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Antioxidant-based interventions in animal models of depression: A systematic review of preclinical evidence

Intervenções antioxidantes em modelos animais de depressão: Revisão sistemática das evidências pré-clínicas

Intervenciones basadas en antioxidantes en modelos animales de depresión: Una revisión sistemática de la evidencia preclínica

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Abstract
Evidence suggests that oxidative stress significantly contributes to the manifestation of depression-related behaviors in animal models. In the central nervous system, this condition triggers cellular damage by increasing the expression of reactive oxygen species and impairing the activity of antioxidant enzymes such as catalase, superoxide dismutase, and the glutathione system. Moreover, the induction of oxidative stress through chronic mild stress or chronic administration of corticosterone (CORT) raises plasma CORT levels, resulting in hyperactivation of the hypothalamic-pituitary-adrenal axis. This imbalance, particularly in regions such as the hypothalamus, prefrontal cortex, and striatum, promotes the expression of depressive-like behaviors in these animal models. In this context, antioxidant substances such as cannabidiol, resveratrol, and silymarin have been extensively investigated for their potential to reverse these behaviors. Therefore, this review aims to analyze the literature from the past 10 years regarding the relationship between oxidative stress and depressive-like behaviors in animal models, as well as to evaluate the efficacy of antioxidants in reversing these behaviors.
Keywords: Reactive Oxygen Species; Antioxidants; Stress Disorders; Depressive Disorder.

Resumo
Evidências sugerem que o estresse oxidativo contribui significativamente para a manifestação de comportamentos relacionados à depressão em modelos animais. No sistema nervoso central, esse quadro desencadeia danos celulares ao aumentar a expressão de espécies reativas de oxigênio e comprometer a ação das enzimas antioxidantes catalase, superóxido dismutase e do sistema glutationa. Além disso, a indução do estresse oxidativo por estresse crônico leve ou administração crônica de corticosterona (CORT) eleva os níveis plasmáticos de CORT, resultando na hiperativação do eixo hipotálamo-hipófise-adrenal. Esse desequilíbrio, em regiões como o hipotálamo, córtex pré-frontal e estriado, favorece a expressão de comportamentos do tipo depressivos nesses modelos animais. Diante disso, substâncias antioxidantes como canabidiol, resveratrol e silimarina têm sido amplamente investigadas pelo seu potencial na reversão desses comportamentos. Assim, esta revisão tem como objetivo analisar a literatura dos últimos 10 anos sobre a relação entre estresse oxidativo e comportamentos tipo depressivos em modelos animais, além de avaliar a eficácia de antioxidantes na reversão desses comportamentos.
Palavras-chave: Espécies Reativas de Oxigênio; Antioxidantes; Transtornos de Estresse; Transtorno Depressivo.

Resumen
La evidencia sugiere que el estrés oxidativo contribuye significativamente a la manifestación de comportamientos relacionados con la depresión en modelos animales. En el sistema nervioso central, esta condición desencadena daño celular al incrementar la expresión de especies reactivas de oxígeno y comprometer la actividad de enzimas antioxidantes como la catalasa, la superóxido dismutasa y el sistema de glutatión. Además, la inducción de estrés

oxidativo mediante estrés crónico leve o la administración crónica de corticosterona (CORT) eleva los niveles plasmáticos de CORT, resultando en una hiperactivación del eje hipotálamo-hipófisis-adrenal. Este desequilibrio, particularmente en regiones como el hipotálamo, la corteza prefrontal y el estriado, favorece la expresión de conductas de tipo depresivo en estos modelos animales. En este contexto, sustancias antioxidantes como el cannabidiol, el resveratrol y la silimarina han sido ampliamente investigadas por su potencial para revertir estos comportamientos. Por lo tanto, esta revisión tiene como objetivo analizar la literatura de los últimos 10 años acerca de la relación entre el estrés oxidativo y los comportamientos de tipo depresivo en modelos animales, así como evaluar la eficacia de los antioxidantes en la reversión de estas conductas.
Palabras clave: Especies Reactivas de Oxígeno; Antioxidantes; Trastornos por Estrés; Trastorno Depresivo.

