meta-analyses, as well as *in vitro* studies and experiments conducted on animal models. Also excluded were duplicate publications, and those limited only to the assessment of the safety of adaptogens without a simultaneous analysis of their potential pharmacological effects.

The literature selection procedure was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which ensures transparency, reliability, and reproducibility of the review process [34].

Analysis of clinical data from selected publications. The analysis presents the results of 24 randomized controlled trials on the adaptogenic properties of *Withania somnifera* and *Rhodiola rosea* extracts in different population groups (Tab. 1). All studies compared experimental groups supplemented with adaptogens, with control groups receiving placebo, using a double-blind study design. The studies varied in terms of population, intervention type, dose, duration of supplementation, and outcome assessment methods. This diversity allowed for a broad assessment of the action profile and clinical significance of both plants.

Types of extracts and doses used. Different types of *Withania somnifera* extracts were used in the studies: alcoholic-aqueous root extracts (KSM-66, Witholytin), aqueous leaf and root extract (Sensoril), standardized leaf and root extract (Shoden), and non-commercial ashwagandha extracts. In the case of *Rhodiola rosea*, standardized root extracts were tested: Arctic Root, Golden Root Extract (GRE), SHR-5, and Vitano. Doses of *W. somnifera* extracts ranged from 120 mg-1,000 mg daily, while for *R. rosea* – from 290 mg-1,500 mg daily, most often oscillating around 600 mg for all studies. The supplementation period ranged from 3 days (GRE, *R. rosea*)-16 weeks (Shoden, *W. somnifera*), with the most common intervention for both adaptogens lasting 6–12 weeks. In most of the analysed studies, the doses of adaptogens used were well tolerated and were not associated with significant adverse effects. Reported symptoms, such as headaches or mild gastrointestinal complaints, were transient and did not affect the course of the intervention or the overall safety profile of the extracts tested.

Participant population and study objectives. The study included healthy volunteers as well as individuals with subclinical or clinical functional disorders, such as chronic stress, anxiety, insomnia, chronic fatigue syndrome, depression, schizophrenia, OCD, and menopause, infertility. Clinical trials of *Withania somnifera* were generally larger (n = 30–590), while studies of *Rhodiola rosea* were small (n = 10–100), which limited their statistical power. Adults aged 18–75 years were recruited, and the gender of participants in the individual experiments varied; some studies were conducted exclusively in men or women. The primary study objectives included determining the potential effects of adaptogens on cognitive function and mood, response to chronic stress (7 studies), exercise adaptation and muscle strength and cardio-respiratory endurance (6 studies), symptoms of depression and anxiety (4 studies), sleep quality (3 studies), hormone levels (5 studies), symptoms of OCD and schizophrenia (2 studies), infertility (1 study), and CYP-mediated drug metabolism (1 study) (Fig. 1).

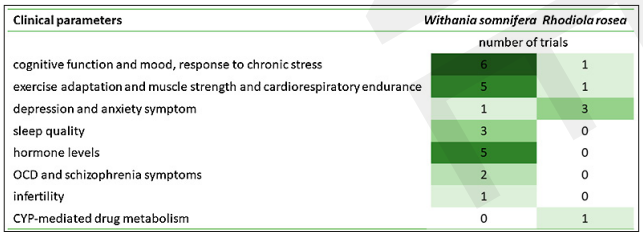

Figure 1. Spectrum of clinical parameters assessed in the analyzed randomized controlled trials of *Withania somnifera* and *Rhodiola rosea*. Colour intensity indicates the frequency with which each parameter was evaluated across studies

Methods of assessing effects. The study used a variety of assessment tools, both psychometric and biomedical, and the range of parameters assessed reflected a wide spectrum of adaptogenic effects. Studies on *Withania somnifera* assessed exercise and regenerative abilities [35, 36, 37, 43], stress level [44, 49, 46, 38], mood and anxiety [46, 50], cognitive functions [39, 50], sleep quality [40, 47, 52], hormonal parameters [37, 41, 46, 48, 49] and fertility [53]. In the case of *Rhodiola rosea*, the main focus was on anti-depressant effects [57, 58], anxiolytic [56], exercise capacity [54] and the effect on drug metabolism [55]. Standardized symptom severity scales (e.g. HAM-D), cognitive function tests (e.g. COMPAS), general quality of life indicators (e.g. WHOQOL), physical fitness (e.g. VO_2max) and clinical parameter tests were used to examine both adaptogens.

