Biomedicine & Pharmacotherapy 178 (2024) 117120

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Linalool-rich rosewood essential oil (*Aniba rosaeodora* Ducke) mitigates emotional and neurochemical impairments induced by ethanol binge-like exposure during adolescence in female rats

Éverton Renan Quaresma dos Santos [a], Lucas Villar Pedrosa da Silva Pantoja [a], Sarah Viana Farias [a], Bruno Gonçalves Pinheiro [a], Eloisa Helena A. Andrade [b], Paulo Fernando Santos Mendes [c], Jorddy Neves Cruz [c], Marta Chagas Monteiro [d], Kelly Davis [d], Rafael Rodrigues Lima [c], Jofre Jacob da Silva Freitas [e], Rommel Mário Rodríguez Burbano [f], Rui Daniel Prediger [g], Enéas Andrade Fontes-Junior [a], José Guilherme S. Maia [d], Cristiane do Socorro Ferraz Maia [a,*]

[a] *Laboratório de Farmacologia da Inflamação e do Comportamento, Faculdade de Farmácia, Universidade Federal do Pará, Belém, PA, Brazil*
[b] *Programa de Pós-Graduação em Química, Universidade Federal do Pará, Belém, PA 66075-900, Brazil*
[c] *Laboratório de Biologia Funcional e Estrutural, Universidade Federal do Pará, Belém, PA 66075-900, Brazil*
[d] *Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal do Pará, Belém, PA 66075-900, Brazil*
[e] *Centro de Estudos Pré-Clínicos da Amazônia, Universidade do Estado do Pará, Belém, Pará, Brazil*
[f] *Laboratório de Biologia Molecular, Hospital Ophir Loyola, Belém, Pará 66063-240, Brazil*
[g] *Departamento de Farmacologia, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina 88049-900, Brazil*

ARTICLE INFO

Keywords:
Aniba rosaeodora
Rosewood oil
Linalool
Ethanol binge-drinking
Neurobehavioral
Adolescence

Chemical compounds studied in this article:
Linalool (PubChem CID: 6549)
Ethanol (PubChem CID: 702)

ABSTRACT

Linalool-rich Rosewood oil (*Aniba rosaeodora* Ducke) is a natural compound widely used in perfumery industry. Evidence suggests that linalool exerts antidepressant and anxiolytic effects. Conversely, ethanol binge drinking (i.e., intermittent and episodic consumption) during adolescence elicits neurobehavioral alterations associated with brain damage. Here, we investigated whether linalool-rich Rosewood oil administration can improve the emotional and molecular impairments associated with ethanol binge-like exposure during adolescence in female rats. Rosewood oil was obtained by hydrodistillation and posteriorly analyzed. Adolescent female Wistar rats received four-cycles of ethanol binge-like pattern (3 g/kg/day, 3 days on/4 days off) and daily Rosewood oil (35 mg/kg, intranasally) for 28 days. Twenty-four hours after treatments, it was evaluated the impact of ethanol exposure and Rosewood oil treatment on the putative emotional impairments assessed on the splash and forced swimming tests, as well as the levels of brain-derived neurotrophic factor (BDNF), S100B, oxidative parameters, and inflammatory cytokines in prefrontal cortex and hippocampus. Results indicated that Rosewood oil intranasal administration mitigated emotional impairments induced by ethanol exposure accompanied by a marked increase in BDNF, S100B, glutathione (GSH), and antioxidant activity equivalent to Trolox (TEAC) levels in brain areas. Rosewood oil treatment also prevented the ethanol-induced increase of interleukin-1β, interleukin-6, tumor necrosis factor α (TNF-α), and neurofilament light chain (NFL) levels. These findings provide the first evidence that Rosewood oil intranasal administration exerts protective effects against emotional and molecular impairments associated with adolescent ethanol binge-like exposure, possibly due to linalool actions triggering neurotrophic factors, rebalancing antioxidant status, and attenuating proinflammatory process.

* Correspondence to: Laboratório de Farmacologia da Inflamação e do Comportamento, Instituto de Ciências da Saúde, Universidade Federal do Pará, Rua Augusto Corrêa 1, Campus do Guamá, Belém-Pará 66075-900, Brazil.
E-mail address: crismaia@ufpa.br (C.S.F. Maia).

https://doi.org/10.1016/j.biopha.2024.117120
Received 16 April 2024; Received in revised form 4 July 2024; Accepted 8 July 2024
Available online 17 July 2024

1. Introduction

The global prevalence of diseases that affect mental health has grown considerably in recent decades [1]. The emergence of the COVID-19 pandemic further aggravated this scenario, as many mental health determinants were highlighted, increasing the prevalence of common mental disorders, such as depression [1]. Depressive disorder is the most prevalent mental health condition among individuals with alcohol use disorder (AUD). This simultaneous occurrence is related to the worsening and adverse prognosis for both disorders when compared to *per se* disturbance, including a greater risk of suicidal behavior [2].

The binge drinking exposure (i.e., intermittent and episodic consumption of ethanol) consists of the most common form of alcohol misuse among adolescents and young adults, characterized by the consumption of high doses of alcohol in a short period (about 2 hours) followed by a period of abstinence [3–5]. The binge drinking pattern results in blood alcohol levels of at least 0.08 g/dL, achieved following consuming four drinks for women or five drinks for men, frequently three days a week among adolescents, displaying physical and mental disabilities [6,7]. Although the global prevalence of alcohol per capita among females aged 15 years and above is markedly lower than among males, during adolescence (i.e., 15–19 years of age) two intriguing phenomena occur: i) the smaller difference in the trends of prevalence of drinking between females and males; ii) the percentage related to the increment of the drinking prevalence from 2000 to 2019 was higher among females compared to males, except in Africa [8].

Epidemiological studies have indicated that alcohol consumption acts as a risk factor for the incidence of depression, and people with AUD exhibit 2.3 times more depressive conditions during the twelve months of analysis of this association [9]. Additionally, nearly 33 % of patients under treatment for AUD experienced depressive symptoms [2].

The relationship between ethanol and depression is complex, with some studies indicating that depression generally precedes the AUD onset, while others suggest the opposite relationship. Furthermore, women seem to be more susceptible to the earlier onset of depression than men [2]. Although the precise neurobiological mechanisms of the crosstalk between depression and AUD remain to be established, there is increasing evidence provided by non-clinical studies. For instance, previous studies have demonstrated that binge drinking paradigm from adolescence till adulthood in female rodents induces emotional and motor alterations as well as cognitive impairments related to oxidative damage, neuroinflammation, and neurotrophic factors dysfunction in several brain areas, such as hippocampus and prefrontal cortex [10–14].

On the other hand, beyond the use of classical psychotropic medications, different therapeutic strategies have been investigated for the treatment of central nervous system (CNS) disorders, including essential oils [15–17]. Due to the biological activity of their majority constituents, essential oils have emerged as therapeutic alternative agents in aromatherapy to manage mental disorders, including depression [18,19].

Linalool-rich Rosewood oil (*Aniba rosaeodora* Ducke) is a natural compound that emerges as a candidate for the treatment of emotional disorders. Rosewood belongs to the Lauraceae family, with 50 genera and 2500–3000 species distributed in tropical and subtropical latitudes [20]. The genus *Aniba* presents significant ecological and economic value due to the large quantity of their essential oils [21,22]. In the Amazon region, *A. rosaeodora* Ducke presents the famous names of "pau-rosa", "pau-rosa-itaúba", "pau-rosa-mulatinho", and "pau-rosa-imbaúba", with significant economic importance for the cosmetics industry, due to the high content of linalool (80–97 %) in its essential oil, which is present in all parts of the tree. However, linalool is generally extracted from the trunk wood and used in the world market as a valuable component of perfumes and fragrances [23–26].

In traditional medicine, Rosewood oil is used as an analgesic, antimicrobial, antiseptic, bactericidal, aphrodisiac, tissue regenerator, and tonic [26,27]. Effects on the CNS have been attributed to linalool, which acts as an anticonvulsant, antidepressant, hypnotic, and sedation [27]. Recently, our research group demonstrated antidepressant and anxiolytic properties of the intraperitoneal administration of essential oils rich in linalool extracted from the leaves of *Aniba rosaeodora* (pau-rosa), *Aniba parviflora* (macacaporanga) and *Aeollanthus suaveolens* (catinga-de-mulata) in rats [28]. As reviewed by Maia and colleagues [29], linalool acts by different molecular mechanisms relevant to both ethanol brain damage and depression, such as inflammatory process, oxidative stress, and neurotrophic factors.

Therefore, in the present study, we investigated whether intranasal administration of linalool-rich Rosewood oil can mitigate the emotional impairments associated with ethanol binge-like exposure during adolescence in female rats. Moreover, putative molecular mechanisms underlying the neurobehavioral effects of Rosewood oil were investigated, including the measurement of neuroinflammatory and oxidative stress markers and neurotrophic factors in the prefrontal cortex and hippocampus.

2. Materials and methods

2.1. Plant material

Samples of Rosewood twigs were collected in an experimental plantation of Prof. Milton Mota at the Universidade Federal Rural da Amazônia (Belém city, Pará, Brazil), coordinates 1° 27' 31" S/48° 26' 4.5" W, in January 2020.

2.2. Essential oils extraction

The leafless twigs were dried at room temperature for 48 h, ground, and subjected to hydrodistillation in a Clevenger-type apparatus (100 g, 3 h, triplicate). Rosewood oil was dried in anhydrous sodium sulfate, and its percentage content was calculated based on the dry weight of the plant. The moisture content of the samples was calculated on a balance measuring moisture using infrared light. The oil was stored in a dark bottle and kept at 5 °C.

2.3. Analysis and identification of oil constituents

The oil constituent's analysis was carried out in the Laboratório Adolpho Ducke, Museu Paraense Emílio Goeldi (Belém city, Pará, Brazil), using a Shimadzu QP-2010 double system gas chromatography-mass spectrometry (GC-MS) and gas chromatography-flame ionization detector (GC- FID), equipped with a DB-5 ms silica capillary column (30 m x 0.25 mm; with 0.25 μm film thickness). Briefly, the hydrogen was the carrier gas, at a linear flow of 36.5 cm/s; injection-type without split flow, volume of 1 μL (2 μL of oil in 1 mL of n-hexane); injector and detector temperature at 250 °C, column temperature program from 60 to 250 °C, with a gradient of 3 °C/min. The identification of volatile components was made based on the comparison of their linear retention times with authentic standards, also using a homologous series of n-alkanes injected under the same analyzed conditions and with the fragmentation patterns observed in the mass spectra of authentic samples stored in the data system and aid of literature libraries [30–32].

2.4. Animals

Female Wistar rats (*Rattus novergicus*) aged 29 days (n = 45) were obtained from the Bioterium of Universidade Federal do Pará. The animals were maintained in a laboratory of Faculdade de Farmácia in collective polypropylene boxes (50 ×35 x 15 cm), 3–4 animals/box to avoid isolation stress. The bioassays used standardized temperature conditions (25 ± 1 °C), exhaustion, and a 12-hour light/dark cycle (lights on 6:00 a.m.) for animal maintenance with pelleted food and water *ad libitum*.

The procedures used in the present study follow the rules of the UFPA Ethics Committee on the Use of Animals [33] (protocol number

7090270319) and respect international guidelines on animal care. In addition, the present study was registered on the platform of *Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado* (SISGEN), Brazil Government, under number AA6B112. The authors further attest that all efforts were made to minimize the number of animals used and their suffering.

