REVIEW ARTICLE

RHODIOLA ROSEA LINNAEUS IMPROVES LEARNING, MEMORY, AND SYMPTOMS OF DEPRESSION – AN INTEGRATIVE REVIEW

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Highlights: (1) The use of *Rhodiola rosea* (RR) improves learning capacity and memory formation. (2) Salidroside, a component of RR, stimulates neurogenesis in the hippocampus. (3) RR increases serotonin levels in neuronal synapses.

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RHODIOLA ROSEA LINNAEUS IMPROVES LEARNING, MEMORY, AND SYMPTOMS OF DEPRESSION – AN INTEGRATIVE REVIEW

ABSTRACT

Traditional antidepressants are associated with side effects that lead to treatment discontinuation. Natural alternatives have been studied, such as *Rhodiola rosea* (RR), for treating depression. This integrative review investigated the effects of RR in animals with induced depression to assess its effectiveness in alleviating depressive symptoms and improving learning and memory. The PubMed, Scopus, Web of Science, and ScienceDirect databases were searched for relevant studies using the terms "Salidroside," "Rhodioloside," "Rhodiola rosea," "depression," "depressive disorder," "depression, chemical," and "animal." The RR extract and salidroside were evaluated in six and eight studies, respectively. RR extract and salidroside improve cognitive function, neuroplasticity, and serotonin and corticosterone levels in rats. Using *Rhodiola rosea* extract or salidroside improves learning and memory and reduces neuronal damage caused by depression.

Keywords: Antidepressant agent; neurogenesis; "golden root".

INTRODUCTION

Approximately 5% of adults suffer from depression, and Brazil ranks first and second in prevalence in Latin America and the Americas, respectively[1,2], following the United States, with 32,237 individuals admitted to hospitals in 2022[3].

Depression is associated with reduced neurotransmitter levels and deficits in attention, learning, memory, concentration, and decision-making ability. The hippocampus is involved in the control of memory and emotion. Reduced hippocampal volume has been observed in major depressive disorders and is considered a diagnostic marker of depression. Hippocampal atrophy results from neuronal and glial cell loss, inhibited neurogenesis, or diminished neurotrophic factors,[7] correlating with the severity of depression. Synaptic plasticity in the hippocampus is crucial for memory formation.[8]

Chronic stress is a risk factor of depression and may induce neuroinflammation. Microglial activation leads to the release of pro-inflammatory cytokines (PICs), which are correlated with the severity of depressive symptoms. Selective serotonin reuptake inhibitors exert anti-inflammatory effects by reducing PIC production. Several studies

have associated reduced monoaminergic neurotransmitter levels with the etiology of depression. Serotonin deficiency may exacerbate negative emotions.[13,14] Reduced norepinephrine levels in patients with depression are associated with negative emotions, such as lack of pleasure, interest, energy, and loss of confidence. The same effect is observed with reduced dopamine levels[16], and according to Dubol et al.[17], healthy individuals exhibit greater presynaptic dopaminergic function than patients with depression.

Stress may induce persistent hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, increasing corticotropin-releasing hormones and cortisol, and hypoactivity of the hippocampus. Adrenal steroids may cause hippocampal neuronal atrophy, resulting in learning and memory impairment.

Traditional antidepressants have several side effects, and natural alternatives have been studied, such as the use of *Rhodiola rosea* L. or its component, salidroside (SAL), in the treatment of depression. *R. rosea* L. contains >140 different compounds, with SAL being the main bioactive component, and its properties include anti-inflammatory, antioxidant, antidepressant, and neuroprotective activities. Phytotherapy is included in the National Policy on Integrative and Complementary Practices implemented within the Brazilian Unified Health System.

Rats with memory deficits treated with *R. rosea* extract (RRE) show improvements in cognitive function. Vasileva et al. observed that RRE improved locomotor activity and reduced PIC levels in rats with depression. Liu et al.[23] revealed in vitro the neuroprotective effects of SAL. The authors reported greater proliferation and viability of the nerve cells. Jin et al. evaluated the use of SAL in young and aged rats and found that aged rats exhibited mental performance (learning and memory) comparable to young rats.

This integrative review of the effects of RRE and SAL in animals with induced depression was conducted to determine their effectiveness in alleviating depressive symptoms and improving learning ability and memory formation.

METHODS

Search strategy and eligibility criteria: The search was conducted on July 20, 2022, and updated on July 16, 2025, using the PubMed, Scopus, Web of Science, and ScienceDirect databases and terms, such as "Salidroside," "Rhodioloside," "Rhodiola rosea," "depression," "depressive disorder," "depression, chemical," and "animal." The search strategy was (Salidroside OR rhodioloside OR Rhodiola rosea) AND (depression OR depressive disorder OR depression, chemical) AND animal. The PICO acronym was used to determine the eligibility criteria for the studies, as follows:

Patients: Laboratory animals with induced depression

Intervention: Salidroside or RRE

Comparison between placebo and traditional antidepressants

Outcome: Improved learning and memory, hippocampal neuroplasticity, hormone and neurotransmitter levels, and reduced production of proinflammatory cytokines (PICs).