1. Introduction

Depressive disorders, such as Major Depressive Disorder (MDD), Persistent Depressive Disorder (dysthymia), and even unspecified depressive disorders, are multifactorial mental illnesses that affect approximately 3.8% of the global population. It is estimated that depressive and anxiety disorders will become the leading cause of reduced global quality of life by 2030 (World Health Organization [WHO], 2024). These conditions are primarily characterized by persistent depressed mood, anhedonia, alterations in sleep and eating patterns, psychomotor dysfunctions, and suicidal ideation (Khan et al., 2020).

Despite advancements, knowledge regarding the underlying mechanisms of depressive behavior remains limited. In this context, animal models have proven to be valuable tools for investigating the immunological, biochemical, and physiological aspects of these disorders (Beurel et al., 2020). Evidence suggests that their etiology involves both genetic and socio-environmental factors, including alterations in the central and peripheral immune systems, maternal immune activation, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which may trigger oxidative stress (OS). Biochemical imbalance in the HPA axis, characterized by increased release of corticosteroids by the adrenal glands, can lead to alterations in brain centers responsible for mood regulation and psychomotor control. Furthermore, it can reduce the dendritic complexity of central and peripheral neurons (Febrer-Serra et al., 2023).

Situations of chronic mild stress (CMS) are associated with increased production of reactive oxygen species (ROS), resulting in tissue oxidative stress. This condition can cause biomolecular damage, such as oxidation of nuclear and mitochondrial DNA, lipids, and proteins. When such damage occurs in critical brain regions — including the prefrontal cortex, hypothalamus, amygdala, and hippocampus — it is associated with the expression of depressive behaviors in animal models (Beurel et al., 2020; Faggio et al., 2016; Gáll et al., 2020; Beckman & Ames, 1998). These behaviors generally reflect a compromise in the brain tissue's antioxidant defenses, which include enzymes such as catalase (CAT), superoxide dismutase (SOD), and the glutathione system (GS), in addition to low-molecular-weight molecules. These systems play an essential role in neutralizing ROS, contributing to the maintenance of physiological homeostasis. However, under conditions of OS induced by CMS, these defenses become insufficient (Beckman & Ames, 1998; Tuon et al., 2021).

In addition to CMS-based protocols, chronic treatment with CORT has also been shown to increase brain oxidation levels. This hormonal elevation triggers biochemical imbalance in the HPA axis, leading to its hyperactivation and disruption of feedback mechanisms. As a result, increased cellular lipid peroxidation was observed, accompanied by elevated levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), as well as reduced levels of brain-derived neurotrophic factor (BDNF). This condition is directly associated with decreased neuroplasticity, reduced dendritic complexity, and increased neuronal vulnerability, which may further contribute to axonal atrophy in the hippocampal formation and deleterious changes in neurotransmission (Ali et al., 2015).

Given this, a wide range of substances with antioxidant potential have been explored for their ability to reduce OS levels in the brain and, consequently, attenuate the expression of depressive behaviors (Reus et al., 2018). Among the most investigated compounds are resveratrol (Willner, 2017), cannabidiol (Beckman & Ames, 1998) and silymarin (Thakare et al.,

2018). Resveratrol is a natural flavonoid with neuroprotective, anti-inflammatory, and antitumor properties, found in the skin of purple grapes and in certain nuts. Studies have shown that resveratrol can reduce inflammation by attenuating microglial activation in the hippocampal region (Liu et al., 2016a). Cannabidiol, in turn, has exhibited antioxidant action by reducing ROS concentration in brain tissue, in addition to anti-inflammatory effects through the reduction of interleukins 6 and 1β levels (Chen et al., 2016). Silymarin has also demonstrated promising results, particularly in reversing anhedonic behaviors induced by CMS, notably by reducing immobility time in the Forced Swim Test (Thakare et al., 2018).

Therefore, this review aims to analyze the literature from the past 10 years regarding the relationship between oxidative stress and depressive-like behaviors in animal models, as well as to evaluate the efficacy of antioxidants in reversing these behaviors. The review analyzed aspects such as the mechanisms by which OS contributes to the expression of depressive behaviors, the validated animal models used to study these disorders, and the main antioxidant agents investigated as potential therapeutic strategies.