2.5. Experimental design

The animals were randomly distributed to the experimental groups. At 29th days old, animals received orally (gavage, through an orogastric cannula) (Insight, Brazil) distilled water or ethanol (3 g/kg/day; 20 % w/v; 3 days on/4 days off) (Êxodo, Brazil) in four binge-type episodes [11]. Rosewood oil (RO) (35 mg/kg/day) or saline solution (0.1 mL/100 g of animal weight) was administered daily intranasally for 28 consecutive days (56th postnatal day). Fluoxetine (10 mg/kg, i.p.) was used as positive control. The RO dose utilized was based on a previous study from our research group in which a positive control group with fluoxetine (10 mg/kg) and a standard linalool group (linalool 97 %, Sigma-Aldrich) were also included [28]. Animals were weighed weekly to adjust the final volume. Behavioral tests were performed 24 hours after the last administration. Fig. 1 illustrates the sequence in which the behavioral tests were performed, from the least aversive (splash test) to the most aversive (forced swimming test), to minimize the chance that behavioral responses were markedly altered by prior test history and the intervals between them (1 h). In addition, samples from the prefrontal cortex and hippocampus were collected for tissue analyses.

2.6. Behavioral assays

Behavioral experiments were conducted at the *Laboratório de Farmacologia da Inflamação e Comportamento* (LAFICO/UFPA, Belém, Brazil) one hour before the test for animal acclimatization. Behavioral assays occurred in a sound-attenuated room with controlled light (14 lux) and temperature (23 ± 1 °C). All behavioral experiments were conducted in a blinded manner between 2 and 6 p.m. to avoid interference with the animals' circadian cycle.

2.6.1. Splash test

The splash test is a pharmacologically validated model supported by motivational behavior (self-cleaning behavior) and linked to animal apathy [34,35]. Thus, anhedonia and depressant-like profile are related to reduced self-cleaning time [36]. Briefly, animals were placed individually in an acrylic box (9 ×7 × 11 cm), and sucrose solution (10 %) was applied to the animal's back, as described elsewhere [37,38]. The self-cleaning time was manually recorded for 5 min as an index of self-care and motivational behavior.

2.6.2. Forced swimming test

A modified version of the forced swimming test was performed as proposed by Overstreet [39] and previously validated in our laboratory [11,13] to mitigate the interference of learning and memory across the preconditioning and test exposures of rats in the forced swim test. The animal was placed in a glass cylinder (50 cm high by 30 cm in diameter) filled with a 40 cm water column at 23 ± 1 °C for 5 min. The first 2 min were considered habituation to the aversive environment. Immobility time, characterized by simple movements sufficient to keep floating, was recorded in the final 3 min of the test. After the test, the animal was removed from the water, dried with flannel, and placed again in the cage.

2.7. Tissue collection and preparation

For this bioassay, the animals were anesthetized with isoflurane for craniotomy procedures 24 hours after the behavioral tests. Then, the prefrontal cortex and hippocampus were collected. The fresh tissue samples were added to microtubes with AllPrep commercial kit solution (1 mL) and stored at −80 °C for subsequent analysis of brain-derived neurotrophic factor (BDNF) and S100B mRNA; levels of Glutathione (GSH), Trolox equivalent antioxidant capacity (TEAC), nitric oxide (NO), and thiobarbituric acid-reactive substances (TBARS), as well as the concentrations of interleukins (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and neurofilament light chain (NFL). Previously of biochemical and molecular evaluations, tissue samples were submitted to homogenization in a specific buffered salt solution, following

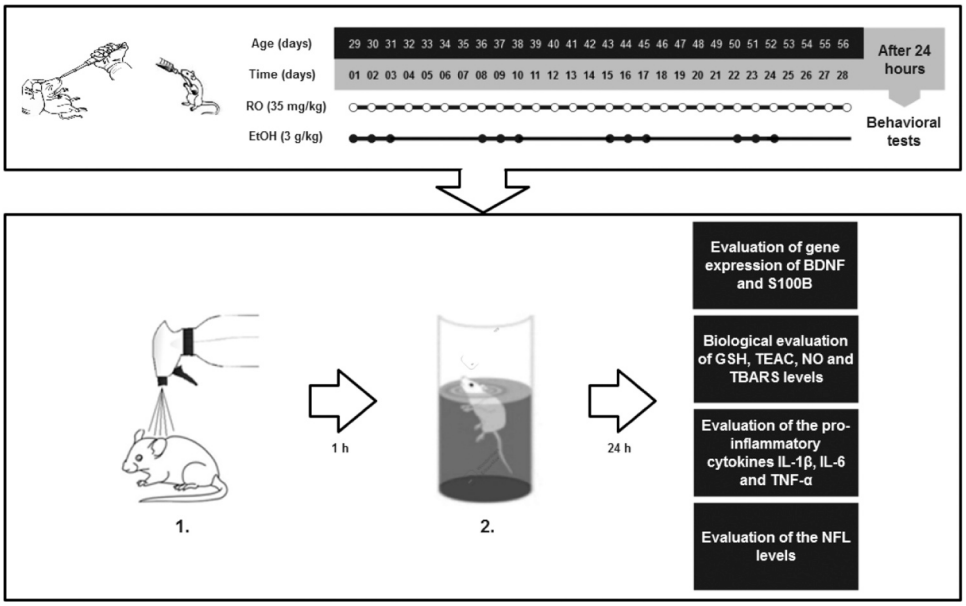

Fig. 1. Illustration of the experimental design. Treatment with Rosewood oil (RO) and ethanol (EtOH; 20 % w/v). Female Wistar rats (29 days old) received orally distilled water or EtOH (3 g/kg/day) in four binge-like episodes (3 consecutive days followed by 4 days of abstinence per week). RO (35 mg/kg) or saline solution (SS; 0.1 mL/100 g) was administered intranasally (0.1 mL/100 g) for 28 consecutive days (56th postnatal days). The behavioral tests were performed 24 hours following the last EtOH/RO administration, from the least aversive (splash test) to the most aversive (forced swim test), with an interval of 1 h between them. Tissue collection (prefrontal cortex and hippocampus) occurred 24 h after the behavior tests for the performance of neurochemical assays.

centrifugation for 10 min and the supernatant collection.

2.8. Evaluation of BDNF and S100B gene expression

Total RNA from each sample was extracted with Tri-reagent (Applied Biosystems, USA), following the manufacturer's instructions. RNA concentration and quality were determined using the NanoDrop spectrophotometer (Kisker, Germany) and 1 % agarose gel electrophoresis. Complementary DNA was synthesized using the High-Capacity cDNA Archive kit (Applied Biosystems, Poland). QRT-PCR assessed BDNF and S100B mRNA expression with TaqMan primers and probes purchased from Assays-on-demand Products for Gene Expression (Applied Biosystems, USA). The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was selected as an internal control for RNA input and reverse transcription efficiency. All real-time qRT-PCR reactions were performed in triplicate. Finally, the data were previously analyzed using the 2-ΔCt method, calculated according to Livak and Schmittgen [40].

2.9. In vitro evaluation of the antioxidant capacity of the rosewood oil

The ABTS•+ and DPPH• assays were used to assess the antioxidant capacities of the rosewood oil, which was determined according to their equivalence to the potent antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylchromono-2-carboxylic acid) and a water-soluble synthetic vitamin E analog.

2.9.1. DPPH method

To evaluate the *in vitro* Trolox Equivalent Antioxidant Capacity (TEAC) of rosewood oil, the 1,1-diphenyl-2-picrylhydrazyl (DPPH•) radical (DPPH•) assay was performed [41]. To measure the antioxidant capacity, the absorbance of DPPH• solution (2,2-diphenyl-1-picrylhydrazyl) 0.1 mM diluted in ethanol was determined. Subsequently, 0.6 mL of DPPH• solution, 0.35 mL of distilled water, and 0.05 mL of the sample were mixed and placed in a water bath at 37 °C for 30 min. After that, the absorbance was determined in a spectrophotometer Nm Kasvi at 517 nm. The synthetic antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylchromono-2-carboxylic acid) was used as a standard solution for the calibration curve. The results were expressed as mM. The values found for the samples were compared to the Trolox standard (1 mM).

2.9.2. ABTS method

The ABTS•+ radical scavenging assay was determined according to the methodology adapted from Miller et al. [42] and Re et al. [43]. ABTS•+ (2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) was prepared using 7 mM ABTS•+, and 140 mM of potassium persulfate (K2O8S2) incubated at room temperature without light for 16 h. Then, the solution was diluted with phosphate-buffered saline until reached an absorbance of 0.700 (± 0.02) at 734 nm. The synthetic antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylchromono-2-carboxylic acid) was used as a standard solution for the calibration curve. To measure the antioxidant capacity, 2.97 mL of the ABTS•+ solution was transferred to the cuvette, and the absorbance at 734 nm was determined using a spectrophotometer (Nm Kasvi, Brazil). Then, 0.03 mL of the sample was added to the cuvette containing the ABTS•+ radical and after 5 min, the second reading was performed. The results were expressed as mM. The values found for the samples were compared to the Trolox standard (1 mM).

2.10. In vivo evaluation of oxidative stress parameters

2.10.1. Determination of total proteins

Total protein concentration was measured according to Bradford's method and adapted by Stoscheck to correct the oxidative stress parameters in tissue [44,45]. This technique binds proteins to the Coomassie Brilliant blue dye G-250, resulting in a blue-colored compound with maximum absorbance at 595 nm [46].

2.10.2. Glutathione (GSH) determination

GSH concentration was evaluated by Ellman's method [47]. It is based on the ability of GSH to reduce 5,5-dithiobis-2-nitrobenzoic acid (Sigma-Aldrich) to 5-thio-2-nitrobenzoic acid, which was quantified by UV/Visible spectrophotometry at 412 nm. GSH concentration was expressed as μg/g protein in homogenized tissue.

2.10.3. ABTS/TEAC method

The $ABTS^{\bullet+}$ radical scavenging assay was determined according to the methodology adapted from Miller et al. [42] and modified by Re et al. [42]. ABTS•+ (2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) was prepared using 7 mM ABTS•+, and 140 mM of potassium persulfate ($K_2O_8S_2$) incubated at room temperature without light for 16 h. Then, the solution was diluted with phosphate-buffered saline until it reached an absorbance of 0.700 (± 0.02) at 734 nm.

The synthetic antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylchromono-2-carboxylic acid) was used as a standard solution for the calibration curve. To measure the antioxidant capacity, 2.97 mL of the ABTS•+ solution was transferred to the cuvette, and the absorbance at 734 nm was determined using an Nm Kasvi spectrophotometer. Then, 0.03 mL of the sample was added to the cuvette containing the ABTS•+ radical and after 5 min, the second reading was performed. The results were expressed as mM. The values found for the samples were compared to the Trolox standard (1 mM).

2.10.4. Nitrite levels

The method is based on converting the nitrate ($NO3^-$) present in the biological samples to nitrite compound, an indirect measure of NO levels, using the nitrate reductase as a catalyst [48]. Shortly, 100 μL Griess reagent [0.1 % N-(1-naphthyl) ethylenediamine dihydrochloride and 1 % sulfanilamide in 5 % phosphoric acid 1:1] plus 100 μL of the biological supernatant samples previously deproteinized was incubated for 10 min at room temperature. Then, the solution was read at 570 nm in a spectrophotometer and compared to the standard curve of sodium nitrate (NaNO2). The values were expressed as μmol/L.