The inclusion and exclusion criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria adopted in the integrative review of the effects of RRE and SAL in animals with induced depression

Inclusion criteria	Exclusion criteria
Studies: 1. Studies involving animals with induced depression. 2. Use of SAL or RRE in the treatment of the animals. 3. Inclusion of a control group. 4. Original, peer-reviewed research. 5. No restriction on language or year of publication.	Studies: 1. Studies that were not original research. 2. Duplicate studies. 3. Studies involving clinical conditions other than depression. 4. Studies involving other plant species or substances other than *R. rosea* or SAL. 5. Studies involving healthy animals.

Study selection: The studies were exported to the Rayyan platform.[25] Two reviewers identified eligible titles and abstracts. Selected studies were read in full and assessed using the same criteria. Duplicates were detected by comparing the authors' names and

excluded from the platform. Discrepancies were identified and resolved via reviewer discussions.

Data extraction process: The following data were extracted and analyzed; authorship, year of publication, intervention, duration of the intervention, main outcomes obtained in behavioral tests, hippocampal neuroplasticity, brain-derived neurotrophic factor (BDNF) expression, serotonin and norepinephrine levels in the brain, levels of PICs in the hippocampus, serum corticosterone (CORT) levels, and corticotropin-releasing hormone (CRH) levels.

RESULTS

Study selection: After searching, 758 references were identified, of which 502 were not research articles. After screening, 256 potentially eligible studies were exported to the Rayyan platform. After excluding duplicates and evaluating the titles, abstracts, and full texts, 11 studies[26–36] met the eligibility criteria (Figure 1).

Study characteristics: RRE and SAL were evaluated in three and eight studies, respectively. The animals were induced to develop depression via stress resulting from corticosterone[36] or lipopolysaccharide[31] injections, food and water deprivation,[28,29,34,35] changes in handling,[34,35] exhaustive physical activity,[26,27] or olfactory bulbectomy.[30,33] Amitriptyline[29,30,33] imipramine,[27] and fluoxetine[28,29,31,34,36] were used in the control groups (Table 2).

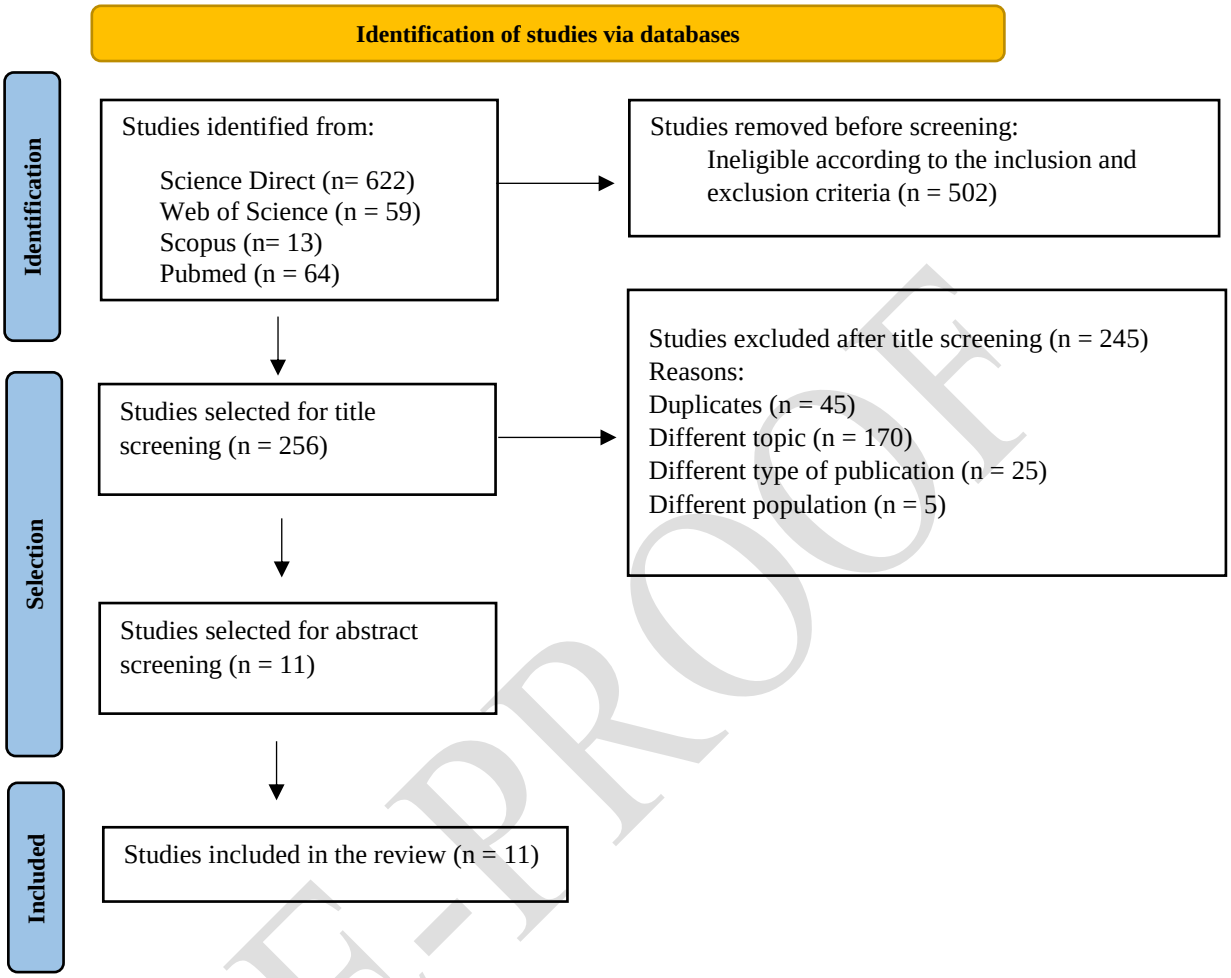

Figure 1. Flowchart of the study selection process for the integrative review on the effects of RRE or salidroside in rats with induced depression.

