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**Antianxiety and antidepressant effects
of aqueous latex extract of *Euphorbia
resinifera***

Antianxiety and antidepressant effects of aqueous latex extract of *Euphorbia resinifera*

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Abstract

This study aims to examine the antianxiety and antidepressant effects of aqueous latex extract of *Euphorbia resinifera* in mice. Antianxiety and sedative effects were examined using the elevated plus maze test, open field test, and thiopental-induced sleeping time respectively. While the antidepressant effect was evaluated, using the forced swimming test. *E. resinifera* reduced the latency of sleeping and increased sleeping time significantly at 75 mg/kg. It reduced the immobility time and increased swimming significantly at all doses assessed (25, 50, and 75 mg/kg). Pretreatment with antagonists reversed these effects indicating the possible involvement of α_2 , 5HT₂, D₂, and GABA_A receptors respectively. These findings confirm the traditional utilization of this plant as an antioxidant, anxiolytic, and antidepressant.

Introduction

Anxiety is the most common psychiatric disorder. Commercial anxiolytics reduce anxiety but have many negative adverse effects on the other biological activities including the risks of dependence and cognitive effects (Stewart, 2005).

Depression is the mental disorder that causes morbidity the most. There is an important relationship between mood disorders and oxidative stress (Xu et al., 2014).

The use of exogenous antioxidants supports organisms against oxidative stress, thus the search for antioxidants of plant origin is a preoccupation of scientists for the benefits that could bring in terms prevention of diseases related to aging.

Euphorbia resinifera L is an endemic plant. All parts of the plant contain irritant latex which was widely used in traditional medicine for different therapeutic purposes as well as treatment of toothaches and pain

(Appendino and Szallasi, 1997). Further pharmacological and biological activities were recently discovered such as anticoagulant and antithrombotic effects (Siritapetawee et al., 2020) and the antiviral activity against the virus of tomato yellow leaf curl (Zhao et al., 2021). Several medicinal plants as *Agaricus blazei* (Haq et al., 2019), *Capsicum annuum* (Jawad et al., 2017), *Citrus limetta* (Kaur et al., 2019), *Glycyrrhiza glabra* (Dhingra and Sharma, 2006), *Hypericum perforatum* (Tian et al., 2014), *Mondia whitei* (Oketch-Rabah, 2012), *Salvia officinalis* (El Gabbas et al., 2018) were reported to possess antidepressant-like effect. There is a need to find new antidepressant biomolecules to respond to the increase in the incidence of anxiety as a modern disease and oxidative stress as a major source of different diseases.

Several studies focused only on the chemical characterization and isolation of terpenic compounds from latex (Benharref and Laverigne, 1985; Xiao-Yang et al., 2012). However, few investigations focused on neuropharma-



cological effects. This study aims to evaluate the anxiolytic, antidepressant, and antioxidant activity of aqueous latex extract of *E. resinifera*. In addition, the involvement of adrenergic, serotonergic, and dopaminergic receptors using antagonist drugs is investigated.

Materials and Methods

Plant material collection and preparation of extracts

E. resinifera aerial parts (seeds and stems) were collected in July 2018 from the province of Azilal, Ait M'hamed village (31°51' latitude N / 6°30'48 longitude W), Morocco. The samples were identified by Prof. Abderrahman Chait and deposited as a voucher specimen (ER18) in the plant herbarium of the laboratory, Department of Biology, Faculty of Sciences, Semlalia, Marrakech, Morocco.

Collection of latex of *E. resinifera*

The latex was manually collected in the morning in a sterile and clean bottle by slicing the leaf phyllode of *E. resinifera* using a razor blade. After the collection, the latex was placed in the oven at 40°C for 24 hours, the resulting powder was added to distilled water under an agitation system for 14 hours. Then, the aqueous extract was filtered using Whatman filter paper No. 1 and lyophilized. Thereafter, the extract was kept in the refrigerator at -20°C for other experiments.

Estimation of total phenolic compounds

Total phenolic compounds of the extract were estimated using the Folin-Ciocalteu method with some

minor modifications. Briefly, 20 µL of the sample was added to 1.16 mL of distilled water, 100 µL of Folin reagent and mixed with 300 µL of Na₂CO₃ (20%). The solutions obtained were incubated for 40 min at 45°C. Then, the optical density was measured at 760 nm. The total phenolic amount was expressed as µg gallic acid equivalents per g (GAE/g) of each sample (Singleton et al., 1999).

Determination of total flavonoids amount

The total flavonoid content was estimated using a similar method described elsewhere (Brighente et al., 2007). Briefly, 1 mL of AlCl₃ (2%) was homogenized with 1 mL of the sample. Then, the sample was incubated for 60 min at ambient temperature. Thereafter, the absorbance was determined at 410 nm. The total flavonoid amount was expressed as quercetin equivalents.

Quantification of condensed tannins

The condensed tannins were determined using the method reported elsewhere (Price et al., 1978). Briefly, a volume of 200 µL of the extract was added to 37% methanol, 8% HCL, and 4% methanolic vanillin which constitutes the vanillin reagent. Thereafter, the tubes were placed in a water bath at 30°C for 20 min. The values were expressed as µg catechol equivalents, CE/g of samples.

Antioxidant activities

DPPH free radical scavenging assay

The stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) was used to determine the antioxidant capacity of the extract, in compliance with the procedure

Box 1: Elevated Plus Maze Test

Principle

Elevated plus maze test is one of the widely used tests for measuring anxiety-like behavior. The mouse is exposed to open and elevated areas to understand the behavior.

Requirements

Arms and central platform; Video camera with software

Procedure

The dispositive is composed of four arms, 10 cm wide and 49 cm long, heighted 50 cm above the floor level.

Step 1: Place one mouse in the center of the apparatus carefully and left exploring for 5 min.

Step 2: The time spent on each arm, numbers of entries into each arm is counted and serve as anxiety index. Between two successive trials, the apparatus was cleaned by a clean tissue impregnated with alcohol.