2. Methodology

This study is characterized as an integrative systematic literature review (Snyder, 2019), with a quantitative approach in relation to the 24 (twenty-four) articles selected to compose the research corpus and qualitative in relation to the discussions (Risemberg et al., 2026; Pereira et al., 2018)

The articles included in this review were obtained through a search in the PubMed database, with the most recent search conducted in June 2025. Initially, the keywords “oxidative stress,” “depression,” “animal model,” “chronic stress,” and “antioxidant” were used, covering the period from 2015 to 2025. This first filter yielded a total of 177 articles. The initial screening aimed to identify studies addressing oxidative stress, depression, and treatment with natural antioxidant compounds in animal models. Based on title analysis, 87 articles were selected. Subsequently, their abstracts were evaluated, resulting in the selection of 24 studies for full-text reading.

This final stage considered the following inclusion criteria:

(I) experimental research using animal models of depressive behavior associated with oxidative stress, including control groups and treatment with natural antioxidant compounds;

(II) evaluation of depressive behaviors using behavioral apparatuses that are highly validated in the scientific literature;

(III) investigation of the underlying pathophysiological and biochemical mechanisms of the condition.

Based on these criteria, 15 articles were deemed eligible for the review. Additionally, 2 articles were included through cross-referencing, and 7 others were incorporated, totaling 24 articles in the final analysis. The results were presented based on the mean differences between groups, respecting the statistical significance levels (α) as established by each reviewed study.

3. Results and Discussion

The following 24 studies were selected for this study:

(1) Oliveira et al. (2022);

(2) Pereira et al. (2020);

(3) Ali et al., 2015;

(4) Khan et al. (2018);

(5) Mugoni et al., 2014;

(6) Gao et al. (2021);

(7) Thakare et al. (2018);
(8) Wang et al. (2018);
(9) Abd El-Fattah et al., 2018;
(10) Zhao et al. (2021);
(11) Ayyub et al., 2017;
(12) Adebesin et al., 2017;
(13) Guan et al., 2021;
(14) Herbet et al., 2021;
(15) Shoval et al. (2016);
(16) Gáll et al. (2020);
(17) Lucindo et al., 2025;
(18) Shbiro et al., 2019;
(19) Liu et al., 2014;
(20) Liu et al., 2016b;
(21) Thakare et al., 2017;
(22) Thakare et al., 2016;
(23) Li et al., 2024 e,
(24) Khan et al. (2018).

Animal Models for Studying Oxidative Stress

Several animal models are applied for the induction of OS. Most of these models aim to alter the physiological homeostasis of the HPA axis, generating a state of hyperactivation and increasing CORT levels. Additionally, this imbalance may alter the feedback mechanism of the axis. Among the induction protocols, Oliveira et al. (2022) employed subcutaneous administration of CORT (20 mg/kg), diluted in 0.9% saline solution with 0.1% polysorbate and 0.1% dimethyl sulfoxide. Chronic CORT treatment for 21 days increased levels of Thiobarbituric Acid Reactive Substances (TBARS) and nitrite/nitrate in the prefrontal cortex (PFC), hippocampus (HC), and striatum (STR). Additionally, there was a reduction in glutathione (GSH) levels and a decrease in BDNF indices, evidencing that the increased concentration of CORT in the blood of female mice was directly connected to chronic corticosterone administration and the increase in oxidative stress in the animals' brains. Similarly, Pereira et al. (2020) obtained similar results in male Swiss mice, in which chronic CORT administration for 21 days increased hydrogen peroxide (H2O2) concentrations in the PFC, HC, and STR, as well as reduced CAT levels in these regions, showing a pattern of OS in nervous tissue.

Another widely explored protocol in the literature for the induction of OS is the chronic unpredictable mild stress (CUMS) paradigm. Although CUMS paradigms vary, they all aim to hyperactivate the HPA axis by exposing animals to stressful situations such as food and water deprivation, swimming in cold water, wet bedding, light/dark cycle inversion, and movement restriction. These stressors tend to reduce BDNF levels and increase Glycogen Synthase Kinase 3-Beta (GSK3β) concentrations in the HC, as well as raise levels of tumor necrosis factor alpha (TNF-α), MDA, and serum CORT (Ali et al., 2015; Oliveira et al., 2022). The results suggest high efficiency of these protocols in triggering OS. In these models, the likely trigger of oxidative stress is a physiological imbalance of the HPA axis. Furthermore, Gao et al. (2021) demonstrated increased CORT and ROS levels in male albino mice subjected to a sleep deprivation model as a stressor. Thus, it is possible to state that, besides being efficient, CUMS protocols present many variables, depending on the experiment to be conducted.