Table 2. Characteristics of the studies on the effects of RRE and SAL in rodents

Reference	Type of extract and content of active compounds	Intervention	Duration (days)
Perfumi and Mattioli[26]	Dry hydroalcoholic extract Rosavin 3% and salidroside 1%	RRE - 10, 15, and 20 mg/kg Placebo	1
Panossian et al.[27]	Type of extract not reported Rosavin: 6%; tirosol: 0.8%, and salidrosídeo: 2.7%	REE - 10, 20, and 50 mg/kg AMI - 3 mg/kg IMI - 30 mg/kg	3
Chen et al. [28]	-	SAL – 60, 120, and 240 mg/kg FLU - 2.2 mg/kg	21
Mattioli et al. [29]	Dry hydroalcoholic extract Rosavin 3% and salidroside 1%	RRE – 10, 15, and 20 mg/kg FLU - 10 mg/kg	21
Yang et al. [30]	-	SAL - 20 and 40 mg/kg AMI - 10 mg/kg	14
Zhu et al. [31]	-	SAL - 12 and 24 mg/kg FLU - 20 mg/kg	5
Palmeri et al. [32]	-	SAL - 25 mg/kg Placebo	3
Zhang et al. [33]	-	SAL - 20 and 40 mg/kg AMI - 10 mg/kg	14
Vasileva et al. [34]	-	SAL - 5 mg/kg FLU - 2.5 mg/kg	8
Fan et al. [35]	-	SAL - 10 mg/kg Placebo	14
Chai et al. [36]	-	SAL - 20 and 40 mg/kg FLU - 20 mg/kg	21

AMI, amitriptyline; IMI, imipramine; FLU, fluoxetine.

Assessment of learning and memory ability: The behavioral test results are presented in Table 3. Exploratory and locomotor abilities were evaluated using the Open Field Test (OFT).[37] Animals with induced depressive-like behavior exhibited reduced locomotor activity in the tests. As demonstrated by Ozcan et al.,[38] animals subjected to olfactory bulbectomy showed abnormal behavior, such as hyperactivity in novel environments. RRE (15–20 mg/kg) or SAL (5–40 mg/kg) administration increased horizontal and

vertical motor activities, total distance traveled, and time spent in the central zone. Additionally, they reduced hyperactivity in bulbectomized rodents, indicating reversed induced behavior. These effects were similar to those obtained with fluoxetine[29,34,36] and amitriptyline.[30]

The Sucrose Preference Test (SPF) is used to assess anhedonia, a main symptom of depression,[39] and based on rodents' preference for sweet substances, assuming that this preference is proportional to the pleasure experienced in consuming them.[40] Animals with induced depression consumed less water and sucrose/glucose, suggesting reduced pleasure associated with drinking the solution. Using SAL (5–60 mg/kg) or RRE (10–20 mg/kg) increased beverage consumption similarly to fluoxetine[28,29,34,36] or amitriptyline.[33]

The Forced Swim Test (FST) is based on the premise that if an animal is placed in a container filled with water, it attempts to escape or exhibits immobility as a measure of behavioral despair. RRE (10–50 mg/kg) or SAL (5–40 mg/kg) increased swimming time and reduced the time the animal took to find the escape platform and decreased immobility time, similarly to the effects observed with imipramine,[26] amitriptyline,[26,30] and fluoxetine.[31,33,36]

Effect of SAL in animals with induced depression on:

a) Neurogenesis and BDNF expression in the hippocampus: SAL (20–60 mg/kg) promotes neurogenesis in the hippocampus of rodents. SAL administration at 12–40 mg/kg resulted in greater BDNF gene expression in the animals' hippocampus, an effect similar to that obtained with fluoxetine[33,36] and superior to that observed with amitriptyline[30] (Table 4).

b) Serotonin (5-HT) levels: SAL (24–120 mg/kg) in rodents increased serotonin levels in the hippocampus[28] and frontal and prefrontal cortex,[31,33] with results similar to those observed with fluoxetine[28] and amitriptyline[33] (Table 4).

c) Expression of PICs in the hippocampus: Reduced PIC levels and neuroinflammation was observed following SAL administration (5–40 mg/kg). This effect was superior to that obtained with amitriptyline[31] and similar to that noted with fluoxetine[33,34,36] (Table 4).

