doi: http://dx.doi.org/10.11606/issn.1679-9836.v104i6e-227539

Rev Med (São Paulo). 2025 Nov-Dec;104(6):e-227539.

Review Article

Rhodiola rosea L. reduces the depression symptoms – A systematic review

Rhodiola rosea L. reduz os sintomas de depressão – revisão sistemática

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Oliveira MC, Santos TFF, Santos JSG. *Rhodiola rosea L.* reduces the depression sympotms – A systematic review / *Rhodiola rosea L. reduz os sintomas de depressão – revisão sistemática* /. Rev Med (São Paulo). Rev Med (São Paulo). 2025 Nov-Dec;104(6):e-227539.

ABSTRACT: Introduction: The pathophysiology of depression has been associated with hippocampal atrophy, neural inflammation, lower activity of monoaminergic neurotransmitters, and high cortisol levels. Traditional antidepressants have side effects, which lead patients to abandon treatment. Studied natural alternatives include the use of *Rhodiola rosea* L. (RR) for treating mild to moderate depression. This systematic review was performed to verify the effectivity of RR in humans with mild to moderate depression. **Methods:** The PubMed, Scopus, Web of Science, Lilacs, Embase, and Science Direct databases were used to search for studies. The terms used were “Salidroside”; “Rhodioloside”; “*Rhodiola rosea*”; “depression”; “depressive disorder”; “depression, chemical”; and “human”. Studies which met the eligibility criteria, as well as their methodological quality, were assessed by two reviewers. **Results:** The RR extract was evaluated in three studies and reduced the intensity of symptoms in humans with mild to moderate depression based on Hamilton Scale and Beck’s Depression Inventory. **Conclusion:** The use of *Rhodiola rosea* extract reduces the severity of depression symptoms.

KEY WORDS: Antidepressive agents; Crassulaceae; Depressive disorder.

RESUMO: Introdução: A patofisiologia da depressão tem sido associada com a atrofia do hipocampo, inflamação neural, baixa atividade de neurotransmissores monoaminérgicos e altos níveis de cortisol. Antidepressivos tradicionais têm efeitos colaterais, os quais levam pacientes a abandonar o tratamento. Alternativas naturais estudadas incluem o uso de *Rhodiola rosea* L. (RR) no tratamento de depressão leve a moderada. Esta revisão sistemática foi realizada para verificar a efetividade da RR em humanos com depressão leve a moderada. **Métodos:** As bases de dados PubMed, Scopus, Web of Science, Lilacs, Embase e Science Direct foram utilizadas para a busca dos estudos. Os termos “Salidroside”; “Rhodioloside”; “*Rhodiola rosea*”; “depression”; “depressive disorder”; “depression, chemical” e “human” foram utilizados. Estudos que atenderam aos critérios de elegibilidade, bem como suas qualidades metodológicas, foram avaliados por dois revisores. **Resultados:** O extrato de RR foi avaliado em três estudos e reduziu a intensidade dos sintomas em humanos com depressão leve a moderada com base na escala Hamilton e Inventário de Depressão de Beck. **Conclusão:** O uso de extrato de *Rhodiola rosea* reduz a severidade dos sintomas da depressão.

PALAVRAS-CHAVE: Antidepressivos; Crassulaceae; Transtorno depressivo.

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INTRODUCTION

Approximately 280 million people in the world have a depressive disorder, and women are more affected than men[1]. Depression is a health public problem which has been growing each year, especially since the COVID-19 pandemic[2], and it is a heterogeneous condition with a great variety of clinical symptoms[3]. Depression pathophysiology has been associated with hippocampal atrophy[4,5], neural inflammation[6,7], lower activity of monoaminergic neurotransmitters[8], and high cortisol levels[9], among other factors.

An increase in the production of pro-inflammatory cytokines is common in depression patients, such as interleukin IL-1β and IL-6, tumoral necrosis factor (TNF-α), as well as higher nitric oxide synthase and cyclooxygenase levels[10]. IL-1β, TNF-α, and IL-6 cytokines may also activate the hypothalamic-pituitary-adrenal axis (HPA)[11] and increase cortisol levels[9].

The hypothesis of depression due to a deficiency or imbalance of monoaminergic neurotransmitters has been considered for a long time. A serotonin (SER) deficiency in the brain may exacerbate negative emotions, such as depressive mood, displeasure, fear, anxiety, hostility, and isolation[12]. According to Liu et al.[13], depressive patients present lower SER levels compared to healthy individuals. Low SER synthesis may occur in depression, or depression may cause a reduction in the SER synthesis and cause depressive behavior[14].

Stress is common in depression and can activate the HPA, thereby causing an increase in glucocorticoid secretion and decreasing the hippocampal neurogenesis[15]. Liu et al.[16] showed that adrenalectomy can promote neurogenesis in the hippocampus in adults, demonstrating the relationship between adrenal function and neurogenesis.