Parameters

1) Open arm frequency: Frequency of mouse entry with all

four paws into the open, unprotected arms

2) Close arm frequency: Frequency of mouse entry with all four paws into the closed, protected arms

3) Central platform frequency: Frequency of mouse entry with all four paws into the central platform

4) Open arm duration: Total time the mouse spent in the open arms

5) Close arm duration: Total time the mouse spent in the closed arms

6) Central platform duration: Total time the mouse spent in the central platform

Advantages

This test is inexpensive and readily available to most laboratories, it's simple to use and simple to score consistently.

Reference

da Silva Almeida et al., 2015

Reference (Video)

Komada et al., 2008; Maqbool and Younus, 2019

described elsewhere (Sahin et al., 2004). 10 μ L of different concentrations of latex extract was added to 2 mL of methanol solution of DPPH (60 μ M). The absorbance was measured at 517 nm after 30 min of incubation at room temperature. BHT (butylated hydroxyanisole) and quercetin were used as a positive control, and the inhibiting concentration IC_{50} was calculated according to the following formula:

$$\text{Inhibition (\%)} = [(Ac-Ae)/Ac] \times 100$$

Where Ac is the absorption of the control at 30 min. Ae is the absorption of the sample.

Reducing power (FRAP assay)

The ferric reducing ability power was performed following the procedure described elsewhere (Oyaizu, 1986). This method consists of inhibiting the formation of the Fe (II)-ferrozine complex after the incubation of the samples with the divalent iron. In fact, 0.5 mL of various concentrations was added to distilled water (1 mL) and mixed with 2.5 mL phosphate buffer (2.5 mL; 0.2 M ; pH = 6.6) and potassium ferricyanide $[K_3Fe(CN)_6]$ (2.5 mL; 1%). Thirty minutes after incubation, 2.5 mL of distilled water, 2.5 mL of 10% trichloroacetic acid and 0.5 mL of $FeCl_3$ were added to the mixture. The absorbance was measured at 700 nm. Quercetin and BHT were used as positive control.

ABTS assay

The antioxidant capacity of *E. resinifera* was estimated with the protocol described elsewhere (Nicoletta al., 1999). Briefly, the solution was prepared by the reaction of 5 mL of 7 mM ABTS solution and 88 μ L of 140 mM potassium persulfate solution. The samples were stored in dark conditions for 16 hours. The ABTS solution was diluted in ethanol until the first absorbance value (0.7) at 734 nm.

Experimental animals

Female and male Swiss mice weighing between (25-32 g) were obtained from the animal house of the Faculty of Sciences Semlalia, Marrakech, Morocco. All animals were housed in a light and controlled temperature room (22°C, 12 hours: 12 hours cycle commences at 8 AM) and were fed and permitted to use water *ad libitum*.

Acute toxicity study

All animals were randomly divided into experimental and control groups (10 per group; 5 males and 5 females), weighing (25-32 g). They have received an administration intragastrically of the extract at doses (0, 100, 200, 500, 1000, and 2000 mg/kg). One hour after a single administration, animals were observed for any sign of toxicity, behavior changes, and mortality, then for 4 hours and thereafter for 24 hours. The animals that received the doses (200 and 500 mg/kg) were additionally supervised for up to 14 days post treat-

ment. During the experiment, food and water consumption, body weight, neurological disorders and mortality were recorded daily. The median lethal dose (LD_{50}), maximal tolerance dose (MTD), and minimal lethal dose (MLD) were calculated (Wu et al., 2018).

On day 14, animals were euthanized by cervical dislocation to recover the blood samples to examine the eventual variation hematological and biochemical parameters. The organs such as liver, spleen, and kidney were fixed in buffered formalin (10%), and incorporated in paraffin. Thereafter, the cuts of 5 μ m were obtained using a microtome and then colored with hematoxylin and eosin for microscopic examination.

Drug administration

The extract was dissolved in a vehicle (saline solution). While the yohimibine, olanzapine, diazepam, propranolol, cyproheptadine and anafranil were purchased from (Novartis Pharma, USA) and dissolved in saline solution (9%NaCl). The utilized doses were chosen from an acute toxicity study. All drugs were injected at a concentration of 10 mL/kg body weight. The control group received an equal volume of the vehicle. All treatment of plant extracts was administered orally by gavage, whereas olanzapine, diazepam, yohimibine, flumazenil, propranolol, and anafrani were administered intraperitoneally.

Animals were randomly divided into different 8 or 6 groups of 6 animals each: Control group (treated with vehicle), *E. resinifera* groups (treated with 25, 50, and 75 mg/kg of latex extract). Another group constitutes the positive control (treated with anafranil 10 mg/kg or diazepam 2 mg/kg). To evaluate the possible mechanism of action and involvement of $GABA_A$, D_2 , $5HT_2$, β and α_2 -receptors, we have constructed other groups treated daily with different antagonists 30 min before administration of the extract at 75 mg/kg (p,o).

All various groups were deprived of food and water. This procedure is similar to that described elsewhere (Patchev and Patchev, 2006). The animals were housed in individual cages, as a method widely used in stress induction. After 7 days of the administration, insomnia, anxiety and depression with a battery of tests such as the elevated plus maze test, forced swimming test, thio-pental-induced sleeping test, and open field test were evaluated.

To determine the implication of $GABA_A$, β , α_2 , $5HT_2$, and D_2 -receptors, the animals were pretreated with flumazenil (2.5 mg/kg), propranolol (5 mg/kg), cyproheptadine (3 mg/kg), yohimibine (1 mg/kg), and olanzapine (2 mg/kg) as specific antagonists of $GABA$ -ergic, adrenergic, serotonergic, and dopaminergic receptors respectively.