Table 3. Results obtained in rodents with induced depression treated with SAL or RRE in behavioral tests

Reference	Main results		
	OFT	SPT	FST
Perfumi and Mattioli[26]	↑ distance traveled, ambulation time, and number of rearings (times the animal stood on its hind legs) RRE (15 mg/kg)	NR	↓ immobility time and ↑ swimming time
Panossian et al. [27]	NR	NR	↓ immobility time, with RRE producing a greater effect than that obtained with IMI or AMI
Chen et al. [28]	NR	↑ consumption with SAL (60 mg/kg) and FLU	NR
Mattioli et al. [29]	↑ ambulation time with RRE (20 mg/kg) and FLU	↑ consumption with RRE (20 mg/kg) and with FLU	NR
Yang et al. [30]	↓ hyperactivity with SAL and AMI	NR	↓ immobility time with SAL and AMI
Zhu et al. [31]	NR	NR	↓ immobility time with SAL and FLU
Palmeri et al. [32]	↑ time spent in the central area and ↑ number of crossings	NR	NR
Zhang et al. [33]	NR	↑ consumption with SAL and AMI	NR
Vasileva et al. [34]	↑ horizontal and vertical locomotion with SAL and FLU	↑ consumption with SAL and FLU	↓ time spent to find the escape platform with SAL and FLU
Fan et al.[35]	↑ mobility and ↓ rest time	No difference between treatments	↑ swimming time with SAL
Chai et al. [36]	↑ mobility, time spent in the central arena, and average movement speed with SAL (40 mg/kg) and FLU	↑ consumption with SAL (20 and 40 mg/kg) and FLU	↓ immobility time with SAL and FLU

OFT, Open Field Test; TSP, Sucrose Preference Test; FST, Forced Swim Test; NR, not reported; AMI, amitriptyline; FLU, fluoxetine; IMI, imipramine.

Table 4. Neurogenesis, hippocampal BDNF expression, serotonin (5-HT) levels, pro-inflammatory cytokines (PICs) in the hippocampus, serum corticosterone (CORT), and corticotropin-releasing hormone (CRH) in the hypothalamus of rodents with induced depression treated with SAL

Authorship	Neurogenesis	BDNF	SER	PICs	CORT	CRH
Chen et al. [28]	↑ with SAL (60 mg/kg) and FLU	NR	↑ with SAL at 60 and 120 mg/kg and with FLU	NR	NR	NR
Yang et al. [30]	NR	↑ with SAL, with the effect being superior to that obtained with AMI	NR	↓ with SAL and AMI Effect more pronounced with SAL use	↓ with SAL and AMI Effect more pronounced with SAL use (20 mg/kg)	↓ with SAL and AMI Effect more pronounced with SAL use (20 mg/kg)
Zhu et al. [31]	NR	↑ with SAL and FLU	↑ with SAL (24 mg/kg) and FLU	↓ with SAL and FLU	NR	NR
Zhang et al. [33]	NR	NR	↑ with SAL (40 mg/kg) and AMI	↓ with SAL and AMI	NR	NR
Vasileva et al. [34]	NR	NR	NR	↓ with SAL and FLU	NR	NR
Fan et al.[35]	NR	NR	NR	↓ with SAL	NR	NR
Chai et al. [36]	↑ with SAL	↑ with SAL (40 mg/kg) and FLU	NR	↓ with SAL and FLU	NR	NR

NR, not reported; AMI, amitriptyline; FLU, fluoxetine.

d) CORT and CRH levels: Lower serum levels of CORT and CRH were observed in rats treated with SAL (20 mg/kg) or amitriptyline[30] (Table 4).

DISCUSSION

Behavioral tests can analyze learning and memory parameters in rodents. Learning abilities and memory can be affected by depression and other mental disorders. RRE (200 and 400 mg/kg) in rats with induced Alzheimer's disease improved learning and memory deficits. SAL was administered by Jin et al.[24] to rats aged four and 16 months; older rats had shorter escape times and traveled shorter distances to reach the escape platform in the FST than younger animals, indicating improved learning and memory capacity in older rats.

Hippocampal plasticity contributes to memory acquisition and retention, whereas neurogenesis is important for hippocampal function. Oxidative stress influences memory and learning because it can cause neuronal deterioration over time; thus, the antioxidant action of *R. rosea* helps maintain cognitive function by enhancing antioxidant enzyme activity.

Moreover, acetylcholine (ACh) is crucial in learning and memory formation in the hippocampus.[45,46] Acetylcholinesterase (AChE) inhibition increases ACh levels at neuronal synapses and improves these functions. Polumackanycz et al. evaluated 15 commercial RREs and observed AChE inhibition rates ranging from 58.47–93.29%. A similar effect was reported by Wang et al.. According to Kim et al., SAL, rosavin, tyrosol, and rosin inhibited AChE by 11.5%, 11.2%, 9%, and 6.6%, respectively.

SAL (20–60 mg/kg) promotes neurogenesis in the hippocampus of rodents. BDNF is a neurotrophin responsible for the neuronal differentiation, maturation, and proliferation. Its gene expression is highly regulated by factors, such as neuronal activity,[51] exercise,[52] antidepressant use,[53] stress level,[54] and hormones.[55]

In *in vitro* studies, Liu et al. demonstrated that SAL promoted growth and increased Schwann cell viability, while stimulating BDNF gene expression. Several studies have shown the neurotrophic and neuroprotective effects of SAL[56] or RRE[43,57] *in vitro*, with neuroprotection attributed to increased neurotrophic factor expression.