Traditional antidepressants have several side effects which lead many patients to abandon treatment[17,18]. Non-adherence to treatment results in a higher risk of relapse[19,20], and according to Sansone and Sansone[21], the non-adherence rate is about 52% at six months of treatment with antidepressants. Thus, natural alternatives have been studied, such as the use of *Rhodiola rosea* L. or its components in treating mild to moderate depression.

R. rosea L. (RR) is a plant known as gold root and has circumpolar distribution in the northern hemisphere from the low-Artic to high-temperature regions of Asia, Europe, and North America[22], and its extract (RRE) increases mental capacity and reduces fatigue[23]. Salidroside (SAL) is the main component of RR and shows numerous pharmacological properties[24].

Adaptogens are a pharmacological group of herbal preparations that improve attention and fatigue resistance, in addition to reducing stress-induced cognitive failures and disorders related to the neuroendocrine and immune systems[25]. RR is considered an adaptogenic plant, and RRE and SAL are associated with neuroprotective and antioxidant effects[26,27]. The positive effects of plants on cognitive functions and the reduction of mental and physical fatigue are well-known in humans, as demonstrated by Ishaque et al.[28]; Cropley et al.[29]; Dimpfel et al.[30], and Koop et al.[31].

Approximately 140 different compounds have been isolated from RR[25], and its main compounds include: SAL, rosavin, rosin, rosarin, tyrosol, and rosiridin[32]. According to Amsterdam and Panossian[33], SAL and tyrosol are active substances, while the others are inactive. The commercial products based on RR are generally standardized to 1% SAL and 3% rosavin[30,34].

Brown et al.[35] mentioned that RR can centrally stimulate noradrenergic, adrenergic, and serotoninergic receptors, improving mood. *R. rosea* roots may inhibit MAO-A, acting as a potent antidepressant, and MAO-B may aid in controlling dementia[36]. In a study with students, Cropley et al.[29] demonstrated that the use of 400 mg RR/day reduced anxiety, stress, anger, confusion, depression, and sleepiness levels, as well as improved mood at 14 days of treatment.

This systematic review of the effects of RR in humans with mild to moderate depression was performed to verify its effectivity and possible action mechanisms and safety.

METHODOLOGY

Search strategy and eligibility criteria

The PubMed, Scopus, Web of Science, Lilacs, Embase, and Science Direct databases were used to search for studies on July 30, 2023. Clinical studies in humans were included in the search. The following terms were used: “Salidroside”; “Rhodioloside”; “*Rhodiola rosea*”; “depression”; “depressive disorder”; “depression, chemical”; and “human”, and the search strategy was (Salidroside OR rhodioloside OR Rhodiola rosea) AND (depression OR depressive disorder OR depression, chemical) AND human. The question was “What is the effectiveness of *Rhodiola rosea* in reducing depression symptoms?”

The PICO acronym (which stands for: patients, intervention, comparison, and outcomes) was used to determine the eligibility criteria for the systematic review, as follows:

- Patients – humans with mild to moderate depression.
- Intervention – *Rhodiola rosea* L. extract (RRE).
- Comparison – placebo or traditional antidepressant.
- Outcomes – an improvement in depressive symptoms.

Inclusion criteria for study selection were: studies (1) with humans with mild to moderate depression; (2) with *R. rosea* extract in the treatment; (3) containing a control group (placebo or traditional depressants); (4) original research and peer-reviewed study; and (5) no language or publication year restriction. Exclusion criteria were: (1) studies which did not correspond to original research; (2) duplicate studies found in more than one database; (3) studies involving a clinical condition different from depression; (4) studies involving another plant (different from *Rhodiola rosea*); and (5) studies involving healthy human beings.

Study selection

Titles and abstracts were exported to the Rayyan platform[37], where they were assessed by two reviewers to identify the studies that potentially meet the inclusion criteria. In the next phase, the selected studies were entirely read and evaluated based on the

eligibility criteria. Discrepancies were identified and resolved through discussion between the reviewers or with a third reviewer, if necessary.

Duplicates were detected by juxtaposition of the author's name and excluded in the first phase (assessment of title and abstracts).

Data extraction process

Two reviewers independently extracted data from each study. The following data were obtained and analyzed from the selected studies: authorship; publication year; intervention, duration, and main results obtained with Hamilton Depression Rating Scales and with Beck's Depression Inventory.

The methodological quality of the studies

Two authors independently evaluated the methodological quality of all the included studies. To evaluate the risk of bias in the studies, it was used the NICE tool[38]. Discrepancies were identified and resolved through discussion between the authors.

There was substantial heterogeneity among the studies, which was detrimental to a meta-analysis. Therefore, narrative synthesis was performed without statistical or sensitivity analysis.

This study was registered in Prospero with the registration number CRD42022339894.

RESULTS

Study selection

A total of 489 references were obtained after running the search algorithms with Boolean operators and free language terms. Next, 152 potentially eligible studies were exported to the Rayyan platform after the screening process of the publications found using the database filters for research articles. Finally, 3 studies met the requirements of this systematic review after filtering out duplicates and evaluating the titles (first screening), abstracts (second screening), and full texts (third screening) (Figure 1).