Research results. Based on the analysis of randomized clinical trials on *Withania somnifera* and *Rhodiola rosea*, it can be concluded that both adaptogens demonstrated a wide spectrum of beneficial physiological and psychological effects, manifested by the improvement of both subjective and objective parameters of psychophysical health. Both

Table 1. Analysis of results regarding the adaptogenic effects of *Withania somnifera* and *Rhodiola rosea* based on randomized clinical trials, 2015–2025

No.	Type of extract	Dose (mg)/ day	Time	No. and (age) of all participants	Study objectives	Measurement methods	Main results	References
Withania somnifera								
1.	KSM-66	600	28 days	30 (18–36)	exercise recovery, muscle strengh	TQR, HI, RPE, MBT, CMJ, hand grip, peak power	faster regeneration after exercise	[35]
2.	KSM-66	600	8 weeks	73 (18–45)	muscle strength, size, cardiorespiratory endurance	1-RM, circumference of arm, chest upper thigh, VO2 max	improving muscle endurance, growth and strength	[36]
3.	KSM-66	600	8 weeks	50 (18–50)	strength and muscle mass	1-RM, testosterone, anthropometric factors	increasing muscle mass and strength	[37]
4.	KSM-66	600	8 weeks	52 (18–60)	chronic stress, weight control, appetite	PSS, FCQ-T, OHQ, TFEQ, cortisol, body weight, body mass index	reduction in psychological and physiological markers of stress, improvement of mental well-being, reduction in cortisol level and food craving, improvement in eating behaviours	[38]
5.	KSM-66	600	8 weeks	50 (>35)	memory and cognitive functions	WMS-III, WCST, EFT, T-MTPA, MCT	improvement in immediate and general memory, executive function, attention and information processing speed	[39]
6.	KSM-66	600	8 weeks	80 (18–50)	quality sleep, insomnia	SOL, TST, WASO,TIB, SE, PSQI, HAM-A, Mental Alertness, Sleep quality	improvement in sleep quality	[40]
7.	KSM-66	600	8 weeks	91 (45–60)	climacteric symptoms, quality of life, hormonal parameters	MRS, MENQoL, sex hormones	alleviation of climacteric symptoms, increase in estradiol level	[41]
8.	KSM-66	600	8 weeks	50 (18–45)	cardio-respiratory endurance, quality of life, anti-oxidant level	VO2max, TQR, RESTQ, DALDA,	improvement in biochemical, physiological and psychological parameters, increase in anti-oxidant level	[42]
9.	Sensoril	500	12 weeks	38 (18–45)	strength training adaptation	DEXA, NSCA, 1-RM, TENDO Power Analizer, aerobic endurance, VAS, clinical chemistry	strength improvement	[43]
10.	Sensoril	125/ 250/ 500	8 weeks	98 (18–60)	stress, HPA axis	PSS, biochemical-related stress parameters, HAM-A, HAM-D, PSQI, VAS-S, VAS-E, WHOQOL, inflammatory parameters	stress reduction via the modulation of the HPA axis	[44]
11.	Sensoril	1,000	12 weeks	66 (18–75)	depression, anxiety in schizophrenia	PANSS	relief of symptoms depression and anxiety	[45]
12.	Shoden	240	60 days	60 (18–65)	stress, mood	HAM-A, DASS-21, DHEA-S, cortisol, testosterone	anxiolytic effects, reduction in cortisol and DHEA-S level, increase in testosterone level	[46]
13.	Shoden	120	6 weeks	144 (18–65)	quality sleep	SOL, TST, WASO,TBT, SE RSQ-W, WHOQOL, awaking time	improvement in sleep quality, improvement in NRS condition	[47]
14.	Shoden	600	16 weeks	43 (40–70)	fatigue, vigour, steroid hormones	POMS-SF, AMS, DHEA-S, testosterone, cortisol, estradiol	increase in levels of DHEA-S, testosterone	[48]
15.	Witholytin	400	12 weeks	120 (40–75)	stress, fatique, sex hormones	PSS, CFS, sex hormone concentration	anti-fatigue effects, increase in testosterone and luteinizing hormone	[49]
16.	liposomal *W.s.* root and leaf extract	225	30 days	590 (18–60)	cognitive function, mood	COMPAS, POMS	improvement in memory, attention, vigilance, executive function	[50]
17.	*W.s.* root extract	120	6 weeks	30	obcessive-compulsive disorder (OCD)	Y-BOCS	reduction of OCD symptoms, adjunct to SSRIs in treatment of OCD,	[51]
18.	*W.s.* root extract	600	6 weeks	150 (18–65)	non-restorative sleep	RSQ-W, TST, SOL, WASO, WHOQOL, HADS, NPSG, CRP	improvement in sleep quality	[52]
19.	*W.s.* root extract	800	90 days	100 (18–45)	idiopathic male infertility	sperm parameters	improvement in sperm count, motility, morphology	[53]
Rhodiola rosea								
20.	GRE	1,500	3 days	10	resistance training performance	1-RM, lactate, epinephrine, norepinephrine	increase in explosive resistance exercise performance	[54]
21.	Arctic Root	290	14 days	13 (20–26)	CYP enzyme activity	HPLC-MSMS	inhibition of metabolic capacity of CYP2C9, drugs metabolized by CYP2C9 could be inhibited to a clinically significant degree	[55]
22.	Vitano	400	14 days	80 (18–35)	anxiety, stress, cognition, mood	STAI, PSS, PMSI, MESS, LSEQ, computer-based task, SART, SDP	reductionin anxiety and stress, improvement in confusion, anger and mood	[56]
23.	SHR-5	340 – 1,360	12 weeks	57 (≥18)	deepressive disorder	HAM-D, BDI, CGI/C	anti-depressant effects	[57]
24.	standardized extract of *R.r.*	300, 600	12 weeks	100 (18–50)	deepressive disorder	HAM-D, BDI, CGI/C	anti-depressive potency, improvement in quality of life and clinical symptoms	[58]