2.10.5. Determination of TBARS levels

Lipid peroxidation was measured using the TBARS method proposed by Winterbourn et al. [49]. The technique is based on the reaction of malondialdehyde (MDA) and other compounds with thiobarbituric acid (TBA; Sigma-Aldrich T5500) at pH 2.5 and 94 °C temperature, forming the MDA-TBA complex (pink color). The method consists of the initial preparation of monobasic potassium phosphate (KH2PO4 75 mM, Synth, 35210) in acidified water (pH 2.5) to prepare TBA compound (10 nM). Then, 100 μL of the sample was added to 500 μL of the TBA solution and submitted to a water bath (94 °C for 60 min). After incubation and cooling at room temperature for 10 min, 4 mL of 1-butyl alcohol was added. The final solution was submitted to vortex homogenization, following centrifugation at 2500 rpm for 10 min. The supernatant was collected (1 mL) for spectrophotometric reading at 535 nm. The results were expressed as nM/g of protein. A high concentration of TBARS indicates oxidative stress and lipid peroxidation [50].

2.11. Evaluation of inflammatory cytokines and NFL levels

The protein fraction of each sample was extracted with Tri-reagent (Applied Biosystems, USA), following the manufacturer's instructions. The cytokines IL-1β, IL-6, and TNF-α were detected using the specific commercial kits (Merck, Germany). For the NFL levels detection, the commercial kit containing specific antibody (E-EL-R2536, Elabscience, USA) was used. Initially, 10 μL of homogenate from each sample was added to a 96-well plate filled with 40 μL of the kit diluent. This procedure was performed in triplicate. Then, the plate was incubated at 37 °C for 30 min, adding 10 μL of chromatin solutions A and B. The process was finished by adding 50 μL of blocking solution to each well. After 15 min in the absence of light, a reader evaluated the microplate at a

wavelength of 450 nm (ELX808, BioTek, USA). The assay has a sensitivity of less than 0.1 picograms per milliliter (pg/mL) of minimum detectable dose of cytokines [51]. It did not show any cross-reactivity in the different related cytokines.

2.12. Statistical analysis

Firstly, using the Shapiro-Wilk test, the Gaussian distribution test (normality) was performed for each experimental group. After checking data homogeneity, one- or two-way analysis of variance (ANOVA) followed by Bonferroni post-hoc test was performed for multiple comparisons. For data with a non-Gaussian distribution, the Kruskal-Wallis test followed by uncorrected Dunn's test was applied. Data were expressed as the mean ± standard error mean (s.e.m.), and the probability used for the existence of a significant difference was $p < 0.05$. The GraphPad Prism 8.0.2 software was used to construct graphs and statistical analysis.

3. Results

3.1. Linalool-rich rosewood oil

The Rosewood oil (RO) yielded 2.8 %, considering its previous % moisture content of 10.4 %. It showed a light-yellow color, a floral-woody scent, and a 0.8665 g/mL density. After GC and GC-MS analysis, RO presented a linalool content of 93.4 %. The natural RO generally comprises the isomers (+)-linalool and (-)-linalool at a ± 1:1 ratio. The oil constituents are listed in Table 1.

3.2. Effects of Rosewood oil treatment and ethanol binge-like model on animals' body weight

The animals were weighed weekly to record the ethanol and RO exposure. Two-way ANOVA with repeated measures revealed that four cycles of binge-type ethanol exposure during adolescence did not change the animals' body weight [$F = 0.52$; $p = 0.86$] (Fig. 2). Furthermore, Rosewood oil *per se* or associated with the administration of the binge-like paradigm showed similar weight to the control individual in all checkpoints evaluated.

Table 1
Rosewood oil composition (%).

Constituents	RI_{Calc}	RI_{Lit}	Oil %
cis-Linalool oxide (furanoid)	1068	1067	2.8
trans-Linalool oxide (furanoid)	1086	1084	0.8
Linalool	1103	1095	**93.4**
cis-Linalool oxide (pyranoid)	1173	1170	0.4
α-Terpineol	1189	1186	0.1
Nerol	1225	1227	0.1
Geraniol	1248	1249	0.1
α-Copaene	1374	1374	0.1
β-Elemene	1387	1389	0.1
(*E*)-Caryophyllene	1417	1417	0.1
β-Selinene	1486	1489	0.1
α-Selinene	1494	1498	0.1
γ-Cadinene	1515	1513	0.1
(*E*)-Nerolidol	1559	1561	0.1
Spathulenol	1573	1577	0.1
Caryophyllene oxide	1579	1582	0.1
Humulene epoxide II	1606	1608	0.1
Pogostol	1655	1651	0.1
14-hydroxy-9-*epi*-(*E*)-Caryophyllene	1666	1668	0.1
Mayurone	1709	1709	0.1
Nootkatol	1719	1714	0.3
Benzyl benzoate	1763	1759	0.3
Total (%)			99.6

$RI_{Calc.}$= Calculated retention index; RI_{Lit}= Literature retention index [30].

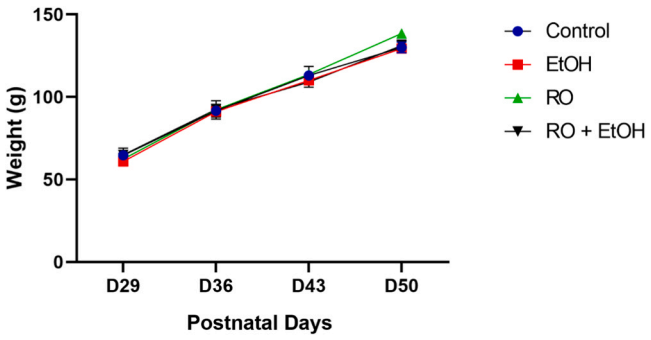

Fig. 2. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on the body weight of adolescent female rats. Results are expressed as mean ± s.e.m. (n = 10 animals/group). Two-way ANOVA with repeated measures.

3.3. Rosewood oil treatment mitigates emotional impairments induced by ethanol binge-like model

In the splash test, it was observed a significant effect of treatment on self-cleaning time [$F = 13.08$; $p < 0.05$]. Post-hoc comparisons indicated that ethanol-exposed animals displayed reduced self-cleaning time ($p < 0.01$) in comparison to the control group. The positive control group increased the self-cleaning time ($p < 0.05$). The intranasal RO administration recovered the self-cleaning parameter in ethanol-exposed animals ($p < 0.0001$) (Fig. 3).

Moreover, it was observed a significant effect of treatment on the immobility time addressed in the modified forced swimming test [$F=10.18$; $p < 0.05$]. Post-hoc comparisons indicated that ethanol-exposed animals displayed increased immobility time ($p < 0.01$) in comparison to the control group (Fig. 4). Fluoxetine-treated animals reduced immobility time ($p < 0.05$). Animals exposed to the ethanol binge-drinking paradigm that received intranasal administration of RO displayed a reduced immobility time, reaching values similar to the control group (Fig. 4).

3.4. Effects of Rosewood oil treatment and ethanol binge-like model on BDNF and S100b mRNA expression in the prefrontal cortex and hippocampus

The statistical analysis revealed significant effects of treatment on BDNF mRNA expression in the prefrontal cortex [Kuskal-Wallis = 37.18; $p < 0.0001$] (Fig. 5A) and hippocampus [Kuskal-Wallis = 37.05; $p <$

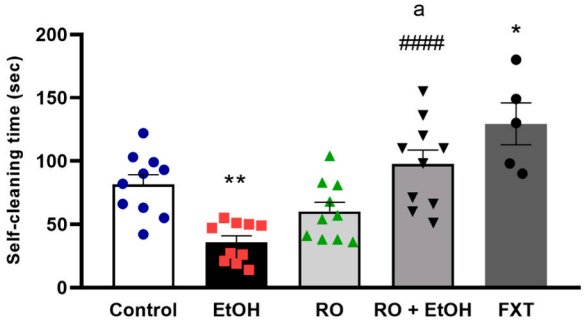

Fig. 3. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on the self-cleaning time on the splash test in adolescent female rats. Results are expressed as mean ± s.e.m. (n = 5–10 animals/group). Fluoxetine (10 mg/kg, i.p., FXT) was used as the positive control. *$p < 0.05$ compared to the control group; **$p < 0.01$ compared to the control group; $^{\#\#\#\#}p < 0.0001$ compared to the ethanol (EtOH) group; $^{a}p < 0.05$ compared to the RO group. One-way ANOVA followed by Bonferroni post-hoc test.

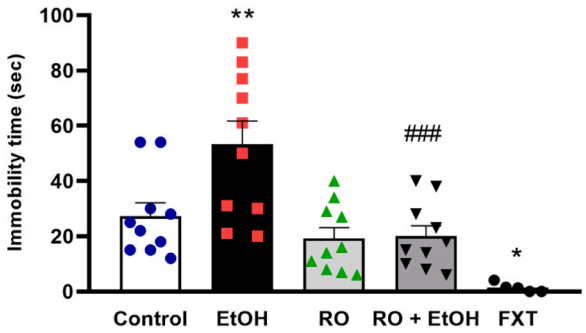

Fig. 4. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on the immobility time on the forced swimming test in adolescent female rats. Results are expressed as mean ± s.e.m. (n = 5–10 animals/group). Fluoxetine (10 mg/kg, i.p., FXT) was used as the positive control. *p < 0.05 compared to the control group; **p < 0.01 compared to the control group; ###p < 0.001 compared to the ethanol (EtOH) group. One-way ANOVA followed by Bonferroni post-hoc test.

0.0001] (Fig. 5C). Adolescent female rats exposed to ethanol binge-like model presented reduced BDNF mRNA expression in the prefrontal cortex (p < 0.05; Fig. 5A) and hippocampus (p < 0.05; Fig. 5C). The intranasal RO administration *per se* increased BDNF mRNA expression in the prefrontal cortex (p < 0.0001) and hippocampus (p < 0.001). Remarkably, intranasal RO administration also increased the BDNF mRNA expression in the prefrontal cortex (p < 0.05) (Fig. 5A) and hippocampus (p < 0.05) (Fig. 5C) of ethanol-exposed rats.

Regarding S100b mRNA expression, the results indicated that RO administration increased this marker equally in the prefrontal cortex (p < 0.0001; Fig. 5B) and hippocampus (p < 0.0001; Fig. 5D). The administration of RO in ethanol-exposure animals also increased S100b mRNA expression in the prefrontal cortex and hippocampus in comparison to the control (p < 0.001) and ethanol-exposed (p < 0.05).

3.5. *Effects of Rosewood oil treatment and ethanol binge-like model on oxidative stress parameters in the prefrontal cortex and hippocampus*

The *in vitro* antioxidant capacity of rosewood oil was evaluated through DPPH and ABTS assays. The oil presented a DPPH value (mean ± e.p.m.) of 0.7320 ± 0.008 and an ABTS value of 0.1648 ± 0.004 related to the antioxidant capacity.

In the *in vivo* experiments, prefrontal cortex and hippocampus samples were collected for biological assessment of oxidative stress parameters, including GSH, TEAC, NO, and TBARS. In the prefrontal cortex, GSH and TEAC were reduced in the ethanol-exposed animals (Fig. 6A and B; p < 0.01 and p < 0.05, respectively). However, the NO and TBARS parameters were not altered (Fig. 6C and D). Similar results were found in the hippocampus, in which ethanol-exposed subjects exhibited a reduction in the GHS and TEAC levels (Fig. 6E and F; p < 0.05), while NO and TBARS levels were not modified (Fig. 6G and H).