Open field test

The exploration and locomotion activity was evaluated

using the open field apparatus (50 × 50 × 50 cm). The test consists of placing the animals individually in the center for 5 min. Different parameters were measured such as immobility time, number of crossing, and redress number depicted elsewhere (Brown et al., 1999).

Forced swimming test

The antidepressant-like effect of *E. resinifera* was assessed by the forced swimming test largely described elsewhere (Detke et al., 1995). The test was divided into 2 sessions, the first session of the experiment (habituation session test), mice were separately placed into cylindrical containers (Ø = 30 cm, H = 59 cm) containing 25 cm of water at 25 ± 1°C. The mice were left to swim for 6 min then were dried and transported back to their cages. 24 hours later, the process was repeated in the same manner (test session). The following parameters were noted: the dynamic swimming and immobility time.

Sedative activity

The potential sedative effect of the extract was investigated using the thiopental-induced sleeping time. To this end, the sleeping state was induced with an intraperitoneal injection of sodium thiopental (60 mg/kg), 30 min after the independent groups received different treatments. In this test, two parameters were recorded such as time of sleeping and latency. Sleeping for more than 120 continuous minutes constitutes a maximal value for animals in each group (Costa et al., 2014; da Silva Almeida et al., 2015).

Statistical analysis

The statistical analysis was performed using GraphPad Prism 7 software Inc., USA version 6. The different results were analyzed by one-way ANOVA followed by the Tukey's post hoc test and given as mean values ± SEM. The values $p < 0.05$ were considered significant.

Results

Phytochemical profile

The results suggest that the extract contains a considerable and increasing amount of total phenol, flavonoid, and condensed tannins (19.1 ± 0.4 mg GAE/g), (9.9 ± 0.2 mg QE/g), and (4.4 ± 0.1 mg CE/g) respectively.

Antioxidant activities

The extract possesses strong antiradical activity similar to that of standard antioxidant. As indicated, the IC₅₀ values reported by FRAP, DPPH and ABTS methods were 2.2 ± 0.2 mg/mL, 1.5 ± 0.2 mg/mL, and 5.4 ± 0.5 mg/mL respectively (Table I).

Acute toxicity assessment

Determination of LD₅₀ and food intake behavior

The animals who received the last three doses of the extract (500, 1000, and 2000 mg/kg) by oral route exhibited neurobehavioral signs of toxicity such as lethargy, piloerection, respiratory distress, motor skills disorders, and grooming. Considering that, symptoms increased as doses increased. All animals were treated with 2000 mg/kg and died at (2-30 hours). The lethal dose₅₀, lethal dose₉₀, minimal tolerance dose and maximal values were 764.8, 1171, 100, and 500 mg/kg, respectively. Concerning the food intake behavior, there were no statistically significant differences in the body weight on the water and food consumption between the control group and treated groups with 100 mg/kg of the extract (data not shown).

Hematological, biochemical and histopathological analysis

The administration of extract did not alter the level of biochemical parameters (serum transaminases, urea, and creatinine) at all doses (200 and 500 mg/kg). The microscopic examination revealed no histological damages in the removed organs of the group treated with 200 mg/kg of extract. However, the extract at a dose of 500 mg/kg induced mild morphological disorganization of the glomerulus, especially in some female mice (data not shown).

Neurobehavioral tests

Elevated plus maze test

The extract decreased the number of entries in the closed arms but did not modify the number of entries in the open arms. Concerning the other parameters, administration of the extract increased significantly ($p < 0.05$) time of permanence in the open arms at all treatments. Furthermore, the extract at doses of 25, 50, and 75 mg/kg decreased the time of permanence in the closed arms compared to the control group. The observed effect of the extract was similar to the group treated with diazepam used as a reference drug, indicating the possible anxiolytic-like effect of the extract (Figure 1).

To determine the implication of GABA_A receptors in the anxiolytic-like effect of the extract, other groups were pretreated with a GABA_A receptor antagonist (flumazenil 2.5 mg/kg). The results demonstrated that the

	Aqueous latex extract	Standard antioxidant (IC ₅₀ µg/mL)	
		Quercetin	BHT
DPPH	1.5 ± 0.2	0.1 ± 0.0	0.2 ± 0.0
FRAP	2.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0
ABTS ^a	5.4 ± 0.5	2.5 ± 0.2	3.3 ± 0.0