AMS – Aging Males'Symptoms, **Arctic Root** – commercially available *R. rosea,* **BDI** – Beck Depression Inventory, **CFS** – Chalder Fatigue Scale, **CGI/C** – Clinical Global Impression Change, **CMJ** – counter-movement jump, **COMPAS** – cognitive function test battery, **CRP** – *C-reactive protein,* **DALDA** – Daily Analysis of Life Demands for Athletes, **DASS-21** – Depression Anxiety Stress Scale-21, **DHEA-S** – dehydroepiandrosterone sulfate, **EFT** – Eriksen Flanker Task, **FCQ-T** – Food Cravings Questionnaire, **GRE** – Golden Root Extract *Rhodiola rosea*, **HADS** – Hamilton Anxiety Depression Scale, **HAM-A** – Hamilton Anxiety Scale, **HAM-D** – Hamilton Depression Scale, **HI** – Hooper Index, **HPA**-hypothalamic-pituitary-adrenal axis, **HPLC-MSMS** – high-performance liquid chromatography-tandem masss spectrometry, **KSM-66** – root extract of ashwagandha, **LSEQ** – Leds Sleep Evaluation Questionnaire, **MBT** – medicine ball throw, **MCT** – Mackworth Clock Test, **MENQoL** – menopause-specific quality of life questionnaire, **MESS** – Milford Epworth Sleepiness Scale, **MRS** – menopause rating scale, **NPSG** – Nocturnal Polysomnography, **NRS** – non-restorative sleep, **NSCA** – National Strength and Conditioning Association, **OHQ** – Oxford Happiness Questionnaire, **PANSS** – Positive and Negative Syndrome Scale, **PMSI** – Profile of Mood States Inventory, **POMS** – Profile of Mood States, **POMS-SF** – Profile of Mood States – Short Form, **PSS** – Perceived Stress Scale, **PSQI** – Pittsburgh Sleep Quality Index, **RESTQ** – Recovery Stress Questionnaire for Athletes, **1-RM** – muscle strength, **RPE** – rate of perceived exertion, ***R.r.*** – *Rhodiola rosea,* **RSQ-W** – restorante sleep questionnaire-weekly, **SART** – Sustained Attention to Response Test, **SDP** – Symbol Digit Processing, **SE** – Sleep efficiency, **Sensoril** – roots and leaves aqueous extract of ashwagandha, **Shoden** – root and leaves extract of ashwagandha, **SHR-5** – roots standardized extract of *Rhodiola rosea,* **SOL** – Sleep Onset Latency, **STAI** – Strate Train Anxiety Inventory, **TBT** – total bed time, **TFEQ** – Three-Factor Eating Questionnaire, **TIB** – Total time in bed, **T-MTPA** – Trail-Making Test Part A, **TST** – Total Sleep Time, **TQR** – total quality recovery, **VAS-E** – Visual Analogue Scale for energy, vitality, drive, **VAS-S** – Visual Analogue Scale for Sleep, **Vitano** – commercially available *R. rosea,* **WASO** – Wake After Sleep Onset**, WCST** – Wisconsin Card Sort Test, **WHOQOL** – World Health Organization Quality: Brief Version questionnaire, **Witholytin** – hydroalcoholic extract of the roots of ashwagandha, **WMS-III** – Wechsler Memory Scale III, ***W.s.*** – *Withania somnifera.*