A neuroprotective mechanism involves the antioxidant activities of *R. rosea* and its components. Oxidative stress can damage the cellular DNA, resulting in apoptosis. SAL, tyrosol, rosin, rosavin, and rosarin can reduce intracellular oxidative stress in nerve cells[48] by increasing the activity of superoxide dismutase, glutathione, glutathione peroxidase, and catalase enzymes and reducing lipid peroxidation.[44]

Higher 5-HT levels were observed in rats treated with SAL. Antidepressants, such as fluoxetine, imipramine, and venlafaxine, inhibit serotonin reuptake and increase its levels in synapses. SAL and RRE can increase the cerebral levels of serotonin and norepinephrine. A possible mechanism for this effect is the inhibition of monoamine oxidase (MAO) enzymes A and B, which degrade serotonin, norepinephrine, and adrenaline. The methanolic and aqueous extracts of *R. rosea* inhibited MAO-A activity by 92.5% and 84.3%, respectively. Compounds in the RRE may enhance the transport of serotonin precursors to the brain, thereby improving neurotransmitter levels.

Reduced neuroinflammation has been observed following SAL administration. Studies suggest that high levels of PICs, such as TNF-α, IL-1β, and IL-6, are common in depression,[62] and antidepressants can reduce the production of these cytokines.[63] Rats challenged with endotoxins and treated with SAL (30, 60, and 120 mg/kg) or RRE (500 mg/kg) showed lower TNF-α, IL-1β, and IL-6 levels.[64]

The effects of *R. rosea* on PICs can be attributed to its anti-inflammatory properties. RRE (250 mg/kg) inhibited cyclooxygenase 1 and 2 activity similarly to acetylsalicylic acid in rats. Additionally, dexamethasone and SAL at 40 mg/kg can reduce IL-6 and TNF-α levels in a similar manner.[66]

Lower serum CORT and CRH levels in the hypothalamus of SAL-treated rats. Neurons express receptors for PICs, which cause neuroinflammation and induce activation of the HPA axis.[67] Exposure to stress activates the HPA axis, initiating CRH production in the hypothalamus. This hormone acts on the pituitary gland, causing ACTH secretion, which stimulates the adrenal gland to release corticosterone.[68] However, RRE (5 g/kg) administration in rats subjected to stress for two weeks resulted in lower hypothalamic corticosterone and CRH levels and serum corticosterone levels compared

to non-stressed animals, demonstrating that *R. rosea* can help restore the HPA axis balance.

STUDY LIMITATIONS

The small number of available studies on the use of RRE and SAL makes it challenging to determine the exact dose for each because different doses and methodologies were evaluated in each study. Another limitation was the duration of RRE and SAL administration, ranging from 1–21 days. This variability hinders the comparison of results across selected studies and may compromise the quality of studies, in which treatments were administered for short periods, and the reliability of the review itself.

CONCLUSIONS

The use of RRE (dose; 15–20 mg/kg) or salidroside (dose; 20–60 mg/kg) was effective in improving learning and memory and reducing neuronal damage caused by depression by enhancing neurogenesis and increasing serotonin levels.

Further research should be conducted to deepen our understanding of the use of medicinal plants in the treatment of mental disorders, particularly *Rhodiola rosea* and its components. Besides their beneficial effects on mental disorders, these compounds may be used to enhance physical endurance, reduce stress and cholesterol levels, and slow the aging process.

REFERENCES

1. Carvalho R. Porque o Brasil tem a população mais depressiva da América Latina? 2023. [access at 2025 Aug 2]. Available at https://ipqhc.org.br/2023/11/05/por-que-o-brasil-tem-a-populacao-mais-depressiva-da-america-latina/#:~:text=Assim%20witho%20Maria%2C%20300%20milh%C3%B5es,de%20atendimento%20para%20a%20depress%C3%A3o

2. MS – Ministério da Saúde. Na América Latina, Brasil é o país with maior prevalência de depressão. 2022. [access at 2023 Nov 17].

3. UMANE – Observatório APS – Número de internações por depressão. 2022. [access at 2023 Nov 17]. Available at: https://observatoriodaaps.with.br/tema/depressao

4. McDonald T. How depression affects your thinking skills. Neuroscience News. 2018. [access at 2023 Aug 13]. Available at: https://neurosciencenews.with/depression-thinking-skills-9297/

5. Tai HH, Cha J, Vedaei F, Dunlop BW, Craighead WD, Mayberg HS, Choi KS. Treatment-specific hippocampal subfield volume changes with antidepressant medication or cognitive-behavior therapy in treatment-naïve depression. Front Psychiatry 2021; 12: 718539. https://doi.org/10.3389/fpsyt.2021.718539

6. 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 Psychiatry Psychother 2018; 40(4): 369-378. https://doi.org/10.1590/2237-6089-2017-0130

7. Borba EM, Duarte JA, Bristot G, Scotton E, Camozzato AL, Chaves MLF. Brain-derived neurotrophic factor serum levels and hippocampal volume in mild cognitive impairment and dementia due to Alzheimer disease. Dement Geriatr Cogn Disord Extra 2016; 6(3): 559-567. https://doi.org/10.1159/000450601

8. Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampus atrophy and the longitudinal course of late-life depression. Am J Geriatr Psychiatry 2014; 22(12): 1504-1512. https://doi.org/10.1016/j.jagp.2013.11.004

9. 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 2020; 53(1): 151-171. https://doi.org/10.1111/ejn.14720

10. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, Le NA, Feinberg R, Tansey MG, Miller, AH. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry 2018; 25(6): 1301-1311. https://doi.org/10.1038/s41380-018-0096-3

11. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation withe from? BMC Med 2013; 11: 200. https://doi.org/10.1186/1741-7015-11-200

12. Shao X, Zhu G. Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder. Front Psychiatry 2020; 11: 381. https://doi.org/10.3389/fpsyt.2020.00381

13. Kanen JW, Arntz FE, Yellowlees R, Cardinal RN, Price A, Christmas DM, Apergis-Schoute AM, Sahakian BJ, Robbins TW. Serotonin depletion amplifies distinct human

social emotions as a function of individual differences in personality. Transl Psychiatry 2021; 11(1): 81. https://doi.org/10.1038/s41398-020-00880-9

14. Obermanns J, Flasbeck V, Steinmann S, Juckel G, Emons B. Investigation of the serotoninergic activity and the serotonin content in serum and platelet, and the possible role of the serotonin transporter in patients with depression. Behav Sci 2022; 12(6): 178. https://doi.org/10.3390/bs12060178

15. Liu Y, Zhao J, Guo W. Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. Front Psychol 2018; 9: 2201. https://doi.org/10.3389/fpsyg.2018.02201

16. Belujon P, Grace AA. Dopamine system dysregulation in major depressive disorders. Int J Neuropsychopharmacol 2017; 20(12): 1036-1046. https://doi.org/10.1093/ijnp/pyx056

17. Dubol M, Trichard C, Leroy C, Granger B, Tzavara E, Martinot JL, Artiges E. Lower midbrain dopamine transporter availability in depressed patients: report from high-resolution PET imaging. J Affect Disord 2020; 262: 273-277. https://doi.org/10.1016/j.jad.2019.10.041

18. Tafet GE, Nemeroff CB. The links between stress and depression: psychoneuroendocrinological, genetic, and environmental interactions. Neuropsychiatry Clin Neursci 2016; 28(2): 77-88. https://doi.org/10.1176/appi.neuropsych.15030053

19. Stojcheva EI, Quintela JC. The effectiveness of *Rhodiola rosea* L. preparations in alleviating various aspects of life-stress symptoms and stress-induced conditions – encouraging clinical evidence. Molecules 2022; 27(12): 3902. https://doi.org/10.3390/molecules27123902

20. Tesser CD, Sousa IMC, Nascimento MC. Práticas integrativas e withplementares na atenção primária à saúde brasileira. Saúde Debate 2018; 42(1): 174-188. https://doi.org/10.1590/0103-11042018S112

21. Vasileva LV, Getova DP, Doncheva ND, Marchev AS, Georgiev MI. Beneficial effect of withmercial Rhodiola extract in rats with scopolamine-induced memory impairment on active avoidance. J Ethnopharmacol 2016; 193: 586-591. https://doi.org/10.1016/j.jep.2016.10.011

22. Vasileva LV, Saracheva KE, Ivanovska MV, Petrova AP, Sucouglu E, Murdjeva MA, Getova-Spasova D. Beneficial effect of chronic treatment with extracts from Rhodiola rosea L. and Curcuma longa L. on the immunoreactivity of animals subjected to a chronic mild stress model. Folia Med 2017; 59(4): 443-453. https://doi.org/10.1515/folmed-2017-0046

23. 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 Withplement Alternat Med 2017; 2017: 4673289. https://doi.org/10.1155/2017/4673289

24. Jin H, Pei L, Shu X, Yang X, Yan T, Wu Y, Wei N, Yan H, Wang S, Yao C, Liu D, Tian Q, Wang L, Lu Y. Therapeutic intervention of learning and memory decays by salidroside stimulation of neurogenesis in aging. Mol Neurobiol 2016; 53(2): 851-866. https://doi.org/10.1007/s12035-014-9045-6

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

26. Perfumi M, Mattioli L. Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside *Rhodiola rosea* L. extract in mice. Phytother Res 2007; 21(1): 37-43. https://doi.org/10.1002/ptr.2013

27. Panossian A, Nikoyan N, Ohanyan N, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Withparative study of Rhodiola preparations on behavioral despair of rats. Phytomedicine 2008; 15(1-2): 84-91. https://doi.org/10.1016/j.phymed.2007.10.003

28. Chen QG, Zeng YS, Qu ZQ, Tang JY, Qin YJ, Chung P, Wong R, Hägg U. The effects of Rhodiola rosea extract on 5-HT level, cell proliferation and quantity of neurons at cerebral hippocampus of depressive rats. Phytomedicine 2009; 16(9): 830-838. https://doi.org/10.1016/j.phymed.2009.03.011

29. Mattioli L, Funari C, Perfumi M. Effects of *Rhodiola rosea* L. extract on behavioural and physiological alterations induced by chronic mild stress in female rats. J Psychopharmacol 2009; 23(2): 130-142. https://doi.org/10.1177/0269881108089872

30. Yang SJ, Yu HY, Kang DY, Ma ZQ, Qu R, Fu Q, Ma SP. Antidepressant-like effects of salidroside on olfactory bulbectomy-induced pro-inflammatory cytokine production and hyperactivity of HPA axis in rats. Pharmacol Biochem Behav 2014; 124: 451-457. https://doi.org/10.1016/j.pbb.2014.07.015

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

32. Palmeri A, Mammana L, Tropea MR, Gulisano W, Puzzo D. Salidroside, a bioactive withpound of Rhodiola rosea, ameliorates memory and emotional behavior in adult mice. J Alzheimers Dis 2016; 52(1): 65-75. https://doi.org/10.3233/jad-151159