^avalues are expressed in mM trolox equivalent per mL

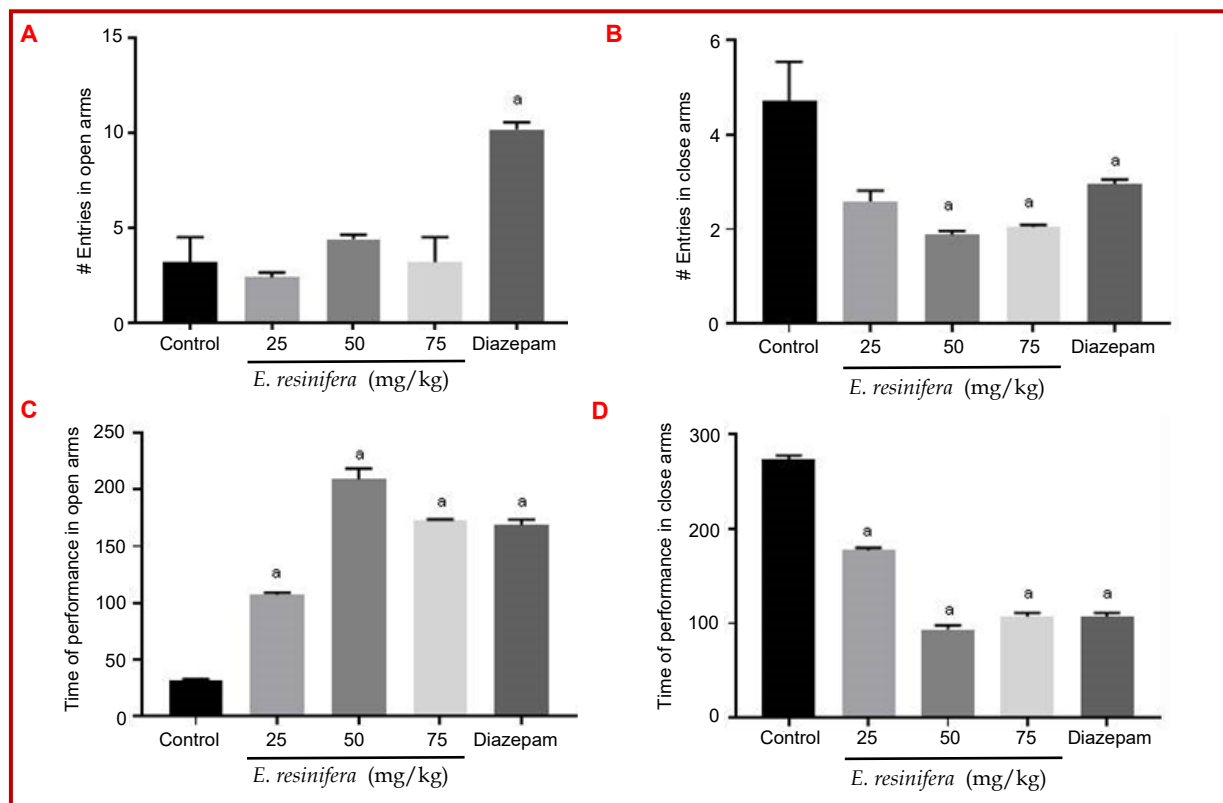


Figure 1: Effect of aqueous latex extract of *Euphorbia resinifera* and diazepam (2 mg/kg) in elevated plus maze test in mice (n=6 per group). The values are expressed as mean \pm SEM, superscript 'a' indicates $p < 0.05$ statistically significant difference between control and treated groups. According to one-way ANOVA followed by Tukey's test

pretreatment with flumazenil inverted the neuropharmacological effect of the extract (75 mg/kg) in all measured parameters. Simultaneously, flumazenil inverted the anxiolytic-like effect of diazepam (Figure 2).

Open field test

The administration of the extract at 50 and 75 mg/kg reduced (68.5 and 76.2%) significantly the number of crossing respectively, and increased the time of immobility compared to the control group (Figure 3A, C). A similar result was recorded for the group treated with diazepam. This implies a possible central nervous system anxiolytic effect dose-dependently.

Thiopental-induced sleeping time

E. resinifera reduced the latency of sleeping compared to the control group and increased sleeping time significantly compared to the negative control only at 75 mg/kg, indicating a possible sedative activity (Figure 3B, D).

Forced swimming test

The administration of *E. resinifera* reduced significantly the immobility time and increased swimming at all doses assessed (25, 50, and 75 mg/kg) when compared to the control group. These results are similar to those obtained from the reference drug (anaftranil). This

suggests a possible antidepressant-like effect of *E. resinifera*.

To determine the involvement of D_2 , $5HT_2$, β and α_2 -receptors, animals were pretreated with olanzapine, cyproheptadine, propranolol and yohimbine receptors antagonists respectively. As indicated in Figure 4 (B), pretreatment of animals with olanzapine (2 mg/kg, a dopamine D_2 -receptor antagonist) reversed significantly the antidepressant-like effect induced by the extract at a high dose (75 mg/kg). Also, the pretreatment with cyproheptadine and yohimbine (3 mg/kg and 1 mg/kg; $5HT_2$ and α_2 -receptor antagonists, respectively) significantly inverted the immobility time in the forced swimming test produced by *E. resinifera*, but pretreatment of animals with propranolol did not reverse the antidepressant-like effect of *E. resinifera*. This indicates the possible implication of D_2 , $5HT_2$ and α_2 receptors in antidepressant-like effect of *E. resinifera*.

Discussion

The present investigation of *E. resinifera* demonstrates an important antioxidant activity, no symptoms of toxicity, and mortality for biological doses used in all pharmacological tests. However, the biochemical and hematological parameters were not significantly