adaptogens contributed to the reduction of symptoms of stress, fatigue, anxiety and depression [38, 44, 45, 46, 49, 50, 56, 57, 58]. Improvement in sleep quality [40, 47, 52], increased rate of post-exercise regeneration, and increased endurance and muscle mass [35, 36, 37, 43, 54] were documented. A positive effect on cognitive functions, such as attention, alertness, memory and executive functions [39, 50, 56], were also observed. Improved mood, reduced anger, and reduced symptoms of obsessive-compulsive disorder (OCD) and schizophrenia have also been reported [45, 51, 56]. Additionally, increased anti-oxidant levels [42], beneficial changes in sex hormone parameters [46, 48, 49], improved fertility rates in men [53], and reduced symptoms associated with menopause [41] have also been observed.

The presented systematic review analyzed in detail the results of clinical studies using two psychometric scales: the Hamilton Anxiety Rating Scale (HAM-A) and the Perceived Stress Scale (PSS) (Fig. 1 and 2). These scales were selected because they were most frequently used in clinical studies and are considered reliable tools for assessing the effects of substances affecting stress and anxiety. The results in all studies were reported in the same unit, which allowed for direct comparison of numerical data and their common interpretation. The HAM-A scale is a classic and commonly used tool in clinical studies to assess the intensity of anxiety symptoms. Importantly, this scale measures both psychological and somatic components of anxiety, which is particularly important in the context of the action of adaptogens with a multi-directional mechanism of action [59]. In turn, the PSS scale assesses the subjective perception of stress, regardless of the diagnosed disease entities. Due to its universality, it can be used in both patients and healthy individuals, which makes it a particularly useful tool for assessing the effectiveness of adaptogenic interventions [60].

The HAM-A scale was used in three articles on *Withania somnifera*. Figure 2 shows the percentage change in the HAM-A scale scores after the intervention with different *W. somnifera* preparations, compared to the baseline values. A negative value indicated a decrease in the intensity of anxiety symptoms. Sensoril [44] in doses of 125 mg, 250 mg and 500 mg was used in people suffering from anxiety, depression and sleep disorders related to chronic stress (over three months). KSM-66 extract [40] in a dose of 600 mg was tested in healthy people (due to the lack of precise data, this group was not included in this analysis) and people with insomnia. Shoden [46] was tested in healthy people in a dose of 240 mg. All studies concerned adult women and men, and the intervention time was eight weeks (60 days for Shoden). The largest decrease was noted in the study [44] at a dose of 250 mg of Sensoril (over -45%), and also in the study [40] in the group receiving KSM-66 (approx. -30%). In the placebo groups, the improvement of the studied parameter was minimal (approx. -10% or less). In each of the analyses comparing *Withania somnifera* with placebo (without Shoden), the researchers noted statistically significant differences in favour of the intervention.