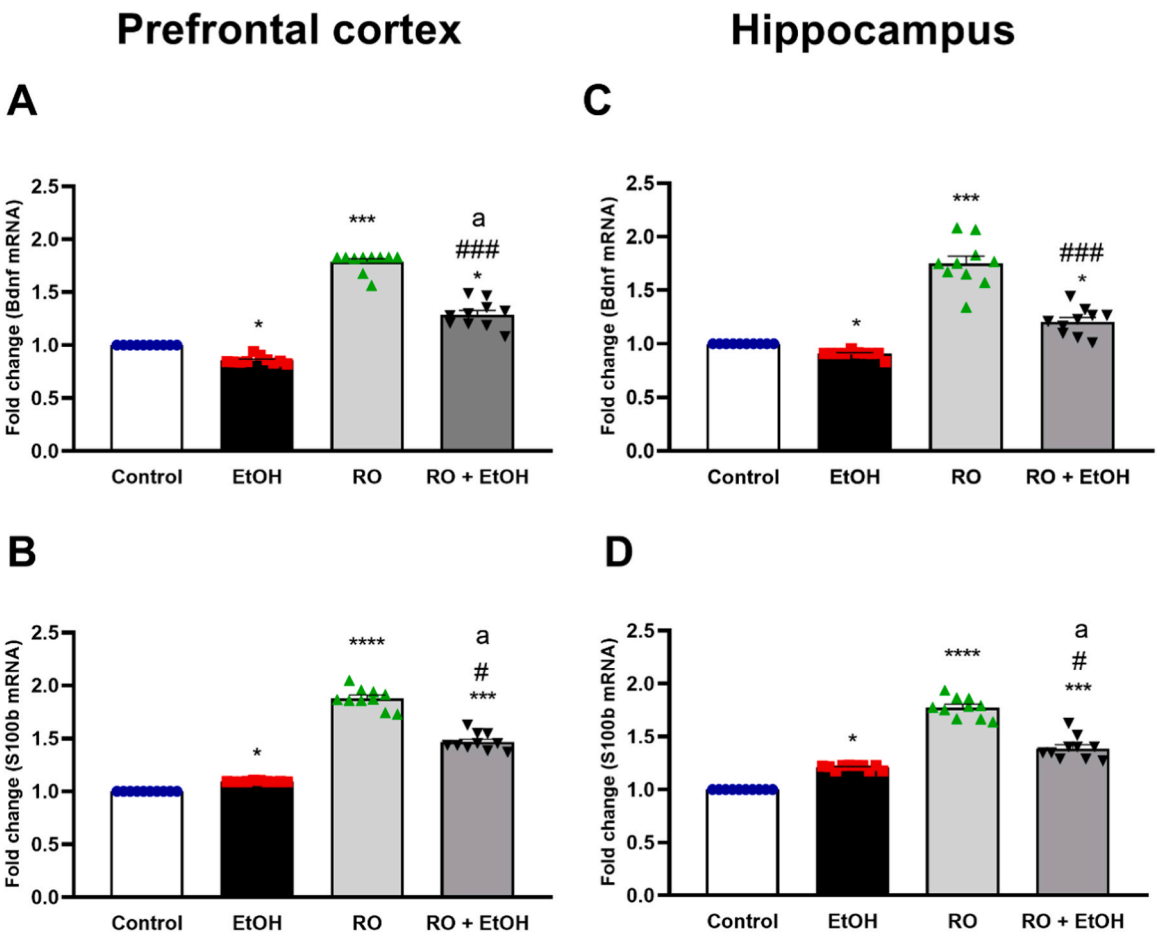

Fig. 5. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on brain-derived neurotrophic factor (BDNF) and S-100b gene expression in the prefrontal cortex (panel A and B) and hippocampus (panel C and D) of adolescent female rats. Results are expressed as mean ± s.e.m. (n = 10 animals/group). *p < 0.05 compared to the control group; ***p < 0.001 compared to the control group; ****p < 0.0001 compared to the control group; #p < 0.05 compared to the ethanol group; ###p < 0.001 compared to the ethanol group; ap < 0.05 compared to the RO group. Kruskal-Wallis followed by uncorrected Dunn's test.

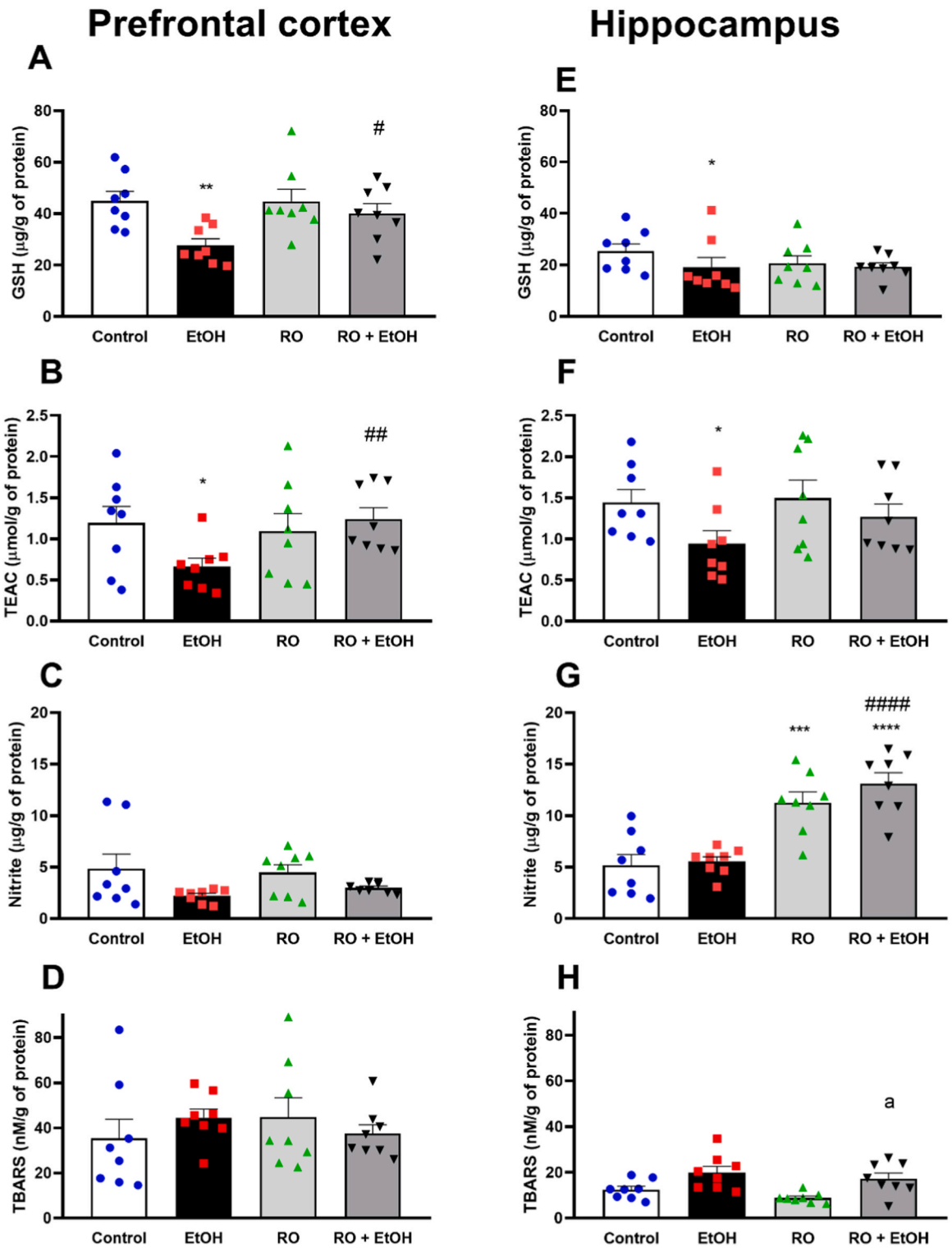

Fig. 6. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on oxidative stress parameters of Glutathione (GSH), Trolox equivalent antioxidant capacity (TEAC), nitric oxide (NO), and thiobarbituric acid-reactive substances (TBARS) in the prefrontal cortex (panels A,B,C,D) and hippocampus (panel E,F,G,H) of adolescent female rats. Results are expressed as mean ± s.e.m. (n = 8 animals/group). *$p < 0.05$, **$p < 0.01$, **$p < 0.001$, and ****$p < 0.0001$ compared to the control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#\#}p < 0.0001$ compared to the ethanol group; $^{a}p < 0.05$ compared to the RO group. Kruskal-Wallis followed by uncorrected Dunn's test.

Surprisingly, the RO *per se* increased the NO parameter in the hippocampus (Fig. 6G; $p < 0.001$).

Of high interest, RO restored the levels of antioxidant parameters in the prefrontal cortex in animals exposed to ethanol (GSH: $p < 0.05$; TEAC: 0.01), reaching values similar to the control group. Similar findings were observed in the hippocampus, where the treatment with RO rescued antioxidant parameters in ethanol-exposed animals (Fig. 6E, F, and H), except for the increase of NO levels when compared to control (Fig. 6G; control: $p < 0.001$; ethanol-exposed animals: $p < 0.0001$).

3.6. Effects of Rosewood oil treatment and ethanol binge-like model on inflammatory parameters in the prefrontal cortex and hippocampus

Four cycles of ethanol binge-type protocol during adolescence triggered the overproduction of pro-inflammatory cytokines (Fig. 7). In the prefrontal cortex, ethanol-exposed animals presented increased levels of IL-1β [$F = 152.6$; $p < 0.0001$] (Fig. 7A), IL-6 [$F = 101.6$; $p < 0.0001$] (Fig. 7B), and TNF-α [$F = 332.4$; $p < 0.0001$] (Fig. 7C). Similar profile was also found in the hippocampus: IL-1β [$F = 170.2$ $p < 0.001$] (Fig. 7D); IL-6 [$F = 156.7$ $p < 0.0001$] (Fig. 7E); TNF-α [$F = 146.3$ $p < 0.0001$] (Fig. 7F).

Remarkably, intranasal administration of RO *per se* reduced the IL-1β ($p < 0.0001$), IL-6 ($p < 0.0001$), and TNF-α ($p < 0.0001$) in the prefrontal cortex (Fig. 7A–C). In the hippocampus, the RO treatment also reduced the IL-6 ($p < 0.0001$) and TNF-α ($p < 0.0001$) levels, but it was not to IL-1β ($p = 0.1274$) (Fig. 7D–F).

In the animals submitted to the ethanol binge model, the RO administration prevented the increase in pro-inflammatory factors in both the prefrontal cortex and hippocampus. The group that received the ethanol administration plus RO treatment presented a reduction in IL-1β ($p < 0.001$), IL-6 ($p < 0.0001$), and TNF-α ($p < 0.0001$) levels compared to ethanol-exposed animals in the prefrontal cortex. In the hippocampus, the group submitted to the binge-like paradigm that received RO treatment presented a significant reduction in IL-6 ($p < 0.0001$) and TNF-α ($p < 0.0001$) compared to the binge-like exposed animals. Albeit this difference was not seen for the IL-1β parameter ($p < 0.05$), the association treatment exhibited values similar to the control group.