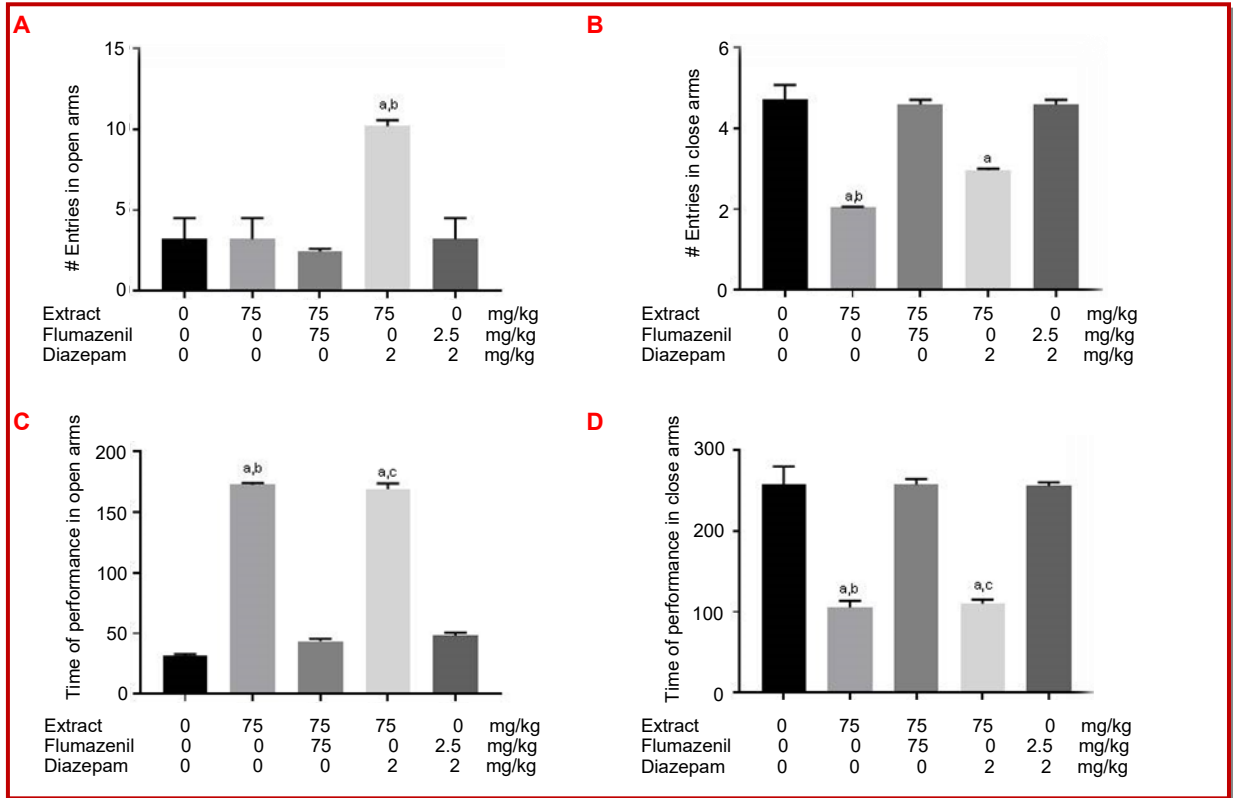


Figure 2: Effect of *Euphorbia resinifera*, diazepam and flumazenil in the EPM test (n=6 per group) values are expressed as mean \pm SEM, where superscript 'a', 'b' and 'c' indicate $p < 0.05$, statistically significant difference groups. One-way ANOVA followed by Tukey's post hoc test

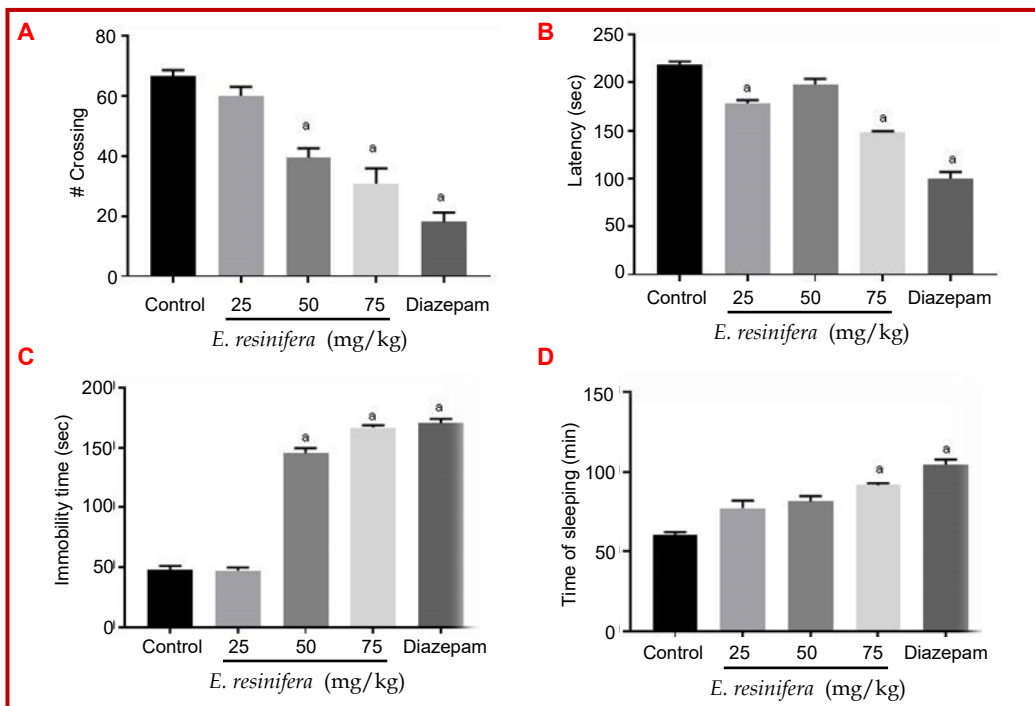


Figure 3: Aqueous latex extract of *E. resinifera* effect and diazepam (2 mg/kg) in open field test (A, C) and thiopental-induced sleeping test (B, D) in mice (n=6/group). Data are given as mean \pm SEM, where superscript 'a' indicates $p < 0.05$, statistically significant difference between the groups. One-way ANOVA followed by Tukey's post hoc test