Characteristics of the studies

Three studies about the effect of the *Rhodiola rosea* extract on depression treatment were included in the review (Table 1). The studies were conducted with depressed humans of both sexes, aged between 18 and 70 years, and diagnosed with mild to moderate depression with an initial score ≥ 13 on Beck's Inventory and ≥ 21 on the Hamilton scale[39]; ≥ 18 years, a score ≥ 10 in Hamilton scale and a score of 3-4 on General Clinical Impression Scale[40]; 18-50 years of age, a score > 12 in Hamilton scale and a score of 3-4 on the General Clinical Impression Scale[41]. The drug used as positive control was sertraline[39,41].

Main effects of RRE administration in humans with mild to moderate depression

RRE effects on the treatments of humans was evaluated using the Hamilton Depression Rating Scales and Beck's Depression Inventory. The Hamilton scale is mostly used to evaluate depression severity in patients who have already been diagnosed with depressive disorder[42]. Beck's Depression Inventory is mostly used to evaluate depressive symptoms and their severity in a normal population or with psychiatric disorders[43].

There was a more significant reduction in the severity of depression symptoms in two of the three studies due to the use of RRE (300-680 mg/d) by the HAM-D and BDI scales compared to the use of SER or placebo[39,41]. There was no difference among the RRE and SER treatments in the study by Mao et al.[40], possibly due to bad distribution of the patients with mild to moderate depression among the experimental groups; however, patients taking RRE and sertraline had 1.4 and 1.9 times improvement odds, respectively, compared to the placebo group (Table 2).

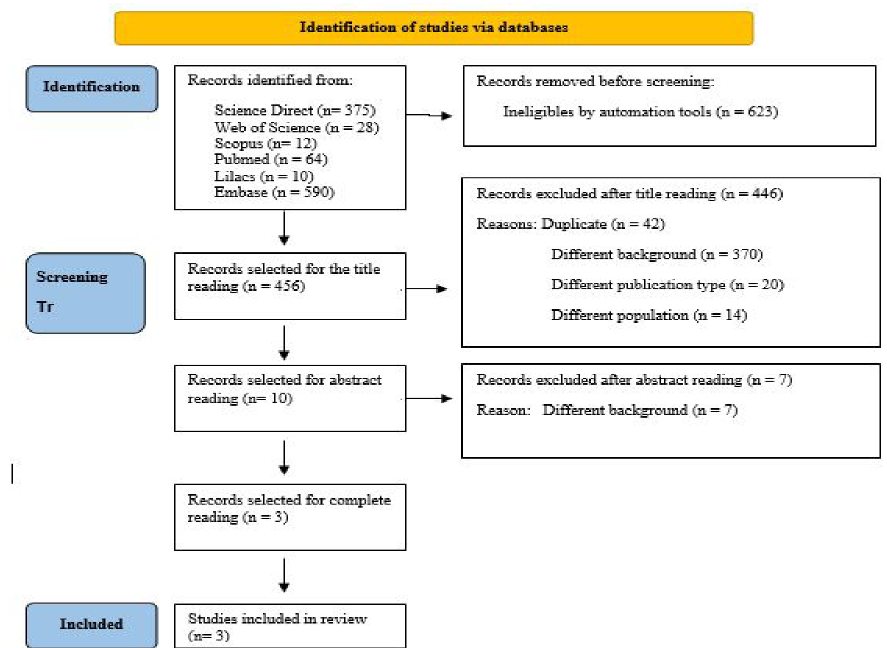

FIGURE 1 - Flow diagram of the selection process of studies for the systematic review on using *Rhodiola rosea* or salidroside in depression treatment

TABLE 1 - Characteristics of the included studies on the effects of *Rhodiola rosea* extract (RRE) in humans with mild to moderate depression

Authors	Design	Participants, age	Level of evidence[1]	Duration (ds)
Darbinyan et al.[39]	Randomized, double blind, placebo-controlled	Males and females, 18 – 70 years	IB	42
Mao et al.[40]	Randomized, double blind, placebo-controlled	Males and females, > 18 years	IB	84
Gao et al.[41]	Randomized, double blind, placebo-controlled	Males and females, 18 – 50 years	IB	84

[1]IB – Evidence level I; good quality B. According to Johns Hopkins Nursing Evidence Based Practice (2023)

TABLE 2 - Main results obtained with depressed humans treated or not with *Rhodiola rosea* extract

Authors	Intervention	Level of depression by Hamilton Scale	Level of depression by BDI
Darbinyan et al.[39]	Placebo (n=31) RRE – 340 mg/d (n=30) 680 mg/d (n=30)	↓ RRE (340 and 680 mg/d)	↓ RRE (340 and 680 mg/d) Higher effect with RRE at 680 mg/d
Mao et al.[40]	Placebo (n=18) RRE - 300 mg/d (n=20) SER - 50 mg/d (n=19)	There was no difference between the treatments	There was no difference between the treatments
Gao et al.[41]	Placebo + SER – NR (n=33) SER + RRE – 300 mg/d (n=34) SER + RRE – 600 mg/d (n=33)	↓ with RRE (300 and 600 mg/kg) and with SER	↓ with RRE (300 and 600 mg/kg) and with SER