Additionally, Khan et al. (2018) reported that CUMS alters enzymes such as CAT, SOD, and TNF-α, as well as reduces the number of 5-HT serotonin receptors, highlighting the effect of OS on nervous tissue.

Oxidative Stress and its Relationship with Depressive Behavior

OS is considered a risk factor for behavioral disorders, particularly those related to depression and anxiety (Mugoni et al., 2014). Thakare et al. (2018) demonstrated, through an animal model of chronic unpredictable mild stress (CUMS), a direct relationship between OS in nervous tissue and the manifestation of depression-like behaviors. In this study, animals subjected to the chronic stress paradigm showed a reduction in 5-HT receptors, which are directly related to serotonin affinity. These results reinforce the connection between OS and depression, as serotonergic receptors play a central role in the pathophysiology of depressive disorders. Additionally, there was a significant increase in TNF-α and IL-6 levels, as well as a reduction in BDNF, CAT, and SOD levels in the HC of animals subjected to CUMS. It is interesting to note that this study highlights a correlation between oxidative stress and neuroinflammation as possible comorbidities associated with the expression of depressive behaviors.

Similarly, Wang et al. (2018) observed elevated levels of IL-1β, TBARS, and Cyclooxygenase-2 (COX-2) in the CUMS groups compared to controls. Stressed animals also showed increased immobility time in the Forced Swimming Test (FST) and reduced sucrose consumption in the Sucrose Preference Test (SPT). The performance of the animals in both behavioral tests reinforces the role of OS in the pathophysiology of depression, since FST and SPT are widely validated in the literature for the analysis of anhedonic behaviors. In addition to these, other behavioral tests such as the Tail Suspension Test (TST) and the Splash Test (ST) are also effective for assessing depression-related behaviors (Abd El-Fattah et al., 2018). In the case of the ST, grooming hypokinesia is observed as an indicator of lack of self-care (abulia), which reinforces the relationship between motivational dysfunctions and depressive disorders.

Zhao et al. (2021), in a study with male C57BL/6 mice, demonstrated a decrease in sucrose consumption in the SPT, as well as an increase in immobility in the TST and FST in animals subjected to CUMS (Zhao et al., 2021; Pereira et al., 2020). These results suggest an anhedonic behavior similar to that observed in depression. Additionally, an increase in ROS, MDA, and TNF-α levels was observed, along with a reduction in BDNF and SOD levels in the HC regions. These findings reinforce the association between OS and the manifestation of depressive behaviors (Wang et al., 2018; Mugoni et al., 2014). The correlation between behavioral tests and biochemical analyses shows a consistent link between OS and depressive disorders (Ayyub et al., 2017; Adebesin et al., 2017).

In this context, studies on antioxidant substances have been increasingly explored as therapeutic alternatives for depressive disorders (Guan et al., 2021; Herbet et al., 2021). Recent experiments demonstrate the potential of some antioxidants in reducing immobility time in the FST and increasing sucrose consumption in the SPT, suggesting a possible attenuation of anhedonic behaviors associated with depression.

Antidepressant Effects of Antioxidant Natural Compounds

Cannabidiol

CBD is the main non-psychotomimetic phytocannabinoid found in species of the Cannabis genus. Several studies have investigated its antidepressant potential, as well as the signaling pathways associated with this effect. Shoval et al. (2016) demonstrated the effects of CBD on depression-related behaviors in an experimental study comparing Wistar and WKY rats, a strain known for higher vulnerability to depressive disorders. Treatment with CBD led to a significant increase in sucrose consumption in the SPT, suggesting a reversal of anhedonic behavior. Control group WKY animals showed reduced

consumption after stress exposure, while groups treated with CBD (45 mg/kg) maintained elevated sucrose consumption levels (Shoval et al., 2016).