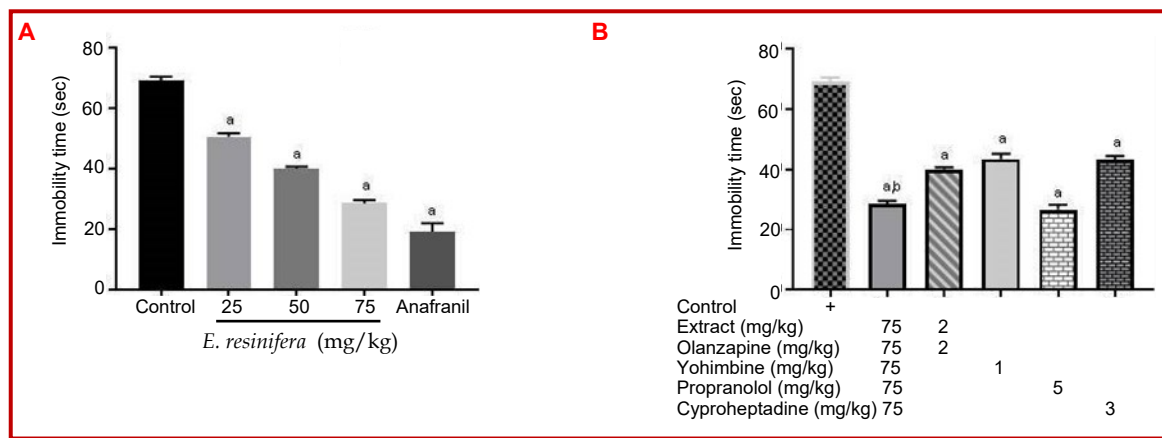


Figure 4: Antidepressant-like effect of *E. resinifera* in forced swimming test (A), and effect of the pretreatment with olanzapine, yohimbine, diazepam, propranolol, cyproheptadine (B) on the aqueous latex extract from *E. resinifera*-induced decrease in immobility time in the animals forced swimming test, (n=6 per group). Data were expressed as mean \pm SEM, where superscript 'a' indicate p < 0.05 significant difference between control group and different treated groups, b indicate p < 0.05 significant difference between groups. One-way ANOVA followed by Tukey's post hoc test

changed. In addition, the histopathological examination has indicated any changes in removed organs. On the other hand, it provides evidence for the beneficial antidepressant, anxiolytic and sedative-like effects of *E. resinifera* in mice under chronic deprivation and isolation stress.

Latex is one of the interesting plant exudates rich in bioactive compounds responsible for several pharmacological activities (Licá et al., 2018). The FRAP, DPPH, and ABTS assays were used to determine the antioxidant activity of the extract. The obtained results revealed high antioxidant capacity with the lowest value of IC₅₀. These results are following those reported by elsewhere in another species *E. dracunculoides* (Majid et al., 2015). They demonstrated an important antioxidant capacity of the fractioned extracts. Also identified the antiradical capacity of *E. characias* latex by determining the total amount of DPPH, flavonoid, and phenols molecules as well as anticholinesterase inhibitory capacities (Pintus et al., 2013).

Concerning acute toxicity assay, the group treated with aqueous latex extract at 500 mg/kg presented a reduction in body weight. This could be associated with a decrease in food intake behavior and not strictly due to metabolic changes. In general, the chemical compound is considered toxic just when there is a weight loss of more than 10%. The hematopoietic system is an indicator of the physiopathological changes caused by toxic compounds (Adeneye et al., 2006).

The elevated plus maze test is an experimental model used to assess the degree of anxiety. Two parameters were recorded: the number of entries in each arm and the time spent in each arm (Foyet et al., 2017). In this regard, aqueous latex extract at all doses increased the time of permanence and number of entries in the open arms, and decreased the time of permanence and

number of entries in the closed arms, indicating a significant anxiolytic-like effect. These outcomes are in concordance with a previous study reported by (Anuradha et al., 2008). To investigate the involvement of GABA_A receptor in the anxiolytic-like effect of aqueous latex extract, animals were pretreated with flumazenil (GABA_A competitive antagonist) before latex extract administration at 75 mg/kg. Flumazenil reversed the neuropharmacological effect of latex extract proposing the possible implication of GABA_A receptors. This is in accord with (Anuradha et al., 2008). Also, these results are following those reported by elsewhere (Lanthers et al., 1990) concerning another species belonging to Euphorbiaceae family namely *E. hirta*. Sleeping disorders constitute among others the consequences of chronic stress, thiopental induced sleeping time is the most used experimental model to evaluate the sedative effect of drugs. Aqueous latex extract of *E. resinifera* reduced latency time and prolonged sleeping time but only at 75 mg/kg. This suggests that the extract has two complementary effects, at low doses (25 and 50 mg/kg) acting as an anxiolytic and at high dose (75 mg/kg) as a sedative.

Concerning the antidepressant-like effect, the administration of *E. resinifera* reduced significantly the time of immobility in the forced swimming test indicating an antidepressant-like effect of the extract dose-dependent. In the present report, the antidepressant-like effect of *E. resinifera* was inverted by the pretreatment with yohimbine, periaxetine and medizapine, but not with propranolol suggesting that aqueous latex extract act by adrenergic, dopaminergic, and serotonergic receptors. These findings confirm with several previous investigations on other species of euphorbia (Frazer, 2000; Masuda et al., 2001; Abbasi-Maleki et al., 2017; Gu et al., 2012).

The phenolic compounds are recognized for their biolo-

gical activities and health care, particularly flavonoids belonging to the phenol family. Natural-derived antioxidants have acquired a good reputation worldwide due to their high content of phenolic compounds. In fact, according to the authors, scavenging capacity could be due to the contribution of hydrogen or electron to neutralize the DPPH free radicals. The strong revealed antioxidant activity of aqueous latex extract could be attributed to the presence of phenol and flavonoid compounds (Majid et al., 2015).

The latex extract of *E. resinifera* possesses a remarkable anxiolytic-like effect in chronic stress induced by immobilization. But the pretreatment with flumazenil, reversed the anxiolytic effect of *E. resinifera*, suggesting that its effects are modulated by the GABA_A receptor benzodiazepine receptor and Cl⁻-channel complex (Anuradha et al., 2008). Major depressive disorders are known to be related to a dysfunction in monoaminergic systems such as noradrenergic, dopaminergic, or serotonergic systems (Nutt, 2008). Also, several recent studies reported the involvement and role of α_2 , β , 5HT₂ and D₂-receptors in antidepressant-like effects (Pytka et al., 2016). The adrenergic receptors (α , β) are the most important receptors targets of noradrenaline and adrenaline in the central nervous system but also in peripheral organs. Furthermore, α - and β -receptors are relevant as targets of many synthetic drugs, which interact with the actions of catecholamines. It was reported that α_2 -receptor acts as a mediator of antidepressant-like effect of some drugs in the experimental animal model of depression (Masuda et al., 2001). In addition, the β -adrenergic receptor was identified in stress-induced depression disorders (Pandey et al., 1995).

Moreover, antioxidant compounds found in the aqueous latex extract of *E. resinifera* could explain the neuropharmacological effects recorded in this plant. There was a report on the relation between flavonoids and antidepressant-like effect. In addition, antioxidant components can inhibit the reuptake of serotonin (Khanzode et al., 2003).