3.7. Effects of Rosewood oil treatment and ethanol binge-like model on neurofilament light chain (NFL) levels in the prefrontal cortex and hippocampus

Regarding the levels of neurofilament light chain (NFL), a marker of

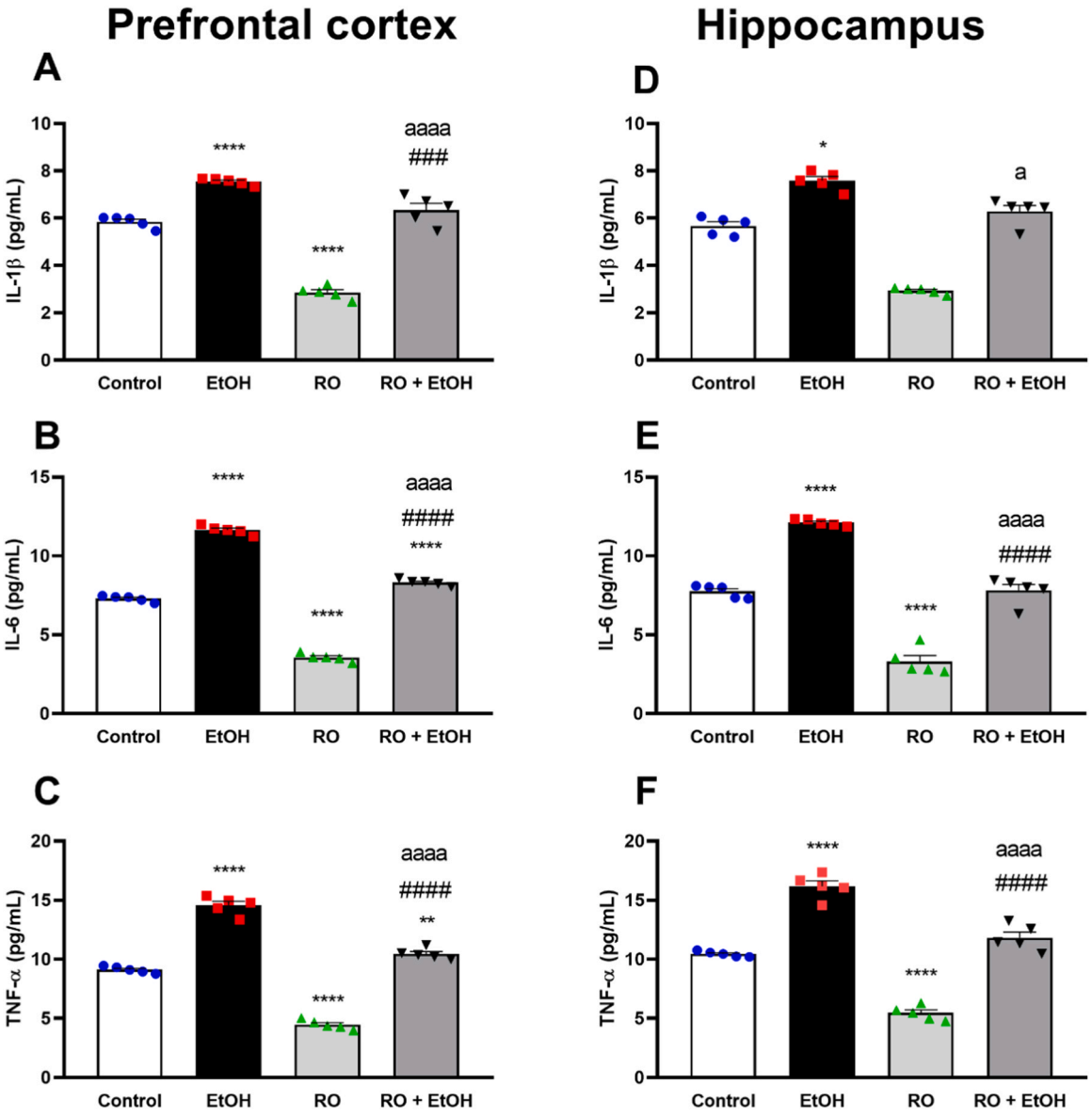

Fig. 7. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on inflammatory markers interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in the prefrontal cortex (panels A,B,C) and hippocampus (panels D,E,F) of adolescent female rats. Results are expressed as mean ± s.e.m. ($n = 5$ animals/group). *$p < 0.05$, **$p < 0.01$, and ****$p < 0.0001$ compared to the control group; ####$p < 0.0001$ compared to the ethanol group; $^{a}p < 0.05$ and $^{aaaa}p < 0.0001$ compared to the RO group. One-way ANOVA followed by Bonferroni's multiple comparisons test.

neurodegeneration, ANOVA revealed significant effect of treatment on this parameter in the prefrontal cortex [$F = 178.8$; $p < 0.0001$] and hippocampus [$F = 115.9$; $p < 0.0001$] (Fig. 8A, B, respectively). Ethanol exposure during adolescence increased the NFL levels in the prefrontal cortex and hippocampus ($p < 0.0001$; Fig. 8A, B). Notably, the intranasal RO administration reduced the NFL levels in both brain regions evaluated in comparison to ethanol-exposed subjects ($p < 0.0001$).

4. Discussion

It is well-documented that ethanol exposure during adolescence is an important factor in eliciting affective disorders including depression [52]. In addition, an increased prevalence of adolescent female drinkers compared to adolescent males was observed in almost all regional levels in the world across the years [8]. The current results demonstrate that the intranasal administration of Rosewood essential oil, rich in linalool bioactive compound, mitigates the emotional impairments observed in female rats exposed to ethanol binge-like paradigm during adolescence. Moreover, these behavioral benefits of Rosewood oil were possibly related to linalool actions triggering neurotrophic factors, rebalancing the antioxidant status, and attenuating the proinflammatory process.

Several factors interfere with essential oils' chemical composition, including different extraction techniques, part of the plant material used, plant age, and harvest time [53]. Environmental and technical variations also influence Rosewood oil's yield and linalool content. For example, the more significant water precipitation during the rainy season increases the oil yield by facilitating its separation by hydrodistillation technique. However, old leaves and excellent water circulation in this plant part may reduce the linalool content. In wood parts, oxidized products of linalool are more observed in old trunkwoods [24]. Furthermore, the oil extracted from the trunk, sold on the international market and used in cosmetic products, has approximately half the actual yield for the species due to the low efficiency of field distilleries, ranging from 0.7 % to 1.2 % [24].

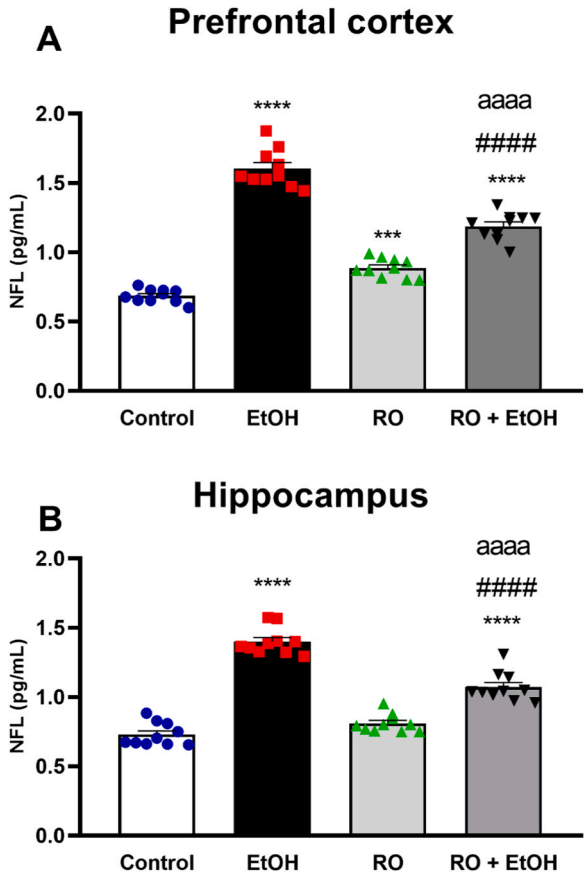

Fig. 8. Effects of ethanol binge-like model (4 cycles; 3 g/kg/day; 3 days on/4 days off, gavage) and intranasal Rosewood oil (RO) administration on neurofilament light chain (NFL) in the prefrontal cortex (panel A) and hippocampus (panel B) of adolescent female rats. Results are expressed as mean ± s.e.m. ($n = 10$ animals/group). ***$p < 0.001$, and ****$p < 0.0001$ compared to the control group; $^{\#\#\#\#}p < 0.0001$ compared to the ethanol (EtOH) group; $^{aaaa}p < 0.0001$ compared to the RO group. One-way ANOVA, Bonferroni's multiple comparisons test.

In our previous investigation, the leaves of Rosewood oil showed a yield of 1.8 % and a linalool content of 88.6 % [28]. The twig's Rosewood oil showed the highest yield (2.8 %) and linalool content (93.4 %) in the current work. The higher oil yield occurred due to the period of plant collection material in January, which is the season of highest rainfall in the Amazon region. The significant linalool content may be related to the young age of the sample plants. Such phytochemical characteristics of Rosewood oil obtained from thin twigs with high yield and linalool content were previously obtained [54], also highlighting the potential of linalool-rich Rosewood oil, as a therapeutic agent in psychiatry disorders, such as depression [29].

In this regard, the present work addressed the effects of intranasal administration of Rosewood oil on the emotional responses of female rats addressed in the splash and forced swimming tests that were submitted to an ethanol binge model during adolescence, previously validated by our group [10,11,13]. As expected, ethanol-exposed rats exhibited decreased self-cleaning behavior in the splash test and increased immobility time in the forced swimming test, both indicative of emotional impairments. Interestingly, when chronically administered by the intranasal route, the Rosewood oil did not alter these behavioral parameters 24 hours after the last administration. These results contrast with the findings described previously in which Rosewood oil and isolated linalool increased the self-cleaning time and reduced immobility time [28]. However, some important methodological differences may explain, at least in part, these discrepancies, since the earlier study addressed the effects of acute intraperitoneal administration (30 min before behavioral tests) of Rosewood oil in adult male rats.

There is increasing evidence of the antidepressant profile of Rosewood oil and its major constituent linalool (for review, see [29]). For instance, in a protocol of stress induced by REM-sleep deprivation, linalool reduced the immobility time in the forced swimming test as well as increased serotonin levels in the hippocampus and plasma [55]. Additionally, the inhalation of linalool-rich lavender oil improved anxiety- and depressive-like behaviors induced by high corticosterone administration in Sprague Dawley rats [56,57]. These authors also provided evidence of the biological effects of linalool on hippocampal neuroplasticity and neurogenesis [56,57].

Over the years, different points of view have emerged in the interpretation of the forced swimming test findings. Some authors have pointed out that the test measures coping with acute and inevitable stress, with stress being an essential factor in the depressive process. In forced swimming, classic antidepressant medications from clinical practice promote strategic adaptations to cope with the aversive environment. Thus, passive coping has become loosely equated with depression, given its complex biology, in addition to the fact that other disorders are also characterized by altered responses to stress [58]. Considering these limitations, behaviors addressed in the forced swimming test must be interpreted with caution and in association with additional behavioral parameters [59], as carried out in the present study through the evaluation of the animals-anhedonic profile in the splash test.