Similarly, chronic CBD treatment proved effective in reducing depressive-like behaviors and cognitive deficits induced by social isolation in mice. Animals were divided according to treatment type (CBD or vehicle) and housing condition (isolation or group interaction). In the SPT, isolated animals exhibited lower sucrose consumption compared to socially housed ones; however, those treated with CBD showed a significant increase in this parameter, indicating reversal of anhedonia. These findings were corroborated by reduced immobility time in the TST observed in the treated groups (Lucindo et al., 2025).

Corroborating these results, Gáll et al. (2020) showed that chronic CBD treatment reversed depressive-like behaviors in a CUMS model. In this study, male Wistar rats subjected to CUMS received CBD treatment (10 mg/kg, i.p.), resulting in increased sucrose consumption in the SPT, indicative of improved emotional state. Additionally, another study evaluated CBD in two genetic models of depression (WKY and FSL), observing a significant reduction in immobility in the FST in both cases, reinforcing its therapeutic potential for treating mental disorders marked by symptoms such as anhedonia and hopelessness (Shbiro et al., 2019).

Resveratrol

RSV is a natural polyphenol widely distributed in nature, notably present in the skin of purple grapes and in some oilseeds. Studies conducted in animal models have demonstrated its antioxidant, anti-inflammatory, and antidepressant properties. In experimental models of CUMS-induced depression in Wistar rats, RSV administration (80 mg/kg) showed efficacy in reversing depressive behaviors, evidenced by increased sucrose consumption in the SPT and reduced immobility time in the FST (Liu et al., 2014; Liu et al., 2016b; Abd El-Fattah et al., 2018).

Liu et al. (2014) reported that RSV, at doses of 40 and 80 mg/kg, significantly reduced depressive-like behaviors, with efficacy comparable to desipramine, a tricyclic antidepressant that inhibits NE reuptake. This equivalence was observed in both the FST and SPT. Furthermore, RSV showed additional antidepressant effects in the CUMS model, associated with the inhibition of ferroptosis via activation of the AKT/NRF2 pathway, which resulted in increased sucrose consumption in treated animals compared to controls (Thakare et al., 2017).

Additionally, RSV treatment induced increased levels of FNDC in the hippocampus (Abd El-Fattah et al., 2018), a protein involved in neuroplasticity and essential for maintaining neurophysiological homeostasis. Reductions in this protein have been associated with depressive behavior expression in rodents. RSV also exhibited anti-inflammatory effects, evidenced by reduced levels of NF-κB, TNF-α, and IL-1β (Liu et al., 2014).

Finally, the compound contributed to the attenuation of oxidative stress, demonstrated by increased activity of antioxidant enzymes SOD and CAT, reduced MDA levels, and consequent reduction in lipid peroxidation in cell membranes (Abd El-Fattah et al., 2018; Liu et al., 2016b).

Silymarin

Silymarin is a polyphenolic flavonoid phytocompound extracted from the plant Silybum marianum, widely recognized for its use in treating various liver diseases. Recently, its neuropharmacological potential has been explored, especially in addressing oxidative stress associated with HPA axis dysfunction. In this context, an increase in 5-hydroxytryptamine (5-HT) levels in the cerebral cortex, as well as dopamine (DA) and norepinephrine (NE) in the cerebellum of normal mice supplemented with silymarin, was observed (Thakare et al., 2016).

The study by Thakare et al. (2018) demonstrated that oral treatment with silymarin (100 and 200 mg/kg) was effective

in reversing anhedonic behaviors induced by CUMS. Treated animals showed a significant reduction in immobility time in the FST and an increase in sucrose preference in the SPT compared to controls. Notably, the effects of silymarin on depressive-like behaviors surpassed those of fluoxetine, possibly due to its antioxidant and anti-inflammatory actions, reflected in the modulation of TNF-α and IL-6, reduction of serum CORT levels, inhibition of MDA formation, and restoration of the activity of antioxidant enzymes SOD and CAT.