BDI – The Beck Depression Inventory; SER – sertraline; NR – not reported

Safety of Rhodiola rosea use

The data suggest that RR administration is safe. In the study by Mao et al.[40], 63.2% of the patients reported adverse effects using sertraline, compared to 30% and 16.7% of patients reporting adverse effects due to the use of RRE or placebo, respectively. No patient prematurely discontinued RRE or placebo therapy. Two patients discontinued sertraline treatment because of palpitations (n=1), and one each for headache, insomnia, and sexual dysfunction (n=1). In the studies by Darbynian et al.[39] and Gao et al.[41], no patients reported serious adverse effects of the medication, and none discontinued treatments due to non-compliance with the prescribed treatments. The study by Gao et al.[41] mentioned that more patients reported related adverse events using sertraline + placebo than sertraline + RR capsule.

DISCUSSION

Two studies[40,41] did not mention if the groups received the same care apart from the intervention studied. According to the Nice tool[38], none of the studies reported if the investigators were kept blind to other important confounding and prognostic factors. All of the included studies described the details of the intervention preparation (quantity of active or inactive constituents per dosage unit form). Insufficient description of the intervention preparation is a common shortfall, preventing a future comparison of the results between the randomized clinical trials.

According to Lu et al.[44], the use of RRE at doses varying from 100 to 1500 mg/d showed no adverse effects when used for 183 individuals. The lack of adverse effects due to RR use was also reported by Bernatoniene et al.[45].

The pathogenesis of depression is a complex process, and it has been associated with neuronal atrophy or loss of neuronal plasticity in the pre-frontal cortex and hippocampus[46], as well as low levels of brain derived neurotrophic factor (BDNF)[47]. Chronic stress causes an increase in cortisol levels[9] and activates the immune system, resulting in increased levels of pro-inflammatory cytokines[48]. Activation of the immune response in the central nervous system, mainly through of microglia and astrocyte activation, plays a role in the development of degenerative processes in the brain[49,50].

High cortisol levels may cause atrophy in the hippocampus[51] and reduction in the serotoninergic reserves[52,53], and according to Tafet et al.[54], high cortisol levels augment serotonin recapture, reducing the serotonin levels in synapses.

Brain derived neurotrophic factor (BDNF) modulates neuronal growth and survival, and according to Tang et al.[55] and Agapouda et al.[56], RRE increases BDNF expression in the hippocampus of rats, indicating the neuroprotective effect of RR. In addition, Lee et al.[57] and Wang et al.[58] demonstrated the anti-inflammatory effect of RR or of salidroside, its major bioactive component, with inhibition of IL-6 and TNF-α expression and nitric oxide generation, reducing neuroinflammation, which in turn may lead to neurodegenerative disorders[59,60]. The mechanism of action of RRE is based on its constituent components, primarily salidroside. Salidroside has neuroprotective effects and mitigates depression symptoms in humans due to improvement in neuronal functions, the integrity and proliferation of hippocampal cells, in addition to reduced neuroinflammation processes, increased serotonin levels, and reduced cortisol levels[61,62].

Neuroprotective activity is attributed to decreased

oxidative stress and increased antioxidant enzymes[63]. Decreased inflammation through suppression of proinflammatory factors inducing nitric oxide synthase (iNOS), IL-1β, and TNF-α in the brain was seen in mice after oral administration of *Rhodiola rosea* crude extract[64].

Chronic stress is associated with neuroinflammation and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated secretion of glucocorticoids[65], predominantly cortisol in humans. Furthermore, evidence from rodent models indicates that *Rhodiola rosea* and its bioactive constituents may enhance serotonin concentrations in the cortex, brainstem, and hypothalamus. This effect appears to be mediated by the inhibition of enzymatic pathways involved in serotonin degradation[66].

Other medicinal plants with antidepressant properties exhibit similar mechanisms of action, such as *Bacopa monnieri* and *Curcuma longa* which inhibit the activity of MAO enzymes and modulate the BDNF expression in the hippocampus; or *Hypericum perforatum* which inhibits the reuptake of monoamine neurotransmitters, thereby increasing their synaptic availability[67-73].

Rhodiola rosea has been safely used in studies lasting 6 to 12 weeks and rarely causes adverse events such as: dizziness, dry mouth or excessive saliva production[74], agitation, insomnia, or irritability[75]. Edwards et al.[76] reported that the adverse events from RR use were mild, and no serious adverse events were reported during the treatment period (4 weeks), since the extract was considered safe and well tolerated by the patients.

Evaluation of the included studies

Evaluations of the methodological quality of the included studies are found in Supplementary Table 1. All 3 studies generally presented good methodological quality and were of low risk of bias. All the studies were categorized as evidence level IB (Supplementary Table 1), according to Johns Hopkins Nursing Evidence Based Practice[77]. This means they reasonably presented consistent results; sufficient sample size for the study design; some control and fairly definitive conclusions; and reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence.