Different hypotheses have been postulated to explain the pathophysiology of depressive states [29]. Beyond the monoaminergic dysfunction, the neurotrophic, neuroinflammatory, and oxidative stress factors underlie depressive symptoms. Thus, 24 hours after the behavioral evaluations of the animals, samples from the prefrontal cortex and hippocampus were collected for biochemical assays to assess

neurotrophic, neuroinflammatory, and oxidative stress parameters.

The ethanol binge-like exposure during adolescence reduced the BDNF RNAm levels in the prefrontal cortex and hippocampus, which was attenuated by the intranasal administration of Rosewood oil. This is the first time that Rosewood oil's effect has been evaluated in terms of BDNF expression. However, the impact of other linalool-rich oils and the isolated linalool on BDNF expression has already been described. In previous research, lavender oil increased neurogenesis, dendritic complexity, and the number of BrdU-positive cells [57]. However, high content of BDNF and oxytocin were only recorded in the lavender oil *per se*. We hypothesize that this occurred due to the lower linalool content found in this species' oil compared to the high content present in rosewood oil. In the work of Ayuob and co-workers [56], basil oil reduced nerve cell atrophy, restored the reduced number of astrocytes, and decreased apoptotic nerve and glial cells in the hippocampus. According to this study, the mechanism of antidepressant action occurs through the positive modulation of gene and protein expression of BDNF, restoring the protein levels associated with synaptic plasticity and connectivity, development, and neuronal plasticity in crucial brain areas [60–62]. These previous data corroborate the current findings and point to the positive modulation of BDNF gene expression as a potential mechanism associated with the protective effects induced by linalool-rich Rosewood oil against ethanol brain damage.

In the present study, intranasal treatment with Rosewood oil increased the S-100b expression in the prefrontal cortex and hippocampus of ethanol-exposed animals. S-100b presents a dual pathway, which at the intracellular mean exerts a proliferative effect, whereas outside the cell, secreted or leaked by injury, the effect can be trophic or toxic, depending on its concentration. S-100b micromolar concentrations induce neuronal death directly through excessive stimulation of the receptor for advanced glycation end products (RAGE) and indirectly through RAGE-dependent activation of microglia and astrocytes, which release NO and pro-inflammatory factors, such as IL-1β, IL-6, and TNF-α, contributing to apoptosis and tissue neuroinflammation [63–65]. Therefore, the S-100b nanomolar concentrations elicit neurotrophic activity, stimulating the growth and differentiation of neurons and astrocytes.

Looking for S-100b signaling, the oxidative balance and cytokine levels were assessed. The DPPH and ABTS assays were performed to determine Rosewood oil's *in vitro* antioxidant capacity. The result of the antioxidant *in vitro* assays confirmed that Rosewood oil was active mainly in the presence of DPPH radicals and showed good antioxidant capacity. In *in vivo* experiments, the oxidative balance indicated that exposure to ethanol during adolescence consumed the antioxidant defenses related to the GSH and TEAC criteria to prevent lipid peroxidation in all regions studied. However, the groups treated intranasally with Rosewood oil presented an increase in NO index in the hippocampus. It has been suggested that the mechanisms of linalool's antioxidant effect are mainly based on antioxidant enzymatic modulation and free radical scavenging activity [29].

The inflammatory factors were more sensible to the hazardous effects of ethanol exposure. The prefrontal cortex and hippocampus of adolescents submitted to the binge-like paradigm presented increased in all inflammatory parameters evaluated. Notably, Rosewood oil administration *per se* exhibited a reduced cytokine profile in tissue, suggesting a neuroprotective activity. In addition, in the scenario of ethanol-induced tissue damage, the Rosewood oil mitigated the overproduction induced by the binge-like model in tissue samples, especially on hippocampus structure, reaching cytokine levels related to control animals, which justifies the recovery of behavioral impairments. The anti-inflammatory effect of Rosewood oil lacks evidence. Conversely, the anti-inflammatory activity of linalool is well documented. In experimental models of neuroinflammation, linalool inhibited the inflammatory response. It reversed the main chemical signals of inflammation in the CNS through the reduction of cytokines and pro-inflammatory mediators, including IL-1β, TNF-α, NO, NOS2, iNOS, mitogen-activated protein kinase (MAPK), cyclo-oxygenase-2 (COX-2), and prostaglandin E2 (PGE2) [66–68]. These properties suggest synergic mechanisms for the anti-inflammatory activity of linalool, especially blocking N-methyl-D-aspartate (NMDA) receptors, protein kinase B (AKT), MAPK, and nuclear factor-kappa B (NF-κB) pathways, suppressing the expression of signaling molecules of Toll-Like Receptor 4 (TLR4) via and microglia activation and, in addition, activating of the nuclear erythroid 2-related factor 2 (Nrf2) signaling [29,69].

Previous studies have postulated that adolescent rodents treated with antidepressant drugs presented increased S-100b levels since adolescence is a highly susceptible period of brain development [70]. Such increased expression of S-100b may be associated with the increase of serotonin levels induced by antidepressant drugs, which, in turn, stimulates the expression of S-100b via the serotonergic receptor 5-HT1A [70]. Additionally, the survival and maturation of serotonergic neurons are also promoted by serotonin and BDNF levels, which stimulates local expression of S-100b in a positive feedback looping. Thus, the serotonergic pathway can be indirectly influenced by BDNF through the stimulation of S-100b expression [71]. It is essential to highlight that linalool interacts with postsynaptic serotonergic 5-HT1A receptors and positively modulates BDNF [29,72].

The NO index also exhibits paradoxical effects. In glutamatergic-induced neurotoxicity, NO plays a role in the activation of NMDA receptors and, consequently, the release of intracellular calcium and sodium, which underlies ethanol-induced neurological impairment [73]. Conversely, NMDA receptor activation also induces NO release that inhibits excitatory currents provided by the NMDA receptor itself, down-regulating the NMDA signaling, and conferring neuroprotection against glutamatergic excitotoxicity mediated by the NMDA receptor [73]. This study demonstrated that Rosewood oil increased NO levels in the hippocampus, which suggests that excitotoxicity-mediated neuroprotection consists of an additional mechanism of action of linalool and rosewood oil, previously hypothesized by our group [29]. Besides, in an investigation of patients undergoing acute alcohol withdrawal syndrome, the authors proposed that higher serum S-100b levels at the start of treatment consist of the neuroprotective and trophic process and represented a protective and counter-regulatory mechanism to alcohol-induced glutamate-mediated neurotoxicity [74].

In recent years, the NFL has emerged as an important biomarker for neurological disorders. Several studies have demonstrated increased levels of NFL in diseases that affect the central and peripheral nervous system and are related to axonal degeneration. NFL is a neuronal cytoskeletal protein expressed in large-caliber myelinated axons [75]. In the current investigation, in an unprecedented perspective, the essential oil recovered the ethanol-induced NFL concentrations in the prefrontal cortex.

Although depression is not considered a neurodegenerative disorder, this disorder is closely related to the increase in pro-inflammatory cytokines [29], which have been correlated with increased levels of NFL [76]. In the CNS infections study, serum and cerebrospinal fluid NFL levels were positively correlated with the inflammatory markers IL-2, IL-4, IL-6, IL-10, IL-17a, TNF-α, and interferon-gamma (IFN-γ) [76], as also observed in NFL versus IL-6, IL-8, and IL-1β levels in mild, moderate, and severe COVID-19 patients [77]. Therefore, our results suggest a robust interaction between the anti-inflammatory effect presented by Rosewood oil and the reduced levels of NFL.

Altogether, the current findings reinforce our hypothesis that Rosewood oil may confer protective effects against the behavioral and neurochemical detrimental effects of ethanol binge exposure during adolescence through pleiotropic effects, including neurotrophic, antioxidant, and anti-inflammatory activities.

5. Conclusion

The present results indicated that the intranasal administration of Linalool-rich Rosewood oil mitigated the emotional impairments

induced by ethanol binge-like exposure in adolescent female rats. These behavioral benefits of Rosewood oil were accompanied by protective effects against molecular impairments associated with ethanol binge exposure during adolescence, possibly due to linalool actions triggering neurotrophic factors, rebalancing the antioxidant status, and attenuating the proinflammatory process.

Funding

This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-FINANCE CODE 001); Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq/ Brazil for the Researcher Productivity Grant (number 303196/2022-0 to CSFM), R.R.L. (312275/2021-8); Research Pro-Rectory of the Federal University of Pará (PROPESP, UFPA, Brazil), which provided the article publication fee. Secretaria de Estado de Ciência, Tecnologia e Educação Profissional e Tecnológica do Pará for the financial support for CEPAM Project (UEPA/PA).

CRediT authorship contribution statement

Lucas Villar Pedrosa da Silva Pantoja: Investigation. **Jofre Jacob da Silva Freitas:** Investigation. **Éverton Renan Quaresma dos Santos:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Rommel Mário Rodríguez Burbano:** Investigation. **Kelly Davis:** Investigation. **Rafael Rodrigues Lima:** Investigation. **Jorddy Neves Cruz:** Investigation. **Marta Chagas Monteiro:** Investigation. **Eloisa Helena A Andrade:** Writing – review & editing, Investigation, Data curation. **Cristiane S. F. Maia:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Paulo Fernando Santos Mendes:** Investigation. **Sarah Viana Farias:** Investigation. **Enéas Andrade Fontes-Junior:** Methodology, Formal analysis. **Bruno Gonçalves Pinheiro:** Formal analysis, Data curation. **José Guilherme S Maia:** Writing – review & editing, Methodology, Investigation. **Rui Daniel Prediger:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

the data is in the supplementary material

Acknowledgements

We are grateful to Research Pro-Rectory of the Federal University of Pará (PROPESP, UFPA, Brazil), Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPq, and Secretaria de Estado de Ciência, Tecnologia e Educação Profissional e Tecnológica do Pará (SECTET).

Competing interests statement

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.117120.