The dopaminergic receptors, especially (D₁ and D₂), have a positive effect on the management of depressive disorders since antagonists of these receptors (D₁ and D₂) reverse the antidepressant-like effect of several drugs belonging to the antidepressants family (Yamada et al., 2004). Many studies regularly demonstrate low dopamine and/or dopamine metabolite level in subjects with depression (Lambert et al., 2000).

Conclusion

The aqueous latex extract of *E. resinifera* possesses an important antioxidant capacity. It also reveals beneficial effects on anxiety and depression in chronic depriva-

tion and isolation stress. These effects could be attributed to interactions with GABAergic, adrenergic, serotonergic, and dopaminergic receptors.

Financial Support

Self-funded

Ethical Issue

All tests were carried out in compliance with the European Community Guidelines (EEC directive 86/609/EEC, dated November 24, 1986). All attempts were made to keep animal suffering to a minimum and to decrease the number of animals used.

Conflict of Interest

Authors declare no conflict of interest

Acknowledgement

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References

- Abbasi-Maleki S, Bakhtiarian A, Nikoui V. Involvement of the monoaminergic system in the antidepressant-like effect of the crude extract of *Menthapiperita* (Lamiaceae) in the forced swimming test in mice. *Synergy* 2017; 5: 21-28.
- Adeneye AA, Ajagbonna OP, Adeleke TI, Bello SO. Preliminary toxicity and phytochemical studies of the stem bark aqueous extract of *Musanga cecropioides* in rats. *J Ethnopharmacol.* 2006; 105: 374-79.
- Anuradha H, Srikumar BN, Rao BSS, Lakshmana M. *Euphorbia hirta* reverses chronic stress-induced anxiety and mediates its action through the GABA A receptor benzodiazepine receptor-Cl⁻ channel complex. *J Neural Transm.* 2008; 115: 35-42.
- Appendino G, Szallasi A. Euphorbium: Modern research on its active principle, resiniferatoxin, revives an ancient medicine. *Life Sci.* 1997; 60: 681-96.
- Benharref A, Lavergne JP. Triterpènes issus des latex des euphorbes cactoides marocaines *E. resinifera*, *E. echinus* et *E. officinarum*: Isolement, étude comparative par RMN 13C des quatre classes tétracycliques, eupho-lanostane, élémolanostane, lanostane etnor-31 lanostane. *Bull Soc Chim.* 1985; 5: 965-72.
- Brighente IMC, Dias M, Verdi LG, Pizzolatti MG. Antioxidant activity and total phenolic content of some Brazilian species. *Pharm Biol.* 2007; 45: 156-61.
- Brown R.E, Corey S.C, Moore A.K. Differences in measures of exploration and fear in MHC-congenic C57BL/6J and B6-H-