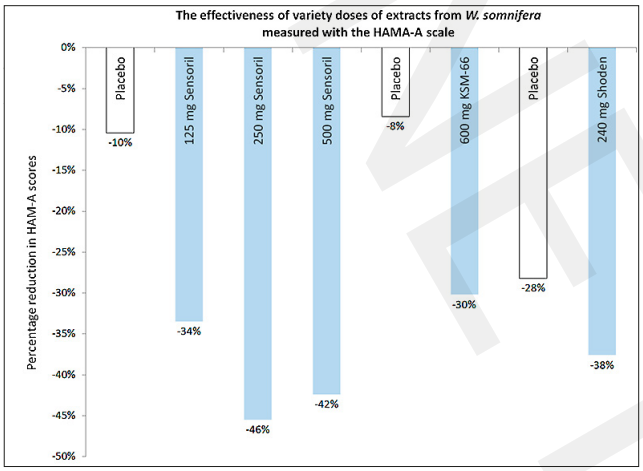

Figure 2. Percentage reduction in HAM-A scores following treatment with various doses and extracts Sensoril – [44], KSM-66 – [40], Shoden – [46] of *Withania somnifera,* compared to placebo.
Negative values indicate a decrease in anxiety symptoms. Values rounded to whole units

The PSS scale was used in three articles on *W. somnifera* and one on *R. rosea*. Figure 3 shows the percentage change in PSS scores after the intervention with adaptogen extracts, compared to the baseline values. A negative value indicates a decrease in the severity of stress-related symptoms. The largest decrease was noted in study [44] at a dose of 250 mg of Sensoril (over -34%), and in study [38] in the group receiving KSM-66 (-33%). Sensoril, KSM-66 and Vitano demonstrated a statistically significant effect of adaptogens. For Witholytin, no statistically significant differences were demonstrated between placebo and ashwagandha extract.

Mechanistic insights into the anti-stress and anxiolytic effects of *Withania somnifera* and *Rhodiola rosea*. The effectiveness of both adaptogens in reducing PSS and HAM-A scores, and consequently improving mood and reducing stress symptoms, is supported by their effects on the HPA axis, neurotransmission, inflammatory markers, and ANS

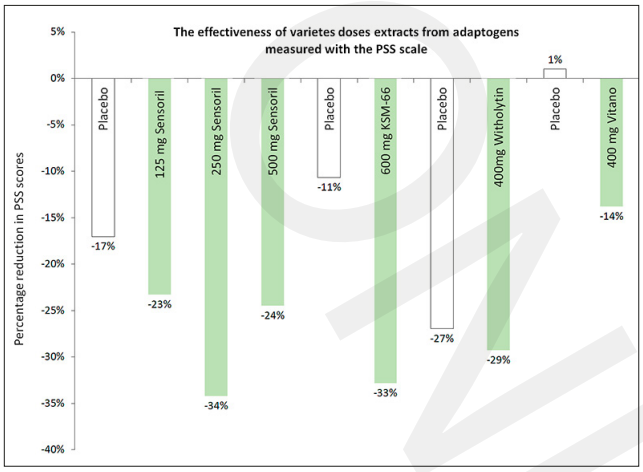

Figure 3. Percentage reduction in PSS scores following treatment with various doses and extracts.
Sensoril – [44]; KSM-66 – [38]; Witholytin – [49]; Vitano – [56] of *Withania somnifera* and *Rhodiola rosea,* compared to placebo. Negative values indicate a decrease in stress symptoms. Values rounded to whole units

activity. In the case of *Withania somnifera*, the analyzed studies described molecular mechanisms of action related to stress reduction and mood improvement. For *Rhodiola rosea*, available clinical data are more limited in this regard, although the results suggest an action based on similar biological pathways, as confirmed by preclinical studies [38, 40, 44, 46, 49, 56].