References

[1] GBD 2019 Mental Disorders Collaborators, Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet Psychiatry 9 (2) (2022) 137–150. https://doi.org/10.1016/S2215-0366(22)00002-5.
[2] R.K. Mchugh, R.D. Weiss, Alcohol use disorder and depressive disorders, Alcohol Res.: Curr. Rev. 40 (1) (2019) e1–e8, https://doi.org/10.35946/arcr.v40.1.01.
[3] A. Crego, S. Rodriguez-holguín, M. Parada, N. Mota, M. Corral, F. Cadaveira, Reduced anterior prefrontal cortex activation in young binge drinkers during a visual working memory task, Drug Alcohol Depend. 109 (3) (2010) 45–56, https://doi.org/10.1016/j.drugalcdep.2009.11.020.
[4] J. Jacobus, S.F. Tapert, Neurotoxic effects of alcohol in adolescence, Annu. Rev. Clin. Psychol. 9 (1) (2013) 703–721, https://doi.org/10.1146/annurev-clinpsy-050212-185610.
[5] G. Petit, C. Kornreich, P. Verbanck, A. Cimochowska, S. Campanella, Why is adolescence a key period of alcohol initiation and who is prone to develop long-term problem use? A review of current available data, Socioaffect. Neurosci. Psychol. 3 (1) (2013) 1–14, https://doi.org/10.3402/snp.v3i0.21890.
[6] A. Flores-Bonilla, H.N. Richardson, Sex differences in the neurobiology of alcohol use disorder, Alcohol Res.: Curr. Rev. 40 (2) (2020) 04, https://doi.org/10.35946/arcr.v40.2.04.
[7] A. Pilatti, P. Etkin, E.U. Parra, R.M. Pautassi, Association between attendance to pregaming events and alcohol-related consequences in argentinean youth, Health Addict. 18 (1) (2018) 5–16.
[8] WHO - World Health Organization, Global status report on alcohol and health and treatment of substance use disorders. Geneva, 2024. Licence: CC BY-NC-SA 3.0 IGO..
[9] B.F. Grant, F.S. Stinson, D.A. Dawson, S.P. Chou, M.C. Dufour, W. Compton, R. P. Pickering, K. Kaplan, Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions, Arch. Gen. Psychiatry 61 (8) (2004) 807–816, https://doi.org/10.1001/archpsyc.61.8.807.
[10] I.J.A. Belém-Filho, P.C. Ribera, A.L. Nascimento, A.R.Q. Gomes, R.R. Lima, M. E. Crespo-Lopez, M.C. Monteiro, E.A. Fontes-Júnior, M.O. Lima, C.S.F. Maia, Low doses of methylmercury intoxication solely or associated to ethanol binge drinking induce psychiatric-like disorders in adolescent female rats, Environ. Toxicol. Pharmacol. 60 (2018) 184–194, https://doi.org/10.1016/j.etap.2018.04.021.
[11] L.M.P. Fernandes, S.C. Cartágenes, M.A. Barros, T.C.V.S. Carvalheiro, N.C. F. Castro, M.G. Schamne, R.R. Lima, R.D. Prediger, M.C. Monteiro, E.A. Fontes-Júnior, R.A. Cunha, C.S.F. Maia, Repeated cycles of binge-like ethanol exposure induce immediate and delayed neurobehavioral changes and hippocampal dysfunction in adolescent female rats, Behav. Brain Res. 350 (2018) 99–108, https://doi.org/10.1016/j.bbr.2018.05.007.
[12] L.M.P. Fernandes, K.S. Lopes, L.N.S. Santana, E.A. Fontes-Júnior, C.H.M.A. Ribeiro, M.C.F. Silva, R.S.O. Paraense, M.E. Crespo-López, A.R.Q. Gomes, R.R. Lima, M. C. Monteiro, C.S.F. Maia, Repeated cycles of binge-like ethanol intake in adolescent female rats induce motor function impairment and oxidative damage in motor cortex and liver, but not in blood, Oxid. Med. Cell. Longev. 2018 (2018), https://doi.org/10.1155/2018/3467531.
[13] L.Y. Queiroz, I.G. De Oliveira, S.C. Cartágenes, L.M.P. Fernandes, S.M. Dos Santos, W.A.S. Ferreira, F.A.R. Mello Junior, L.O. Bittencourt, E.B.C. Paiva, R.M. R. Burbano, E.H.C. De Oliveira, M.C. Monteiro, R.R. Lima, E.A. Fontes-Júnior, C.S. F. Maia, Repeated cycles of binge-like ethanol exposure induces neurobehavioral changes during short- and long-term withdrawal in adolescent female rats, Oxid. Med. Cell. Longev. (2022) 1–11, https://doi.org/10.1155/2022/7207755.
[14] K. Lamarão-Vieira, D. Pamplona-Santos, P.C. Nascimento, M.G. Corrêa, L. O. Bittencourt, S.M. Dos Santos, S.C. Cartágenes, L.M.P. Fernandes, M.C. Monteiro, C.S.F. Maia, R.R. Lima, Physical exercise attenuates oxidative stress and morphofunctional cerebellar damages induced by the ethanol binge drinking paradigm from adolescence to adulthood in rats, Oxid. Med. Cell. Longev. 2019 (2019), https://doi.org/10.1155/2019/6802424.
[15] S.M.K. Rates, Plants as source of drugs, Toxicon 39 (5) (2001) 603–613, https://doi.org/10.1016/s0041-0101(00)00154-9.
[16] E.M. Melo, D.V.N. Silva, J.G. Martins, D.P. Veiga, P.M. Pereira, R.C.R. Cruz, S. Almeida-Junior, Mini-revisão sobre óleos essenciais utilizados na aromaterapia e sua ação farmacológica, In: Almeida-Junior, S. (org.), Produtos naturais e suas aplicações, 1 ed. Guarujá: Científica Digital (2021) 143–155. https://doi.org/10.37885/210303835.
[17] WHO - World Health Organization, The world medicines situation 2011, Traditional medicines: global situation, issues and challenges, 3rd ed. Geneva: WHO (2011).
[18] A. Gurib-Fakim, Medicinal plants: traditions of yesterday and drugs of tomorrow, Mol. Asp. Med. 27 (1) (2006) 1–93, https://doi.org/10.1016/j.mam.2005.07.008.
[19] Y. Zhang, Y. Long, S. Yu, D. Li, M. Yang, Y. Guan, D. Zhang, J. Wan, S. Liu, A. Shi, N. Li, W. Peng, Natural volatile oils derived from herbal medicines: A promising therapy way for treating depressive disorder, Pharmacol. Res. 164 (105373) () (2021), https://doi.org/10.1016/j.phrs.2020.105376.
[20] J.K.A.M. Xavier, L. Maia, P.L.B. Figueiredo, A. Folador, A.R. Ramos, E.H. Andrade, J.G.S. Maia, W.N. Setzer, J.K.R. Da Silva, Essential oil composition and DNA barcode and identification of *Aniba* species (Lauraceae) growing in the Amazon region, Molecules 26 (7) (2021) 1914, https://doi.org/10.3390/molecules26071914.
[21] L.A.S. Contim, C.R. Carvalho, F.A. Martins, D.V. Freitas, Nuclear DNA content and karyotype of rosewood (*Aniba rosaeodora*), Genet. Mol. Biol. 28 (4) (2005) 754–757, https://doi.org/10.1590/S1415-47572005000500017.

