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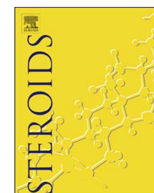

# Ferulic acid reverses depression-like behavior and oxidative stress induced by chronic corticosterone treatment in mice

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ARTICLE INFO

*Chemical compounds studied in this article:*
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Corticosterone (PubChem CID: 5753)
Fluoxetine (PubChem CID: 3386)
Ferulic acid (PubChem CID: 445858)
Thiobarbituric acid (PubChem CID: 2723628)
1,1,3,3-tetramethoxypropane (PubChem CID: 66019)
Sulfanilamide (PubChem CID: 5333)
N-(1-Naphthyl)ethylenediamine dihydrochloride (PubChem CID: 15106)
2,4-dinitrophenylhydrazine (PubChem CID: 5361190)
Guanidine hydrochloride (PubChem CID: 5742)
5,5′-Dithiobis(2-nitrobenzoic acid) (PubChem CID: 6254)

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ABSTRACT

Corticosterone (CORT) treatment has been evidenced to develop a depression-like state in animals, that mimic hypothalamic–pituitary–adrenal (HPA)-axis dysregulation implicated in the development of depression. The present study aimed to examine the ferulic acid (FA), a natural phenolic compound, antidepressant and antioxidant activities on the CORT chronic model. Mice orally treated with 20 mg/kg of CORT for 21 days were connsidered control group, while mice treated with FA (1 mg/kg) or fluoxetine (10 mg/kg) for the last week of CORT treatment, as drug groups. Three weeks of CORT treatment resulted in depressive-like behavior, as indicated by the increase on the immobility time in the tail suspension test, grooming in the splash test and an increase in the oxidative stress markers in the brain. It was observed that FA ameliorated the behavioral and oxidative stress alterations induced by CORT, which may plausibly suggest a mode of action for the FA antidepressant effect. The involvement of FA repairing the stress caused by HPA-axis dysfunction evidenced that this phenolic acid could be further investigated as a novel potential agent to improve the management of depression.

## 1. Introduction

Depression is a devastating and debilitating disorder that has a huge impact on the functioning and well-being of modern society [1]. Besides, it is a disorder with a high overall incidence (affects up to 20% of the population) and is a widespread threat to public health [2]. Despite all efforts to understand the depression mechanism and also the pathogenesis and biology of these disorder it is not fully elucidated, probably because of their multifactorial nature [3]. In recent years some theories have been proposed in order to explain the pathophysioloy of the illness as for instance monoamine deficiency, hypothalamic-pituitaryadrenal (HPA)-axis hyperactivity, neurodegeneration, low levels of brain-derived neurotrophic factor (BDNF) and oxidative stress [4–7].

Moreover, stress has an important relationship with the onset of depressive episodes, raising glucocorticoids level in humans [8] which induces the reactive oxygen species (ROS) and nitrogen (RNS) production [9], increasing of extracellular glutamate concentration [10,11]. The overproduction of these agents generally observed in depressed patients shows that the glucocorticoids may be involved in the antioxidant defenses reduction and hiperactivaction of N-methyl-D-aspartate receptor (NMDAR) leading to cell death due to a serie of events named excitotoxicity [12–17].

Even with the improvement of pharmacological therapy, the most common treatments used for depression are still related to the monoaminergic system. It has been evidenced that antioxidant molecules or NMDAR antagonists may have antidepressant effect, as ketamine, an NMDAR antagonist that exhibited fast antidepressant property [12,13]. Since the physiopathology of depression still remains unclear there is a need for innovative researches searching new therapeutic agents

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essentials for the management of depression [18].

Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is a phenolic compound widely present in plant species, including many grains, fruits and vegetables, easily metabolized [19,20], also capable to traverse the blood-brain barrier and to reach into hippocampus [21]. Given these characteristics, it does not come as a surprise that the FA demonstrates several neuropharmacological properties. There are evidences that the antidepressant activity of FA involves the serotonergic and noradrenergic systems [22,23] and, signaling cascades related to synaptic plasticity, neurogenesis and cell survival [24]. In addition, the FA which is a well-known antioxidant and a glutamate analogue molecule that protects the hippocampus against glutamatergic excitotoxicity which indicates a NMDAR antagonism effect [25] with the involvement of antioxidant defense modulation [26,27].

Our research recently demonstrated that chronic administration of 1 mg/kg and also 20 mg/kg of FA, showed antidepressant-like activity through the forced swimming (FST) and tail suspension (TST) tests [26] and in the FST in a chronic mild stress model [28]. Additionally, apigenin and resveratrol, both phenolic compounds, reverses depression-like behavior induced by chronic corticosterone (CORT) treatment in mice [29,30]. In previous studies, it was shown that chronic treatment with CORT prevented the possibility of habituation response to stress stimuli [31] and was effective to induce depressive behavior in rodents evaluated through several parameters, such as a consumption of sucrose [32], latency and total time of grooming [33] and immobility time in the FST [34] and TST [33] tests. In addition, the excess of glucocorticoids in the brain led to an oxidative and nitrosative stress [9,35] in rodents. Since this model induces behavioral and neurological alterations that mimic some symptoms presented by depressed patients, our objectives were to further investigate the FA antidepressant effect and the involvement of the antioxidant activity, in the mice model of depression, the CORT chronic treatment. And also, to assess a comparison with fluoxetine, the most widely used antidepressant.