It has been demonstrated that the central action of *W. somnifera* is its ability to regulate the activity of the hypothalamic-pituitary-adrenal (HPA) axis, whose excessive activation during mental stress leads to chronically-elevated cortisol levels, increased appetite for sugars and fats, and the accumulation of visceral fat. The results of the analyzed studies indicate that ashwagandha supplementation reduces levels of cortisol, ACTH, and salivary α-amylase (recognized biomarkers of stress) while simultaneously improving the subjective perception of stress and sleep quality. Additionally, normalization of leptin levels was observed, which is important in the context of reducing stress-related weight gain [38, 44]. Reduced DHEA-S levels, combined with cortisol reduction, indicate the restoration of neuroendocrine balance and reduced excessive reactivity of the HPA axis [46].

Researchers also linked the improved HAM-A scores to *W. somnifera* ability to modulate the GABAergic and serotonin systems. In pre-clinical studies, *W. somnifera* plant extracts increased chloride ion influx through GABA-A receptors, acting similarly to agonists of this system. This mechanism, although not directly assessed in a clinical study, was proposed by the authors as a possible explanation for the observed anxiolytic and sedative effects of ashwagandha [40].

At the immunological level, supplementation with *W. somnifera* root and leaf extracts led to a reduction in the concentrations of pro-inflammatory cytokines, such as IL-6, IL-1β and TNF-α. This observation confirms the plant's anti-inflammatory activity and suggests that reducing inflammation may mediate its anti-depressant effects [44].

Another interesting aspect of *W. somnifera* action is its impact on the hormonal profile. Clinical studies have reported increased testosterone and luteinizing hormone (LH) concentrations in men, and increased estradiol in perimenopausal women, while maintaining values within physiological norms. These phenomena may indirectly contribute to improved mood, energy, and fatigue reduction. The proposed mechanism is the effect of ashwagandha on of GnRH (gonadoliberin) expression in the hypothalamus, as well as an indirect effect through modulation of the HPA axis [46, 49].

Additionally, beneficial changes in heart rate variability (HRV) parameters, considered a non-invasive marker of the balance between sympathetic and parasympathetic activity of the autonomic nervous system, have been observed in individuals taking ashwagandha. Increased HRV correlated with reduced stress levels and increased psychophysical well-being [49].

Although the analyzed clinical studies are dominated by short-term interventions, the obtained results confirm an impact on subjectively perceived stress, improved sleep, reduced mental tension, and increased psychophysical performance in healthy individuals and those with mild mood disorders. The integrated nature of these processes indicates that the adaptogenic effects of *W. somnifera* and *R. rosea* result from the synergy of multiple interdependent biological pathways that work together to support the return o0f the body to a state of physiological equilibrium in the face of chronic stress. Consequently, the plants support the body's resilience to environmental stressors, contributing to an improved quality of life and psychophysiological balance.

DISCUSSION

The results of the analyzed randomized clinical trials indicate the significant potential of *Withania somnifera* and *Rhodiola rosea* as adaptogens, especially in the context of modulating the body's response to stress and supporting the general psychophysical condition. Analysis of the results obtained using the HAM-A and PSS scales indicated a significant clinical effect of *W. somnifera* and *R. rosea* in reducing anxiety symptoms and subjectively experienced stress. The obtained results show that the effectiveness of these adaptogens may depend not only on the dose and duration of the intervention, but also on the characteristics of the preparation and the studied population. The HAM-A and PSS scales proved to be useful, complementary tools for assessing the effectiveness of adaptogenic interventions in clinical trials.

In the face of contemporary health challenges, such as chronic stress, sleep disorders, lifestyle diseases, and deteriorating mental well-being, there is a growing need for effective, safe and multi-directional interventions supporting the body's homeostasis. Adaptogen supplementation seems to be a promising pro-health strategy, consistent with the growing interest in prevention, and a holistic approach to health [14, 16].