[22] C.A. Marques, Importância econômica da família Lauraceae Lindl, Floresta e Ambient. 8 (1) (2001) 195–206.
[23] P.H. May, L.E.S. Barata, Rosewood exploitation in the Brazilian Amazon: Options for sustainable production, Econ. Bot. 58 (2) (2004) 257–265, https://doi.org/10.1663/0013-0001(2004)058[0257:REITBA]2.0.CO;2.
[24] J.G.S. Maia, E.H.A. Andrade, H.A.R. Couto, F. Marx, C. Henke, Plant sources of Amazon rosewood oil, Química Nova 30 (8) (2007) 1906–1910, https://doi.org/10.1590/S0100-40422007000800021.
[25] J.G.S. Maia, R.H.V. Mourão, Amazon Rosewood (*Aniba rosaeodora* Ducke) Oils, in: V.R. Preedy (Ed.), Essential Oils in Food Preservation, Flavor and Safety, Academic Press, USA, 2016, pp. 193–201.
[26] A.C. Aprotosoaie, M. Hancianu, I.-I. Costache, A. Miron, Linalool a review on a key odorant molecule with valuable biological properties, Flavor Fragr. J. 29 (4) (2014) 193–219, https://doi.org/10.1002/ffj.3197.
[27] R.N. Almeida, D.A.M. Araújo, J.C.R. Gonçalves, F.C. Montenegro, D.P. Sousa, J. R. Leite, R. Mattei, M.A.C. Benedito, J.G.B. Carvalho, J.S. Cruz, J.G.S. Maia, Rosewood oil induces sedation and inhibits compound action potential in rodents, J. Ethnopharmacol. 124 (3) (2009) 440–443, https://doi.org/10.1016/j.jep.2009.05.044.
[28] E.R.Q. dos Santos, C.S.F. Maia, E.A. Fonte-Júnior, A.S. Melo, B.G. Pinheiro, J.G. S. Maia, Linalool-rich essential oils from the Amazon display antidepressant-type effect in rodents, J. Ethnopharmacol. 212 (2018) 43–49, https://doi.org/10.1016/j.jep.2017.10.013.
[29] E.R.Q. dos Santos, J.G.S. Maia, E.A. Fontes-Júnior, C.S.F. Maia, Linalool as a therapeutic and medicinal tool in depression treatment: a review, Curr. Neuropharmacol. 20 (6) (2022) 1073–1092, https://doi.org/10.2174/1570159X19666210920094504.
[30] H. Van Den Dool, P.A. Kratz, A generalization of the retention index system including linear temperature programmed gas-liquid partition chromatography, J. Chromatogr. A 11 (1963) 463–471, https://doi.org/10.1016/S0021-9673(01)80947-X.
[31] R.P. Adams, Identification of essential oil components by gas chromatography/mass spectrometry, 4th ed. Carol Stream: Allured Publishing Corporation (2007).
[32] L. Mondello, FFNSC 2: Flavors and Fragrances of Natural and Synthetic Compounds 2, Mass Spectral Database, Wiley-Blackwell, Hoboken, 2011.
[33] National Research Council (US, Committee for the update of the guide for the care and use of laboratory animals, Guide for the care and use of laboratory animals, National Academies Press, Washington, 2011, https://doi.org/10.17226/12910.
[34] P. Willner, Chronic mild stress (CMS) revisited: Consistency and behavioural-neurobiological concordance in the effects of CMS, Neuropsychobiology 52 (2) (2005) 90–110, https://doi.org/10.1159/000087097.
[35] S. Liang, Y. Wu, L. Hanxiaoran, A.J. Greenshaw, T. Li, Anhedonia in depression and schizophrenia: brain reward and aversion circuits, Neuropsychiatr. Dis. Treat. 18 (2022) 1385–1396, https://doi.org/10.2147/NDT.S367839.
[36] E.R. Butelman, B.D. Mcelroy, T.E. Prisinzano, M.J. Kreek, Impact of pharmacological manipulation of the k-opioid receptor system on self-grooming and anhedonic-like behaviors in mice, J. Pharmacol. Exp. Ther. 370 (1) (2019) 1–8, https://doi.org/10.1124/jpet.119.256354.
[37] E. Isingrini, V. Camus, A.M. Le Guisquet, M. Pingaud, S. Devers, C. Belzung, Association between repeated unpredictable chronic mild stress (UCMS) procedures with a high fat diet: a model of fluoxetine resistance in mice, PloS One 5 (4) (2010) 1–8, https://doi.org/10.1371/journal.pone.0010404.
[38] A.E. Freitas, D.G. Machado, J. Budni, V.B. Neis, G.O. Balen, M.W. Lopes, L.F. De Souza, A.L. Dafre, R.B. Leal, A.L.S. Rodrigues, Fluoxetine modulates hippocampal cell signaling pathways implicated in neuroplasticity in olfactory bulbectomized mice, Behav. Brain Res. 237 (2013) 176–184, https://doi.org/10.1016/j.bbr.2012.09.035.
[39] D.H. Overstreet, Modeling depression in animal models, Methods Mol. Biol. 829 (2012) 125–144, https://doi.org/10.1007/978-1-61779-458-2_7.
[40] K.J. Livak, T.D. Schmittgen, Analysis of relative gene expression data using real-time quantitative PCR and the 2−ΔΔCT method, Methods 25 (4) (2001) 402–408, https://doi.org/10.1006/meth.2001.1262.
[41] M.S. Blois, Antioxidant determinations by the use of a stable free radical, Nature 181 (1958) 1199–1200, https://doi.org/10.1038/1811199a0.
[42] M. Miller, J.K.M. Rao, A. Wlodawer, M.R. Gribskov, A left-handed crossover involved in amidohydrolase catalysis. Crystal structure of Erwinia chrysanthemi l-asparaginase with bound l-aspartate, FEBS Lett. 328 (1993) 275–279, https://doi.org/10.1016/0014-5793(93)80943-O.
[43] R. Re, N. Pellegrini, A. Proteggente, A. Pannala, M. Yang, C. Rice-Evans, Antioxidant activity applying an improved ABTS radical cation decolorization assay, Free Radic. Biol. Med. 26 (9–10) (1999) 1231–1237, https://doi.org/10.1016/s0891-5849(98)00315-3.
[44] M.M. Bradford, A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding, Anal. Biochem. 72 (1–2) (1976) 248–254, https://doi.org/10.1006/abio.1976.9999.
[45] C.M. Stoscheck, Quantitation of protein, Methods Enzymol. 182 (1990) 50–68, https://doi.org/10.1016/0076-6879(90)82008-p.
[46] A.D.N. Rodrigues, D.C.B. Da Silva, D.C. Baia Da Silva, P.F.S. Mendes, M.K. M. Ferreira, G.S. Rocha, M.A.M. Freire, L.M.P. Fernandes, C.S.F. Maia, W. Gomes-Leal, R.R. Lima, Aerobic physical training attenuates oxidative stress in the spinal cord of adult rats induced by binge-like ethanol intake, Antioxidants 12 (5) (2023) 1051, https://doi.org/10.3390/antiox12051051.
[47] G.L. Ellman, Tissue sulfhydryl groups, Arch. Biochem. Biophys. 82 (1) (1959) 70–77, https://doi.org/10.1016/0003-9861(59)90090-6.
[48] L.C. Green, D.A. Wagner, J. Glogowski, P.L. Skipper, J.S. Wishnok, S. R. Tannenbaum, Analysis of nitrate, nitrite, and (15N) nitrate in biological fluids, Anal. Biochem. 126 (1) (1982) 131–138, https://doi.org/10.1016/0003-2697(82)90118-X.
[49] C.C. Winterbourn, J.M. Gutteridge, B. Halliwell, Doxorubicin-dependent lipid peroxidation at low partial pressure of oxygen, J. Free Radic. Biol. Med. 1 (1) (1985) 43–49, https://doi.org/10.1016/0748-5514(85)90028-5.
[50] A. Ayala, M.F. Muñoz, S. Argüelles, Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal, Oxid. Med. Cell. Longev. 2014 (2014), https://doi.org/10.1155/2014/360438.
[51] M.M. Majeed, I. Ahmed, T. Roome, Y. Alali, K.A. Al-Aali, N. Ahmed, Z. Saleem, A. A. Alhumaidan, W.A. Farooqui, S. Ahmed, F. Vohra, T. Abduljabbar, Association of the unstimulated whole salivary cytokine IL-1β levels with initial, moderate and severe periodontitis. A case control study, Int. J. Environ. Res. Public Health 19 (2022) 2889.
[52] T.L. Briones, J. Woods, Chronic binge-like alcohol consumption in adolescence causes depression-like symptoms possibly mediated by the effects of BDNF on neurogenesis, Neuroscience 254 (2013) 324–334, https://doi.org/10.1016/j.neuroscience.2013.09.031.
[53] G. Nattudurai, K. Baskar, M.G. Paulraj, V.I.H. Islam, S. Ignacimuthu, V. Duraipandiyan, Toxic effect of *Atalantia monophylla* essential oil on *Callosobruchus maculatus* and *Sitophilus oryzae*, Environ. Sci. Pollut. Res. 24 (2) (2017) 1619–1629, https://doi.org/10.1007/s11356-016-7857-9.
[54] A.M. Teles, J.V. Silva-Silva, J.M.P. Fernandes, K.D.S. Calabrese, A.L. Abreu-Silva, S. C. Marinho, A.N. Mouchrek, V.E.M. Filho, F. Almeida-Souza, *Aniba rosaeodora* (var. amazonica Ducke) essential oil: chemical composition, antibacterial, antioxidant and antitrypanosomal activity, Antibiotics 10 (1) (2021) 24, https://doi.org/10.3390/antibiotics10010024.
[55] B.K. Lee, A.N. Jung, Y.-S. Jung, Linalool ameliorates memory loss and behavioral impairment induced by REM-sleep deprivation through the serotonergic pathway, Biomol. Ther. 26 (4) (2018) 368–373, https://doi.org/10.4062/biomolther.2018.081.
[56] N.N. Ayuob, A.E.-D.L. Firgany, A.A. El-Mansy, S. Ali, Can *Ocimum basilicum* relieve chronic unpredictable mild stress-induced depression in mice? Exp. Mol. Pathol. 103 (2) (2017) 153–161, https://doi.org/10.1016/j.yexmp.2017.08.007.
[57] D.I. Sánchez-Vidaña, K.K.-T. Po, T.K.-H. Fung, J.K.-W. Chow, W.K.-W. Lau, P.-K. So, B.W.-M. Lau, H.W.-H. Tsang, Lavender essential oil ameliorates depression-like behavior and increases neurogenesis and dendritic complexity in rats, Neurosci. Lett. 701 (2019) 180–192, https://doi.org/10.1016/j.neulet.2019.02.042.
[58] K.G. Commons, A.B. Cholanians, J.A. Babb, D.G. Ehlinger, The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior, ACS Chem. Neurosci. 8 (5) (2017) 955–960, https://doi.org/10.1021/acschemneuro.7b00042.
[59] A. Armario, The forced swim test: Historical, conceptual and methodological considerations and its relationship with individual behavioral traits, Neurosci. Biobehav. Rev. 128 (2021) 74–86, https://doi.org/10.1016/j.neubiorev.2021.06.014.
[60] A. Nakamura, S. Fujiwara, T. Ishijima, S. Okada, Y. Nakai, I. Matsumoto, T. Misaka, K. Abe, Neuron differentiation-related genes are up-regulated in the hypothalamus of odorant-inhaling rats subjected to acute restraint stress, J. Agric. Food Chem. 58 (13) (2010) 7922–7929, https://doi.org/10.1021/jf101200p.
[61] P. Xu, K. Wang, C. Lu, L. Dong, L. Gao, M. Yan, S. Aibai, Y. Yang, X. Liu, The protective effect of lavender essential oil and its main component linalool against the cognitive deficits induced by D-galactose and aluminum trichloride in mice, Evid. -Based Complement. Altern. Med. 2017 (2017), https://doi.org/10.1155/2017/7426538.
[62] K. Yoshida, N. Yamamoto, S. Fujiwara, A. Kamei, K. Abe, A. Nakamura, Inhalation of a racemic mixture (R, S)-linalool by rats experiencing restraint stress alters neuropeptide and MHC class I gene expression in the hypothalamus, Neurosci. Lett. 653 (2017) 314–319, https://doi.org/10.1016/j.neulet.2017.05.046.
[63] G. Sorci, R. Bianchi, F. Riuzzi, C. Tubaro, C. Arcuri, I. Giambanco, R. Donato, S100B protein, a damage-associated molecular pattern protein in the brain and heart, and beyond, Cardiovasc. Psychiatry Neurol. 2010 (2010), https://doi.org/10.1155/2010/656481.
[64] M. Schroeter, J. Sacher, J. Steiner, P. Schoenknecht, K. Mueller, Serum S100B represents a new biomarker for mood disorders, Curr. Drug Targets 14 (11) (2013) 1237–1248, https://doi.org/10.2174/13894501113149990014.
[65] U. Langeh, S. Singh, Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders, Curr. Neuropharmacol. 19 (2) (2021) 265–277, https://doi.org/10.2174/1570159X18666200729100427.
[66] Y. Li, O. Lv, F. Zhou, Q. Li, Z. Wu, Y. Zheng, Linalool inhibits LPS-induced inflammation in BV2 microglia cells by activating Nrf2, Neurochem. Res. 40 (7) (2015) 1520–1525, https://doi.org/10.1007/s11064-015-1629-7.
[67] A.M. Sabogal-Guaqueta, E. Osorio, G.P. Cardona-Gomez, Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer's mice, Neuropharmacology 102 (2016) 111–120, https://doi.org/10.1016/j.neuropharm.2015.11.002.
[68] A.M. Sabogal-Guaqueta, F. Hobbie, A. Keerthi, A. Oun, A. Kortholt, E. Boddeke, A. Dolga, Linalool attenuates oxidative stress and mitochondrial dysfunction mediated by glutamate and NMDA toxicity, Biomed. Pharmacother. 118 (2019), https://doi.org/10.1016/j.biopha.2019.109295.
[69] A.M. Barrera-Sandoval, E. Osorio, G.P. Cardona-Gomez, Microglial- targeting induced by intranasal linalool during neurological protection postischemia, Eur. J. Pharmacol. 857 (2019), https://doi.org/10.1016/j.ejphar.2019.172420.
[70] N. Bock, E. Koc, H. Alter, V. Roessner, A. Becker, A. Rothenberger, T. Manzke, Chronic fluoxetine treatment changes S100B expression during postnatal rat brain

development, J. Child Adolesc. Psychopharmacol. 23 (7) (2013) 481–489, https://doi.org/10.1089/cap.2011.0065.
[71] S. Djalali, M. Holtje, G. Grosse, T. Rothe, T. Stroh, J. Grosse, D.R. Deng, R. Hellweg, R. Grantyn, H. Hortnagl, G. Ahnert-Hilger, Effects of brainderived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development, J. Neurochem. 92 (3) (2005) 616–627, https://doi.org/10.1111/j.1471-4159.2004.02911.x.
[72] S.L. Guzman-Gutierrez, H. Bonilla-Jaime, R. Gomez-Cansino, R. Reyes-Chilpa, Linalool and β-pinene exert their antidepressant-like activity through the monoaminergic pathway, Life Sci. 128 (2015) 24–29, https://doi.org/10.1016/j.lfs.2015.02.021.
[73] F. Fadda, Z.L. Rossetti, Chronic ethanol consumption: from neuroadaptation to neurodegeneration, Prog. Neurobiol. 56 (4) (1998) 385–431, https://doi.org/10.1016/S0301-0082(98)00032-X.
[74] D. Wedekind, K. Neumann, P. Falkai, B. Malchow, K.R. Engel, K. Jamrozinski, U. Havemann-Reinecke, S100B and homocysteine in the acute alcohol withdrawal syndrome, Eur. Arch. Psychiatry Clin. Neurosci. 261 (2) (2011) 133–138, https://doi.org/10.1007/s00406-010-0121-2.
[75] L. Gaetani, K. Blennow, P. Calabresi, M. Di Filippo, L. Parnetti, H. Zetterberg, Neurofilament light chain as a biomarker in neurological disorders, J. Neurol. Neurosurg. Psychiatry 90 (8) (2019) 870–881.
[76] T.C. Hsiao, J. Chang, J.Y. Wang, D. Wu, K.J. Chuang, J.K. Chen, T.J. Cheng, H. C. Chuang, Serum neurofilament light polypeptide is a biomarker for inflammation in cerebrospinal fluid caused by fine particulate matter, Aerosol Air Qual. Res. 20 (2020) 1665–1674, https://doi.org/10.4209/aaqr.2019.08.0376.
[77] C. Hirzel, D. Grandgirard, B. Surial, M.F. Wider, D. Leppert, J. Kuhle, L.N. Walti, J. C. Schefold, T. Spinetti, F. Suter-Riniker, R. Dijkman, S.L. Leib, Neuro-axonal injury in COVID-19: the role of systemic inflammation and SARS-CoV-2 specific immune response, Ther. Adv. Neurol. Disord. 15 (2022), https://doi.org/10.1177/17562864221080528.