## 2. Material and methods

### 2.1. Animals

Male Swiss mice (30–40 g) were maintained at 21–23 °C with free access to water and food, under 12:12 h light/dark cycle (lights-on at 07:00h). The procedures were performed in accordance to the National Institute of Health Guide for the Care and Use of Laboratory Animals and developed after approval of the protocol by the Institutional Ethics Committee (CEUA/FURB – 007/15). All efforts were done in order to minimize animal's suffering and to reduce their number to the minimum necessary to demonstrate consistent effects in the experiments.

### 2.2. Drugs and treatments

To conduct chronic treatment mice were divided into six groups: (1) vehicle + vehicle; (2) vehicle + ferulic acid; (3) vehicle + fluoxetine; (4) CORT + vehicle; (5) CORT + ferulic acid and (6) CORT + fluoxetine. For the treatments CORT (20 mg/kg) was dissolved in distilled water with 2% of Tween 80 and 0.2% of DMSO, ferulic acid (FA, 1 mg/kg) in saline containing 1% of Tween 80 and fluoxetine (FLU, 10 mg/kg) in saline only. The CORT and FA were purchased from Sigma Chemical Co., St. Louis, USA and FLU from Cadila Healthcare, India. All drugs were orally and once a day administered, CORT during 21 days [33] and FA or FLU, as well as the vehicle (saline containing 2% of Tween 80 and 0.2% of DMSO), immediately after CORT, during the last 7 days of the 21 days of the treatment. On the 22nd day, 24 h after the last treatment, the animals were submitted to the behavioral tests. Mice were weighted once a week. Fig. 1 depicts a detailed experimental design of the treatments, behavioral and biochemical evaluations. All behavioral tests were conducted in a noise-free, illumination controlled room and the readings were recorded by a blind observer to the experimental groups.

### 2.3. Behavioral tests

#### 2.3.1. Tail suspension test (TST)

The total immobility time in the TST was measured according to Steru et al. [36]. The animals, acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape of the tail and immobility time recorded during 6 min [37]. Mice were only considered immobile when hung passively and completely motionless.

#### 2.3.2. Open-field test

Ten minutes after the TST, the behavior parameters were assessed in the open-field test as previously described by Lenzi et al. [26], using an open field arena, which consists of a wooden box measuring 40 × 60 cm and 50 cm height with the floor divided into 12 equal squares. At the start of each trial a mouse was placed in the left corner of the field and allowed to freely explore the arena. Three observational moments were considered: the number of crossings (squares crossed with all paws) as indicative of locomotor activity, the number of rearings (the animal standing upright on its back legs) as exploratory behavior and the number of fecal boluses as emotionality, registered during 6 min. The arena floor was cleaned between the tests avoiding anxiety behavior.

#### 2.3.3. Splash test

The splash test, which consists of squirting a 10% sucrose solution on the dorsal coat of a mouse placed individually in clear boxes (9 × 7 × 11 cm) as described by Moretti et al. [38], was performed ten minutes after the open field test. Due to its viscosity, the sucrose solution dirties the mouse fur which initiates a grooming behavior. After applying sucrose solution, the time of the start of the first grooming and the total time of grooming were recorded for a period of 5 min as an index of self-care and motivational behavior, considering any apathetic behavior as symptoms of depression [39]. The apparatus was cleaned between the tests in order to hide any other animal clues.

### 2.4. Biochemical analysis

Immediately after behavior tests mice were decapitated, the serum and brains collected and the homogenates prepared according to Lenzi et al. [26].

#### 2.4.1. Evaluation of lipid peroxidation

Thiobarbituric acid-reactive substances (TBARS) assay was determined according to the method described by Ohkawa et al. [40] that measures malondialdehyde (MDA), a product of lipoperoxidation caused mainly through hydroxyl free radicals by the absorbance at 535 nm. The calibration curve developed using 1,1,3,3-tetramethoxypropane and TBARS levels calculated as nmol of malondialdehyde formed per milligram of protein.

#### 2.4.2. Nitrite determination

The production of the nitrites was determined based on Griess reaction [41]. After centrifugation (1800*g* for 10 min) of the homogenate 50 µl of the supernatant was incubated with 100 µl of Griess reagent at room temperature for 10 min. The absorbance was measured at 525 nm via microplate's reader. The standard curve was prepared with several concentrations of $NaNO_2$ (ranging from 0 to 100 µM) and expressed as µmol/g of protein.

#### 2.4.3. Protein carbonyl (PC) assay

The PC content was assayed following the method of Reznick and Packer [42]. After the homogenate preparation, supernatant was discarded and the pellet resuspended in 10 mM 2,4-dinitro-phenyl

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