Moreover, evidence suggests that silymarin exerts robust antidepressant effects through the regulation of BDNF levels in the hippocampus and cerebral cortex (Thakare et al., 2017; Thakare et al., 2018; Thakare et al., 2016). Modulation of monoamines such as 5-HT, NE, and DA in these regions is also observed, reinforcing the hypothesis that its antidepressant effect is related to enhanced monoaminergic neurotransmission. Thus, silymarin emerges as a promising therapeutic alternative in managing stress-induced depression and anxiety-related disorders.

Hydroxytyrosol

Hydroxytyrosol (HT), the main phenolic compound present in olives and olive-derived products, stands out for its antioxidant, anti-inflammatory, and neuroprotective properties, among other physiological functions. Recently, its effects on depressive-like behaviors have been under investigation. Zhao et al. (2021) demonstrated that HT treatment (50, 100, and 200 mg/kg), in a CUMS model, was effective in reversing behavioral changes, evidenced by improvements in the FST, SPT, and TST.

Biochemical analysis of animals treated with 100 mg/kg of HT revealed reduced ROS production in the HIP, decreased MDA levels, and increased activity of the antioxidant enzyme SOD, reinforcing the compound's antioxidant potential. Additionally, a significant reduction in IL-1β and TNF-α levels in the HIP was observed, indicating attenuation of the neuroinflammatory response. These findings highlight HT's therapeutic potential in treating depressive disorders, supported by its ability to modulate oxidative stress and inflammation in the central nervous system.

Moreover, the antioxidant and antidepressant effects of HT were corroborated in chronic restraint stress models, which induce oxidative and inflammatory states in brain regions. Animals treated with HT showed reduced immobility time in both the FST and TST, suggesting a robust antidepressant effect. These results establish HT as a promising candidate for managing neuropsychiatric conditions, especially those associated with oxidative stress and neuroinflammation (Li et al., 2024).

Quercetin

Quercetin is a phenolic compound that has shown antidepressant effects both behaviorally and biochemically. In the study by Khan et al. (2018), using a CUMS model, treatment with 25 mg/kg significantly reduced immobility time in the TST and modified FST, in addition to increasing exploration in the OFT. These effects were comparable to those observed in animals treated with fluoxetine, reinforcing the therapeutic potential of quercetin in depression management.

From a biochemical perspective, treated animals showed a significant increase in GSH, SOD, and CAT levels, indicating strengthening of the endogenous antioxidant system. Quercetin's anti-inflammatory activity was also evidenced by reduced IL-6 and TNF-α levels, suggesting a correlation between the reversal of the inflammatory process and improvement in depressive-like behaviors. Moreover, treatment promoted increased 5-HT levels and reduced glutamate levels, effects similar to those observed with fluoxetine.

Considering that dysfunctions in the glutamatergic and serotonergic systems are widely associated with behavioral changes in individuals with depression, these findings support the hypothesis that quercetin possesses significant

antidepressant effects, likely mediated by antioxidant, anti-inflammatory, and neurotransmission modulation mechanisms.

Additionally, recent analyses demonstrated that animals subjected to the CUMS model showed reduced sucrose consumption in the SPT, reflecting anhedonia. However, treatment with a high dose of quercetin (50 mg/kg) effectively restored sucrose preference, indicating reversal of this symptom. Furthermore, increased activity of SOD, CAT, and GSH, as well as reduced MAO enzyme activity, were observed, reinforcing the compound's antioxidant and neuroprotective profile (Guan et al., 2021).

4. Conclusion

Experimental models using rodents remain fundamental tools for understanding the neurobiological mechanisms involved in oxidative stress and its association with depressive spectrum disorders. Recent evidence indicates that natural compounds, such as resveratrol and cannabidiol, possess relevant antioxidant and anti-inflammatory properties, being capable of modulating biochemical pathways associated with neuroinflammation and redox imbalance, with effects comparable to those of traditionally used synthetic antidepressants.

Despite the robustness of the available behavioral and biochemical models, the molecular mechanisms linking OS to the pathophysiology of depression are not yet fully elucidated. In this context, studies that deepen the understanding of the implicated signaling pathways, as well as integrative reviews such as the present one, play a crucial role in consolidating knowledge and in the development of innovative, alternative therapeutic approaches with a more favorable safety profile.

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