Due to the growing importance of adaptogens, modern medicine is making more and more attempts to verify their effectiveness based on the methodology of evidence-based medicine (EBM), with an emphasis on randomized clinical trials (RCT) [15]. An undoubted advantage of RCTs is their high internal validity, which allows for the precise determination of cause-effect relationships thanks to randomization, the use of a control group and strict control of confounding variables. This allows the evaluation of the effectiveness of pharmacological or phytotherapeutic interventions.

However, despite its numerous advantages, the RCT methodology also has significant limitations, both

methodological and practical [32, 33]. Cost, time and difficulty in recruiting and retaining participants, as well as loss of data and poor adherence to the intervention protocol, may reduce the credibility of the results. Moreover, the experimental conditions in which RCTs are conducted often differ significantly from the realities of everyday clinical practice, which limits their generalizability [33]. In the case of adaptogens, extracts differ in phytochemical composition depending on the plant variety, part of the raw material used, cultivation conditions, and extraction methods. Consequently, the same nominal dose of an ashwagandha extract may contain vastly different amounts of withanolides and other active constituents, which likely accounts for the variability in clinical outcomes across studies. Therefore, in cases where conducting RCTs is not possible for ethical or practical reasons – e.g. in studies of risk factors in healthy populations – an alternative is well-designed observational studies which, with appropriate use of statistical methods, can be a valuable source of data [32, 61].

In light of the above, more and more researchers advocate the complementary use of both RCTs and observational studies, treating both approaches as complementary research tools. Combining data from different types of studies can provide a more complete picture of the actual therapeutic effects – especially in the case of substances with a complex mechanism of action, such as adaptogens [62, 63].

Adaptogens, by definition, modulate the mechanisms of physical, mental and metabolic stress, supporting the restoration of homeostasis in the body. These effects result from their influence on a number of systems: neuroendocrine (regulation of the HPA axis), immune (anti-inflammatory effect), mitochondrial (support for energy production) and metabolic (normalization of lipid and glucose metabolism) [14, 15]. Classical clinical indicators used in RCTs – such as the PSS scale, cortisol level, VO_2 max or quality of life questionnaires – are not sufficient to capture the multilevel biological activity of adaptogens. Furthermore, in studies involving herbal preparations where efficacy is assessed using subjective scales (stress, fatigue, mood, sleep), placebo effect can both mask and exaggerate the true pharmacological effect. Therefore, study protocols should incorporate methods to verify the reliability of blinding and combine subjective measurements with objective markers, such as biochemical or physiological indicators. It seems reasonable to extend classic RCT protocols with systemic approaches, such as transcriptomic, proteomic, metabolomic or epigenetic analysis. Integration of systemic methodology would enable the identification of biomarkers of adaptogenic response, assessment of the impact on biological networks and differentiation of adaptogenic effects from placebo or non-specific nootropic effects. This approach could also contribute to better patient selection, dosage optimization and prediction of therapeutic response [16].

Personalized medicine increasingly emphasizes the need for interventions with a favourable safety profile. In this context, adaptogens can be an important component of supportive therapies, especially for individuals exposed to chronic stress or with chronic diseases. However, their broader clinical application requires well-designed studies of appropriate duration that take into account individual variability, risk groups, and potential interactions with commonly used medications.

The literature is particularly lacking in data on under-represented populations. Elderly individuals should be included intentionally due to their distinct pharmacokinetic profiles, varying cognitive functions, and high prevalence of polypharmacy. Similarly, patients with metabolic diseases and perimenopausal women remain groups of significant clinical importance, but are rarely analyzed. Systematic pharmacokinetic studies and assessment of drug interactions are essential for reliable safety assessments in these populations. Incorporating these aspects will increase the translational value of the results, and enable the development of practical recommendations regarding dosage and contraindications [14, 16].

CONCLUSIONS

Withania somnifera and *Rhodiola rosea* show real potential as agents supporting mental and physical health, but their full clinical application requires further development of research methods and integration of classical EBM tools with a systemic approach. The importance of adaptogens may increase in the future with the development of personalized integrative medicine aimed at restoring the physiological balance of the body, and improving the quality of life of patients.

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