LIMITATIONS

This study presents some limitations. First, it was not possible to determine a dosage recommendation for humans due to the small number of studies involving human beings. Another limitation is the fact that there were no studies found involving children or lactating or pregnant women with some depression level. The age variation among the participants in studies (18-70 years in Darbinyan et al.[39], 18-50 years in Gao et al.[41], and above 18 years in Mao et al. [40]) may be a limitation because different effects can occur in people with such different ages. It was not possible to evaluate the effect of *Rhodiola rosea* in combination with another intervention type. Finally, non-inclusion of the Embase database may have influenced the small number of obtained studies.

CONCLUSION

Using *Rhodiola rosea* extract reduces the severity of depression symptoms and the conditions which trigger depression.

AUTHOR CONTRIBUTIONS: Maria Cristina de Oliveira: conceptualization, methodology, investigation, writing-original draft preparation, and editing. Thwphysow Fhelyphy Ferreira Santos: data collection. Jacqueline da Silva Guimarães dos Santos: investigation, supervision, reviewing and editing.

REFERENCES

1. WHO – World Health Organization. Depressive disorder (depression). 2023. https://www.who.int/news-room/fact-sheets/detail/depression
2. WHO – World Health Organization. COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. 2022. https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide
3. Park LT, Zarate Jr CA. Depression in the primary care setting. N Engl J Med. 2019. 380(6):559-68. Doi: https://doi.org/10.1056/NEJMcp1712493
4. Opel N, Redlich R, Zwanzger P, Grotegerd D, Arolt V, Heindel W, Konrad C, Kugel H, Dannlowski U. Hippocamapl atrophy in major depression: a function of childhood maltreatment rather than diagnosis? Neuropsychopharmacol. 2014;39:2723-31. Doi: https://doi.org/10.1038/npp.2014.145
5. Santos MAO, Bezerra LS, Carvalho ARMR, Brainer-Lima AM. Global hippocampal atrophy in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Trends Psych Psychot. 2018;40(4):369-78. Doi: https://doi.org/10.1590/2237-6089-2017-0130
6. Aleem D., Thid H. Pro-inflammatory cytokines, biomarkers, genetics and the immune system: a mechanistic approach of depression and psoriasis. Rev Colomb Psiquiatr. 2018;47(3):177-86. Doi: https://doi.org/10.1016/j.rcp.2017.03.002
7. Troubat R. Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C, Camus V. Neuroinflammation and depression: a review. Eur J Neurosci. 2021;53(1):151-71. Doi: https://doi.org/10.1111/ejn.14720
8. Shao X, Zhu G. Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder. Front Psychiat. 202;11:381. Doi: https://doi.org/10.3389/fpsyt.2020.00381
9. Qin DD, Rizak J, Feng XL, Yang SC, Lü LB, Pan L, Yin Y, Hu XT. Prolonged secretion of cortisol as a possible

mechanism underlying stress and depressive behaviour. Sci Rep. 2016;6:30187. Doi: https://doi.org/10.1038/srep30187