33. Zhang X, Du Q, Liu C, Yang Y, Wang J, Duan S, Duan J. Rhodioloside ameliorates depressive behavior via up-regulation of monoaminergic system activity and anti-

inflammatory effect in olfactory bulbectomized rats. Int Immunopharmacol 2016; 36: 300-304. https://doi.org/10.1016/j.intimp.2016.05.008

34. Vasileva LV, Saracheva KE, Ivanovska MV, Petrova AP, Marchev AS, Georgiev MI, Murdjeva MA, Getova DP. Antidepressant-like effect of salidroside and curcumin on the immunoreactivity of rats subjected to a chronic mild stress model. Food Chem Toxicol 2018; 121: 604-611. https://doi.org/10.1016/j.fct.2018.09.065

35. Fan Y, Bi Y, Chen H. Salidroside improves chronic stress induced depressive symptoms through microglial activation suppression. Front Pharmacol 2021; 12: 635762. https://doi.org/10.3389/fphar.2021.635762

36. Chai Y, Cai W, Fu Y, Wang Y, Zhang Y, Zhang X, Zhu L, Miao M, Yan T. Salidroside ameliorates depression by suppressing NLRP3-mediated pyroptosis *via* P_2X_7/NF-κB/NLRP3 signaling pathway. Front Pharmacol 2022; 13: 812362. https://doi.org/10.3389/fphar.2022.812362

37. Valvassori SS, Varela RB, Quevedo J. Animal models of mood disorders: focus on bipolar disorder and depression. *In:* Coon PM (Ed.) Animal models for the study of human disease. 2. ed. Londres: Elsevier, 2017. p. 991-1001. https://doi.org/10.1016/B978-0-12-809468-6.00038-3

38. Ozcan H, Aydin N, Aydin MD, Oral E, Gündogdu C, Sipal S, Halici Z. Olfactory bulbectomy and raphe nucleus relationship: a new vision for well-known depression model. Nord J Psychiatry 2020; 74(3): 194-200. https://doi.org/10.1080/08039488.2019.1689294

39. De Fruyt J, Sabble B, Demyttenaere K. Anhedonia in depressive disorder: a narrative review. Psychopathology 2020; 53(5-6): 274-281. https://doi.org/10.1159/000508773

40. Hoffman K. What can animal models tell us about depressive disorders? In: Hoffman K. Modeling Neuropsychiatric Disorders in Laboratory Animals. London: Elsevier, 2015. p. 35-86. https://doi.org/10.1016/B978-0-08-100099-1.00002-9

41. Yankelevitch-Yahave R, Franko M, Huly A, Doron R. The forced swim test as a model of depressive-like behavior. J Vis Exp 2015; 97: 52587. https://doi.org/10.3791/52587

42. 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): 509-514. https://doi.org/10.4314/tjpr.v16i3.3

43. Yau SY, Li A, So KF. Involvement of adult hippocampal neurogenesis in learning and forgetting. Neural Plast 2015; 2015: 717958. https://doi.org/10.1155/2015/717958

44. Limanaqi F, Biagioni F, Busceti CL, Polzella M, Fabrizi C, Fornai F. Potential antidepressant effects of Scutellaria baixalensis, Hericium erinaceus and Rhodiola rosea. Antioxidants 2020; 9(3): 234. https://doi.org/10.3390/antiox9030234

45. Haam J, Yakel JL. Cholinergic modulation of the hippocampal region and memory function. J Neurochem 2017; 142 (Suppl. 2): 111-121. https://doi.org/10.1111/jnc.14052

46. Maurer SV, Williams CL. The cholinergic system modulates memory and hippocampal plasticity *via* its interactions with non-neuronal cells. Front Immunol 2017; 8: 1489. https://doi.org/10.3389/fimmu.2017.01489

47. Polumackanycz M, Konieczynski P, Orhan IE, Abaci N, Viapiana A. Chemical withposition, antioxidant and anti-enzymatic activity of golden root (*Rhodiola rosea* L.) withmercial samples. Antioxidants 2022; 11(5): 919. https://doi.org/10.3390/antiox11050919

48. Wang CH, Safwan S, Cheng MC, Liao TY, Cheng LC, Chen TA, Kuo YH, Lin YF, Lee CK. Protective evaluation of withpounds extracted from root of *Rhodiola rosea* L. against methylglyoxal-induced toxicity in a neuronal cell line. Molecules 2020; 25(12): 2801. https://doi.org/10.3390/molecules25122801

49. Kim KJ, Jung YS, You DM, Lee SH, Lee G, Kwon KB, Kim DO. Neuroprotective effects of ethanolic extract from dry *Rhodiola rosea* L. rhizomes. Food Sci Biotechnol 2021; 30(2): 287-297. https://doi.org/10.1007/s10068-020-00868-7

50. Chen BY, Wang X, Wang ZY, Wang YZ, Chen LW, Luo ZJ. Brain-derived neurotrophic factor stimulates proliferation and differentiation of neural stem cells, possibly by triggering the Wnt/β-catenin signaling pathway. J Neurosci Res 2013; 91(1): 30-41. https://doi.org/10.1002/jnr.23138