- 2K mice. Behav Genet. 1999; 29: 263-71.
- Costa JP, de Oliveira GA, de Almeida AA, Islam MT, de Sousa DP, de Freitas RM. Anxiolytic-like effects of phytol: Possible involvement of GABAergic transmission. Brain Res. 2014; 1547: 34-42.
- da Silva Almeida JR, de Souza AV, de Oliveira AP, dos Santos US, de Souza MD, dos Passos Bispo L, Turatti IC, Lopes NP. Chemical composition of essential oils from the stem barks of *Croton conduplicatus* (Euphorbiaceae) native to the Caatinga biome. Afr J Pharm Pharmacol. 2015; 9: 98-101.
- Detke M.J, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 1995; 121: 66-72.
- Dhingra D, Sharma A. Antidepressant-like activity of *Glycyrrhiza glabra* L. in mouse models of immobility tests. Prog Neuro-Psychopharmacol Biol Psychiatry. 2006; 30: 449-54.
- El Gabbas Z, Bezza K, Laadraoui J, Makbal R, Aboufatima R, Chait A. *Salvia officinalis* induces antidepressant-like effect, anxiolytic activity and learning improvement in hippocampal lesioned and intact adult rats. Bangladesh J Pharmacol. 2018; 13: 367-78.
- Fellegrini N, Ke R, Yang M, Rice-Evans C. Screening of dietary carotenoids and carotenoid-rich fruit extracts for antioxidant activities applying 2, 2'-azinobis (3-ethylenebenzothiazoline-6-sulfonic acid radical cation decolorization assay. Meth Enzymol. 1999; 299: 379-89.
- Foyet SH, Balmus IM, Hervé NAH, Emmanuel AA, Guenne S, Kiendrebéogo M, Ciobica A. Ethnopharmacological approaches in mood and anxiety disorders: The relevance of the oxidative stress status. J Complement Integr Med. 2017; 2017.
- Frazer A. Norepinephrine involvement in antidepressant action. J Clin Psychiatry. 2000; 61: 25-30.
- Gu L, Liu YJ, Wang YB, Yi LT. Role for monoaminergic systems in the antidepressant-like effect of ethanol extracts from *Hemerocallis citrina*. J Ethnopharmacol. 2012; 139: 780-87.
- Haq IU, Aslam M, Ahmed H, Sultana N. Antidepressant-like activity of hydroalcoholic extract of *Agaricus blazei* in stressed and unstressed mice. Bangladesh J Pharmacol. 2019; 14: 136-43.
- Kaur J, Bhatia M, Nain P. Antidepressant activity of *Citrus limetta* leaves in mice using battery of behavior models modulating via serotonergic systems. Bangladesh J Pharmacol. 2019; 14: 181-87.
- Komada M, Takao K, Miyakawa T. Elevated plus maze for mice. JoVE. 2008; 2008.
- Jawad M, Khan H, Pervaiz S, Bawazeer SS, Abu-Izneid T, Saeed M, Kamal MA. Pharmacological validation of the anxiolytic, muscle relaxant and sedative like activities of *Capsicum annuum* in animal model. Bangladesh J Pharmacol. 2017; 12: 439-47.
- Khanzode S.D, Dakhale G.N, Khanzode S.S, Saoji A, Palasodkar R. Oxidative damage and major depression: The potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Report. 2003; 8: 365-70.
- Lambert G, Johansson M, Ågren H, Friberg P. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: Evidence in support of the catecholamine hypothesis of mood disorders. Arch Gen Psychiatry. 2000; 57: 787-93.
- Lanhers MC, Fleurentin J, Cabalion P, Rolland A, Dorfman P, Misslin R, Pelt JM. Behavioral effects of *Euphorbia hirta* L.: Sedative and anxiolytic properties. J Ethnopharmacol. 1990; 29: 189-98.
- Licá ICL, dos Santos Soares AM, de Mesquita LSS, Malik S. Biological properties and pharmacological potential of plant exudates. Food Res Int. 2018; 105: 1039-53.
- Majid M, Khan M.R, Shah N.A, Haq I.U, Farooq M.A, Ullah S, Sharif A, Zahra Z, Younis T, Sajid M. Studies on phytochemical, antioxidant, anti-inflammatory and analgesic activities of *Euphorbia dracunculoides*. BMC Complement Alternat Med. 2015; 15: 1-15.
- Masuda Y, Ohnuma S, Sugiyama T. Mouse forced swimming. Methods Find Exp Clin Pharmacol. 2001; 23: 19-21.
- Maqbool S, Younus I. Anxiolytic and hypnotic effects of *Cocculus laurifolius* leaf extract in mice. Bangladesh J Pharmacol. 2019; 14: 45-53.
- Nicoletta F, Roberta R, Min Y, Catherine RE. Screening of dietary carotenoids and carotenoid-rich fruit extracts for antioxidant activities applying 2, 2'-azinobis (3-ethylenebenzothiazoline-6-sulfonic acid radical cation decolorization assay. Meth Enzymol. 1999; 299: 379-89.
- Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. J Clin Psychiatry. 2008; 69: 4-7.
- Oketch-Rabah HA. *Mondia whitei*, a medicinal plant from Africa with aphrodisiac and antidepressant properties: A review. J Diet Suppl. 2012; 9: 272-84.
- Oyaizu M. Studies on products of browning reaction antioxidant activities of products of browning reaction prepared from glucosamine. Japanese J Nutr Diet. 1986; 44: 307-15.
- Pandey SC, Ren X, Sagen J, Pandey GN. β -Adrenergic receptor subtypes in stress-induced behavioral depression. Pharmacol Biochem Behav. 1995; 51: 339-44.
- Patchev VK, Patchev AV. Experimental models of stress. Dialogues Clin Neurosci. 2006; 8: 417.
- Pintus F, Spanò D, Mascia C, Maccone A, Floris G, Medda R. Acetylcholinesterase inhibitory and antioxidant properties of *Euphorbia characias* latex. Rec Nat Prod. 2013; 7, 147-51.
- Price M.L, van Scoyoc S, Butler L.G. A critical evaluation of the vanillin reaction as an assay for tannin in sorghum grain. J Agric Food Chem. 1978; 26: 1214-18.
- Pytko K, Podkowa K, Rapacz A, Podkowa A, Żmudzka E, Olczyk A, Sapa J, Filipiek B. The role of serotonergic, adrenergic and dopaminergic receptors in antidepressant-like effect. Pharmacol Rep. 2016; 68: 263-74.
- Sahin F, Güllüce M, Daferera D, Sökmen A, Sökmen M, Polissiou M, Agar G, Özer H. Biological activities of the essential oils and methanol extract of *Origanum vulgare* ssp.

- vulgare in the Eastern Anatolia region of Turkey. Food Control. 2004; 15: 549-57.
- Singleton VL, Orthofer R, Lamuela-Raventós RM. Analysis of total phenols and other oxidation substrates and antioxidants by means of Folin-Ciocalteu reagent. Meth Enzymol. 1999; 299: 152-78.
- Siritapetawee J, Khunkaewla P, Thumanu K. Roles of a protease from *Euphorbia resinifera* latex in human anticoagulant and antithrombotic activities. Chem Biol Interact. 2020; 329: 109223.
- Stewart SA. The effects of benzodiazepines on cognition. J Clin Psychiatry. 2005; 66: 9-13.
- Tian J, Zhang F, Cheng J, Guo S, Liu P, Wang H. Antidepressant-like activity of adhyperforin, a novel constituent of *Hypericum perforatum* L. Sci Rep. 2014; 4: 1-6.
- Wu MX, Ma XJ, Shi JL, Wang SN, Zheng ZQ, Guo JY. Acute and sub-acute oral toxicity studies of the aqueous extract from radix, radix with cortex and cortex of *Psammosilene tunicoides* in mice and rats. J Ethnopharmacol. 2018; 213: 199-209.
- Xiao-Yang WA, Li-Ping LI, Ting-Guo KA, Hong-Bing WA. Chemical constituents of *Euphorbia fischeriana*. Chinese J Nat Med. 2012; 10: 299-302.
- Xu Y, Wang C, Klabnik JJ, O'donnell JM. Novel therapeutic targets in depression and anxiety: Antioxidants as a candidate treatment. Curr Neuropharmacol. 2014; 12: 108-19.
- Yamada J, Sugimoto Y, Yamada S. Involvement of dopamine receptors in the anti-immobility effects of dopamine reuptake inhibitors in the forced swimming test. Eur J Pharmacol. 2004; 504: 207-11.
- Zhao ND, Li YL, Song Y, Yang BJ, Ding X, Gao F, Ye J, Hao XJ, Zhang Y, Li S. Ten new nortriterpenes from *Euphorbia resinifera* and their anti-tomato yellow leaf curl virus activities. Fitoterapia 2021; 153: 104989.
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