10. Lively S, Schlichter L. Microglia responses to pro-inflammatory stimuli (LPS, IFN_Y + TNFα) and reprogramming by resolving cytokines (IL-4, IL-10). Fron Cell Neurosci. 2018;12:215. Doi: https://doi.org/10.3389/fncel.2018.00215
11. Wohleb ES, Powell ND, Godbout JP, Sheridan JF. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. J Neurosci. 2013;33(34):13820-33. Doi: https://doi.org/10.1523/jneurosci.1671-13.2013
12. Coppen A. The biochemistry of affective disorders. Br J Psychiatry. 1967;113(504):1237-64. Doi: https://doi.org/10.1192/bjp.113.504.1237
13. Liu Y, Zhao J, Guo W. Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Front Psychol. 2018;9:2201. Doi: https://doi.org/10.3389/fpsyg.2018.02201
14. Rot MAH, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ. 2009;180(3):305-13. Doi: https://doi.org/10.1503/cmaj.080697
15. Masi G, Brovedani P. The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. CNS Drugs. 2011;25:913-31. Doi: https://doi.org/10.2165/11595900-000000000-00000
16. Liu H, Lv P, Wu H, Zhang K, Xu F, Zheng L, Zhao J. The proliferation enhancing effects of salidroside of Schwann cells in vitro. Evid Based Complem Alternat Med. 2017;2017: 4673289. Doi: https://doi.org/10.1155/2017/4673289
17. Ho SC, Jacob SA, Tangiisuran B. Barriers and facilitators of adherence to antidepressants among outpatients with major depressive disorder: a qualitative study. PLoS One. 2017;12(6): e0179290. Doi: https://doi.org/10.1371/journal.pone.0179290
18. Solmi M, Miola A, Croatto G, Pigato G, Favaro A, Fornaro M, et al. How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. Braz J Psychiatry. 2021;43(2): 189-202. Doi: https://doi.org/10.1590/1516-4446-2020-0935
19. Hirschfeld RMA. The epidemiology of depression and the evolution of treatment. J Clin Psychiatry. 2012;73(Suppl. 1):5-9. Doi: https://doi.org/10.4088/jcp.11096su1c.01
20. Marasine NR, Sankhi S. Factors associated with antidepressant medication non-adherence. Turk J Pharm Sci. 2021;18(2):242-9. Doi: https://doi.org/10.4274/tjps.galenos.2020.49799
21. Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? Innov. Clin. Neurosci. 2012; 9(4-5): 41-6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398686/pdf/icns_9_5-6_41.pdf
22. Kubentayev SA, Zhumagul MZ, Kurmanbayeva MS, Alibekov DT, Kotukhouv J, Sitpayeva GT, et al. Current state of populations of *Rhodiola rosea* L. (Crassulaceae) in East Kazakstan. Bot Stud. 2021;62:19. Doi: https://doi.org/10.1186/s40529-021-00327-4
23. Shevtsov VA, Zholus BI, Shrevarly VI, Vol'skij VB, Korovin YP, Khristich MP, et al. A randomized trial of two different doses of a SHR-5 Rhodiola rosea extract versus placebo and control of capacity for mental work. Phytomedicine. 2003;10(2-3): 95-105. Doi: https://doi.org/10.1078/094471103321659780
24. Zhang L, Yu H, Zhao X, Lin X, Tan C, Gao G, et al. Neuroprotective effects of salidroside against beta-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells. Neurochem Int. 2010;57(5):547-55. Doi: https://doi.org/10.1016/j.neuint.2010.06.021
25. Panossian A, Wikmar G. Effects of adaptogens on the central nervous system and the molecular mechanisms associated with their stress – protective activity. Pharmaceuticals. 2010;3(1):188-224. Doi: https://doi.org/10.3390/ph3010188
26. Cai L, Wang H, Li Q, Qian Y, Yao W. Salidroside inhibits H_2O_2-induced apoptosis in PC_{12} cells by preventing cytochrome C release and inactivating of caspase cascade. Acta Biochim Biophys Sin. 2008;40(9):796-802. Doi: https://doi.org/10.1111/j.1745-7270.2008.00463.x
27. Jacob R, Nalini G. Chidambaranathan, N. Neuroprotective effect of Rhodiola rosea Linn against MPTP induced cognitive impairment and oxidative stress. Ann Neurosci. 2013;20(2): 47-51. Doi: https://doi.org/10.5214/ans.0972.7531.200204
28. Ishaque S, Shamseer L, Bukutu C, Vohra S. Rhodiola rosea for physical and mental fatigue: a systematic review. BMC Complement. Altern Med. 2012;12:70. Doi: https://doi.org/10.1186/1472-6882-12-70
29. Cropley M, Banks AP, Boyle J. The effects of *Rhodiola rosea* L. extract on anxiety, stress, cognition and other mood symptoms. Phytother Res. 2015;29(12):1934-9. Doi: https://doi.org/10.1002/ptr.5486
30. Dimpfel W, Schombert L, Panossian AG. Assessing the quality and potential efficacy of commercial extracts of *Rhodiola rosea* L. by analyzing the salidroside and rosavin content and the electrophysiological activity in hippocampal long-term potentiation, a synaptic model of memory. Front Pharmacol. 2018;9:425. Doi: https://doi.org/10.3389/fphar.2018.00425
31. Koop T, Dienel A, Heldmann M, Münte TF. Effects of a *Rhodiola rosea* extract on mental resource allocation and attention: an event-related potential dual task study. Phytother Res. 2020;34(12):3287-97. Doi: https://doi.org/10.1002/ptr.6778
32. Hamidpour R, Hamidpour S, Hamidpour M, Shahlari M, Sohraby M, Shahlari N, et al. Chemistry, pharmacology and medicinal property of *Rhodiola rosea* from the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. Int J Case Rep. Images. 2015;6(11):661-71. Doi: https://doi.org/10.5348/ijcri-201458-RA-10013
33. Amsterdam JD, Panossian AG. *Rhodiola rosea* L. as a putative botanical antidepressant. Phytomedicine. 2016;23(7):770-83. Doi: https://doi.org/10.1016/j.phymed.2016.02.009
34. Kapalka GM. ADHD. *In:* Kapalka GM. (ed.) Nutritional and Herbal Therapies for Children and Adolescents. 2010; p. 101-40. Doi: https://doi.org/10.1016/B978-0-12-374927-7.00005-4
35. Brown RP, Gerbarg PL, Ramazanov Z. Rhodiola rosea: a phytomedicinal overview. HerbalGram. 2002; 56: 40-52. https://www.herbalgram.org/resources/herbalgram/issues/56/table-of-contents/article2333/
36. van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. J Ethnopharmacol. 2009;122(2):397-401. Doi: https://

doi.org/10.1016/j.jep.2009.01.007

37. Ouzzani M, Hammady H, Fedorowicz Z. Elmagarmid, A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5:210. Doi: https://doi.org/10.1186/s13643-016-0384-4

38. Nice – National Institute for Health and Care Excellence. Methods for development of NICE public health guidance. 3rd ed. https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies

39. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmström C, Panossian A. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. Nord J Psychiatry. 2007;61(5):343-8. https://doi.org/10.1080/08039480701643290

40. Mao JJ, Xie SX, Zee J, Soeller I, Li QS, Rockwell K, et al. Rhodiola rosea versus sertraline for major depressive disorder: a randomized placebo-controlled trial. Phytomedicine. 2015;22(3):394-9. https://doi.org/10.1016/j.phymed.2015.01.010

41. Gao L, Wu G, Liao Y, Wang J. Antidepressants effects of Rhodiola capsule combined with sertraline for major depressive disorder: a randomized double-blind placebo-controlled clinical trial. J Affect Disord. 2020;265,99-103. Doi: https://doi.org/10.1016/j.jad.2020.01.065

42. Bech P. Fifty years with the Hamilton scales for anxiety and depression. Psychother Psychosom. 2009;78(4):202-11. https://doi.org/10.1159/000214441

43. Jackson-Koku G. Bech depression inventory. Occup Med. 2016;66(2):174-75. Doi: https://doi.org/10.1093/occmed/kqv087

44. Lu Y, Deng B, Xu L, Liu H, Song Y, Lin F. Effects of Rhodiola rosea supplementation on exercise and sport: a systematic review. Front Nutr. 2022;9:856287. Doi: https://doi.org/10.3389/fnut.2022.856287

45. Bernatoniene J, Jakstas V, Kopustinskiene DM. Phenolic compounds of *Rhodiola rosea* L. as the potential alternative therapy in the treatment of chronic diseases. Int J Mol Sci. 2023;24(15):12293. Doi: https://doi.org/10.3390/ijms241512293

46. Duman RS, Deyama S, Fogaça MV. Role of BDNF in the pathophysiology and treatment of depression: activity-dependent effects distinguish rapid-acting antidepressants. Eur J Neurosci. 2021;53(1):126-39. Doi: https://doi.org/10.1111/ejn.14630

47. Castrén E, Monteggia L. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021;90(2):128-36. Doi: https://doi.org/10.1016/j.biopsych.2021.05.008

48. Himmerich H, Patsalos O, Lichtblau N, Ibrahim MAA. Cytokine research in depression: principles, challenges, and open questions. Front Psychiatry. 2019;10:30. Doi: https://doi.org/10.3389/fpsyt.2019.00030

49. Pu WL, Zhang MY, Bai RY, Sun LK, Li WH, Yu YL, et al. Anti-inflammatory effects of *Rhodiola rosea* L: a review. Biomed Pharmacother. 2020;121:109552. Doi: https://doi.org/10.1016/j.biopha.2019.109552

50. Schramm E, Waisman A. Microglia as central protagonists in the chronic stress response. Neurol Neuroimmunol Neuroinflamm 2022;9: e200023. Doi: https://doi.org/10.1212/NXI.0000000000200023

51. White S, Mauer R, Lange C, Klimecki O, Huijbers W, Wirth M. The effect of plasma cortisol on hippocampal atrophy and clinical progression in mild cognitive impairment. Alzheimer's Dement. 2023;15:e12463. https://doi.org/10.1002/dad2.12463

52. Chaves LGS, Gama DRN, Castro JBP, Oliveira KRSG, Vale RGS. Cortisol and serotonin levels in schizophrenic in patients undergoing aerobic training. Rev Bras Med Esp. 2020;26(4):307-11. Doi: https://doi.org/10.1590/1517-869220202604224027

53. Sumekar TA, Jusup I, Wardani ND, Hadiati T, Sulchan M, Fitrikasari A. The role of zinc intake in serotonin and cortisol level in patient with depression. J Biomed Transl Res. 2022;8(1):26-31. Doi: https://doi.org/10.14710/jbtr.v1i1.13808

54. Tafet GE, Toister-Achituv M, Shinitzky M. Enhancement of serotonin uptake by cortisol: a possible link between stress and depression. Cogn Affect Behav Neurosci. 2001;1(1):96-104. Doi: https://doi.org/10.3758/cabn.1.1.96

55. Tang H, Wang J, Zhao L, Zhao XM. Rhodiola rosea L extract shows protective activity against Alzheimer's disease in 3xTg-AD mice. Trop J Pharm Res. 2017;16(3):509-14. Doi: http://dx.doi.org/10.4314/tjpr.v16i3.3

56. Agapouda A, Grimm A, Lejri I, Eckert A. Rhodiola rosea extract counteracts stress in an adaptogenic response curve manner via elimination of ROS and induction of neurite outgrowth. Oxid Med Cell Longev. 2022;2022:5647599. Doi: https://doi.org/10.1155/2022/5647599

57. Lee Y, Jung JC, Jang S, Kim J, Ali Z, Khan IA, et al. Anti-inflammatory and neuroprotective effects of constituents isolated from *Rhodiola rosea.* Evid Based Complement Alternat Med. 2013;514049. Doi: http://dx.doi.org/10.1155/2013/514049

58. Wang J, Zhang YL, Zhuang N. Salidroside inhibits inflammatory factor release in BV-2 cells through p38 JNK pathways. Acta Phys Sin. 2018;70(3):245-52. Doi: https://doi.org/10.13294/j.aps.2018.0017

59. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Front Aging Neurosci. 2024;16:1347987. Doi: https://doi.org/10.3389/fnagi.2024.1347987

60. Giri PM, Banerjee A, Ghosal A, Layek B. Neuroinflammation in neurodegenerative disorders: current knowledge and therapeutic implications. Int J Mol Sci. 2024;25(7):3995. Doi: https://doi.org/10.3390/ijms25073995

61. Yang SJ, Yu HY, Kang DY, Ma ZQ, Qu R, Fu Q, et al. Antidepressant-like effects of salidroside on olfactory bulbectomy-induced pro-inflammatory cytokine production and hyperactivity of HPA axis in rat. Pharmacol Biochem Behav. 2014;124:451-7. Doi: https://doi.org/10.1016/j.pbb.2014.07.015

62. Zhu L, Wei T, Gao J, Chang X, He H, Miao M, et al. Salidroside attenuates lipopolysaccharide (LPS) induced serum cytokines and depressive-like behavior in mice. Neurosci Lett. 2015;606:1-6. Doi: https://doi.org/10.1016/j.neulet.2015.08.025

63. Zhou Q, Han X, Li R, Zhao W, Bai B, Yan C, et.al. X. Anti-atherosclerosis of oligomeric proanthocyanidins from Rhodiola rosea on rat model via hypolipemic, antioxidant, anti-inflammatory activities together with regulation of endothelial function. Phytomed. 2018;51:171-80. Doi: https://doi.org/10.1016/j.phymed.2018.10.002

64. Lee Y, Jung JC, Jang S, Kim J, Ali Z, Khan IA, et al. Anti-inflammatory and neuroprotective effects of constituents isolated from *Rhodiola rosea.* Evid Based Compplem Alternat Med.

2013;2013:514049. Doi: https://doi.org/10.1155/2013/514049

65. Panossian A, Hambardzumyan M, Hovhanissyan A, Wikman G. The adaptogens rhodiola and schizandra modify the response to immobilization stress in rabbits by suppressing the increase of phosphorylated stress-activated protein kinase, nitric oxide and cortisol. Drug Target Insights. 2007;2:39-54. https://pmc.ncbi.nlm.nih.gov/articles/PMC3155223/

66. Van Diermen D, Marston A, Bravo J, Reist M, Carrupt PA, Hostettmann K. Monoamine oxidase inhibition by Rhodiola rosea L. roots. J Ethnopharmacol. 2009;122(2):397-401. Doi: https://doi.org/10.1016/j.jep.2009.01.007

67. Oliveira JT, Pieniz S. Curcumin in Alzheimer's disease and depression: therapeutic potential and mechanisms of action. Braz Arch Biol Technol. 2024;67:e24220004. Doi: https://doi.org/10.1590/1678-4324-2024220004

68. Nurzyńska-Wierdak R. Plants with potential importance in supporting the treatment of depression: current trends, and research. Pharmaceuticals. 2024;17:1489. Doi: https://doi.org/10.3390/ph17111489

69. Moragrega I, Ríos JL. Medicinal plants in the treatment of depression: evidence from clinical trials. Planta Med. 2022;88(12):1092-110. Doi: https://doi.org/10.1055/a-1517-6882

70. Moragrega I, Ríos JL. Medicinal plants in the treatment of depression: evidence from preclinical studies. Planta Med. 2021;87(9):656-85. Doi: https://doi.org/10.1055/a-1338-1011

71. Setorki M. Medicinal herbs with anti-depressant effects. J Herbmed Pharmacol. 2020;9(4):309-17. Doi: https://doi.org/10.34172/jhp.2020.39

72. Pardhe HA, Nagalakshmi NC, Hariprasad MG, Chourasia PK, Nandini S. A review: medicinal plants with antidepressant properties. IP Indian J Neurosci. 2020;6(1):1-5. Doi: https://doi.org/10.18231/j.ijn.2020.001

73. Martins J, Brijesh S. Phytochemistry and pharmacology of anti-depressant medicinal plants: a review. Biomed Pharmacother. 2018;104:343-65. Doi: https://doi.org/10.1016/j.biopha.2018.05.044

74. National Center for Complementary and Integrative Review. 2020. Rhodiola. https://www.nccih.nih.gov/health/rhodiola

75. Berry J, Eagle R. 2024. What are the health benefits of Rhodiola rosea? https://www.medicalnewstoday.com/articles/319619#physical-performance

76. Edwards D, Heufelder A, Zimmermann A. Therapeutic effects and safety of *Rhodiola rosea* extract WS® 1375 in subjects with life-stress symptoms – results of an open-label study. Phytother Res. 2012;26(8):1220-5. Doi: https://doi.org/10.1002/ptr.3712

77. MCW – Medical College of Wisconsin. 2023. Evidence based practice: study designs & evidence levels. Doi: https://mcw.libguides.com/c.php?g=644314&p=4643389

Received: 2024, August 07
Accepted: 2025, August 12