51. Miyasaka Y, Yamamoto N. Neuronal activity patterns regulate brain-derived neurotrophic factor expression in cortical cells *via* neuronal circuits. Front Neurosci 2021; 15: 699583. https://doi.org/10.3389/fnins.2021.699583

52. Ramos JM, Galdeano DS. Educação física e o fator neurotrófico derivado do cérebro (BDNF) na aprendizagem escolar. Conexões 2019; 17: e019005. https://doi.org/10.20396/conex.v17i0.8651312

53. 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): 126-139. https://doi.org/10.1111/ejn.14630

54. Calabrese F, van der Doelen RHA, Guidotti G, Racagni G, Kozicz T, Homberg JR, Riva MA. Exposure to early life stress regulates Bdnf expression in SERT mutant rats in an anatomically selective fashion. J Neurochem 2015; 132(1): 146-154. https://doi.org/10.1111/jnc.12846

55. Numakawa T, Yokomaku D, Richards M, Hori H, Adachi N, Kunugi H. Functional interactions between steroid hormones and neurotrophin BDNF. World J Biol Chem 2010; 1(5): 133-143. https://doi.org/10.4331/wjbc.v1.i5.133

56. Zhao HB, Ma H, Ha XQ, Zheng P, Li XY, Zhang M, Dong JZ, Yang YS. Salidroside induces rat mesenchymal stem cells to differentiate into dopaminergic neurons. Cell Biol Int 2014; 38(4): 462-471. https://doi.org/10.1002/cbin.10217

57. 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. https://doi.org/10.1155/2022/5647599

58. Kubera M, Grygier B, Wrona D, Rogóz Z, Roman A, Basta-Kaim A, Budziszewska B, Leskiewicz M, Jantas D, Nowak W., Maes M, Lason W. Stimulatory effect of antidepressant drug pretreatment on progression of B16F10 melanoma in high-active male and female C57BL/6J mice. J Neuroimmunol 2011; 240-241: 34-44. https://doi.org/10.1016/j.jneuroim.2011.09.006

59. Concerto C, Infortuna C, Muscatello MRA, Bruno A, Zoccali R, Chusid E, Aguglia E, Battaglia F. Exploring the effect of adaptogenic Rhodiola rosea extract on neuroplasticity in humans. Withplement Ther Med 2018; 41: 141-146. https://doi.org/10.1016/j.ctim.2018.09.013

60. Mannucci C, Navarra M, Calzavara E, Caputti AP, Calapai G. Serotonin involvement in Rhodiola rosea attenuation of nicotine withdrawal signs in rats. Phytomedicine 2012; 19(12): 1117-1124. https://doi.org/10.1016/j.phymed.2012.07.001

61. 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. https://doi.org/10.1016/j.jep.2009.01.007

62. Sha Q, Madaj Z, Keaton S, Galvis MLE, Smart LA, Krzyzanowski S, Fazleabas AT, Leach R, Postolache TT, Achtyes ED, Brundin L. Cytokines and tryptophan metabolites can predict depressive symptoms in pregnancy. Transl Psychiatry 2022; 12: 35. https://doi.org/10.1038/s41398-022-01801-8

63. Bleibel L, Sokolowska P, Henrykowska G, Owczarek J, Wiktorowska-Owczarek A. Unveiling the anti-inflammatory effects of antidepressants: a systematic review of human studies over the last decade. Pharmaceuticals 2025; 18(6): 867. https://doi.org/10.3390/ph18060867

64. Vasileva LV, Ivanovska MV, Murdjeva MA, Saracheva, KE, Georgiev MI. Immunoregulatory natural withpounds in stress-induced depression: an alternative or an

adjunct to conventional antidepressant therapy? Food Chem Toxicol 2019; 127: 81-88. https://doi.org/10.1016/j.fct.2019.03.004

65. Pooja, Bawa AS, Khanum F. Anti-inflammatory activity of *Rhodiola rosea* – "a second-generation adaptogen". Phytother Res 2009; 23(8): 1099-1102. https://doi.org/10.1002/ptr.2749

66. Song D, Zhao M, Feng L, Wang P, Li Y, Li W. Salidroside attenuates acute lung injury via inhibition of inflammatory cytokine production. Biomed Pharmacother 2021; 142: 111949. https://doi.org/10.1016/j.biopha.2021.111949

67. 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): 13820-13833. https://doi.org/10.1523/jneurosci.1671-13.2013

68. Jesus MBN, Assunção JR. Implicações metabólicas do exercício físico no eixo hipotálamo-pituitária-adrenal. Prát. Cuidado: Rev Saúde Col 2020 [access at 2022 Jul 22]; 1: e9995. Avaliable at: https://revistas.uneb.br/index.php/saudecoletiva/article/view/9995

69. Dinel AL, Guinobert I, Lucas C, Blondeau C, Bardot V, Ripoche I, Berthomier L, Pallet V, Layé S, Joffre C. Reduction of acute mild stress corticosterone response and changes in stress-responsive gene expression in male Balb/c mice after repeated administration of a *Rhodiola rosea* L. root extract. Food Sci Nutr 2019; 7(11): 3827-3841. https://doi.org/10.1002/fsn3.1249

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RHODIOLA ROSEA LINNAEUS MELHORA O APRENDIZADO, A MEMÓRIA E OS SINTOMAS DE DEPRESSÃO – REVISÃO INTEGRATIVA

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