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Research Article

Antidepressant effects of *Artemisia herba-alba* (Asso.) essential oil in adult female rats

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Abstract: The present study aimed to evaluate the antidepressant effects of *Artemisia herba-alba* essential oil in adult female rats. A depressive-like state was induced by exposing the animals to various stressors over a periof of 28 days. The antidepressant potential of *A. herba-alba* EO (administered orally at doses of 20 mg/kg and 40 mg/kg) was assessed using neurobehavioral tests, namely the Forced Swimming Test (FST) and the Open Field Test (OFT). In addition, cortisol levels were measured as a biochemical marker of stress. The results were compared across the following groups: a non-depressed control group, an untreated depressed group, and a standard treatment group receiving fluoxetine (10 mg/kg). Oral administration of *A. herba-alba* EO significantly reduced immobility time in the FST (p<0.0001), and significantly increased both the number of squares crossed and the number of entries into the central area in the OFT (p<0.0001). Furthermore, the EO significantly lowered cortisol levels at doses of 20 mg/kg (p <0.05) and 40 mg/kg (p<0.01). These findings support the potential antidepressant efficacy of *Artemisia herba-alba* essential oil in adult female rats.

1. INTRODUCTION

Depression is a serious mood disorder, in which several factors – genetic, biological and environmental – contribute to its onset (Ekong & Iniodu, 2021). According to the World Health Organization (WHO), this mental disorder negatively affects quality of life; approximately 280 million people worldwide suffer from depression, and by 2030, it may become the leading cause of mortality (Cohn *et al.*, 2012). This disorder is more common among females due to hormonal fluctuations (Albert, 2015). The reduction in the three main monoamine neurotransmitters (dopamine, noradrenaline and serotonin) in the brain is considered the primary cause of depression (Nutt, 2008). Pharmacotherapy with medications such as selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors and tricyclic antidepressants is

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the most commonly used form of depression treatment (Jakobsen *et al.*, 2020). However, the use of antidepressants is often associated with adverse effects such as drowsiness, intolerance, dependence, and so on (Bekara *et al*., 2020).

Herbal medicines may be effective alternatives in the treatment of depression (Machado *et al.*, 2013). The use of medicinal plants has increased in the treatment of neurological disorders, and they have been tested for their acetylcholinesterase inhibitory activity, as well as their affinity for the γ-aminobutyric acid type A (GABAA) benzodiazepine site and the serotonin transporter (Salah & Jäger, 2005). *Artemisia herba-alba Asso* is an aromatic and medicinal herb belonging to the Asteraceae family, one of the largest and most important families of flowering plants (Rolnik & Olas, 2021). In Algeria, it is commonly known as "Chih". The essential oils of this species have been extensively studied for their notable therapeutic applications, particularly in neurological disorders such as Alzheimer's disease and epilepsy (Moufid & Eddouks, 2012; Cheraif *et al.,* 2020).

Essential oils are complex mixtures of volatile compounds; monoterpenes and sesquiterpenes constitute the major class of essential oil compounds (De Sousa *et al.*, 2015). Animal model experiments have demonstrated the influence of essential oils on the nervous system, particularly in reducing anxiety and depression (Lizarraga-Valderrama, 2021). Gas chromatography-mass spectrometry (GC-MS) analysis of the studied *A. herba-alba* essential oil revealed a dominance of oxygenated monoterpenes, primarily camphor, *α*-thujone, chrysanthenone, 1,8-cineole and *β*-thujone (Amara *et al.,* 2024). Several studies have shown that these essential oil compounds exert antidepressant-like effects (Gomes *et al.,* 2010; Cioanca *et al.,* 2016; Akbaba *et al.,* 2018).

This work is the first to evaluate the antidepressant effect of the *A. herba-alba Asso* essential oil, highlighting a gap that remains open for further research. Therefore, the present study aimed to investigate the effect of essential oil extracted from aerial parts of *A. herba-alba* on depression in adult female rats using neurobehavioral tests commonly employed to assess depressive-like behavior in animal models.

2. MATERIAL and METHODS

2.1. Plant material and essential oil isolation

The aerial parts (stems, leaves, and flowers) of *Artemisia herba-alba* were harvested from the M'sila region, Wilaya of M'sila, Algeria, in November 2021. A voucher specimen (N° 03/AST/2022) was deposited in the Research Laboratory of Plant Biodiversity Conservation and Valorization of the University of Sidi Bel Abbes, Algeria. The plant material was air-dried at 25°C for two weeks. The essential oil was obtained by hydrodistillation of 100 g of dried aerial parts in 600 mL of distilled water for 3 hours using a Clevenger-type apparatus (Council of Europe, 2007). The obtained essential oil was stored in the dark at 4 °C until the time of the experiment.

2.2. Physicochemical Analysis of Essential Oil

The physicochemical characteristics of the essential oil, represented by relative density *d(20,20)*, refractive index (ή20), hydrogen potential (pH) and acid index (AI) were determined according to the methods described by the standards of the French Association for Standardization (AFNOR, 2000).

2.3. Animals

Twenty-five female Wistar rats, weighing between 220 and 280 grams, obtained from the Pasteur Institute (Algeria) were used in this study. The animals were acclimated for 15 days in clean polypropylene cages under controlled conditions: an average temperature of 22–25 °C, relative humidity of 60%, and a 12-hour light/dark photoperiod. The rats had ad libitum access to water and a standard diet. All experimental procedures were reviewed and approved by the

Ethics Committee of Sidi Bel Abbes, Algeria. The protocol was approved under Reference: Opinion No. 9 / February 8, 2024.

2.4. Experimental Process

2.4.1. *Groups and drug administration*

The animals were divided into five groups, each consisting of five rats. Essential oil, diluted in 1% Tween 80 solution, was administered at the doses of 20 mg/kg and 40 mg/kg. Fluoxetine (reference standard) was given at a dose of 10 mg/kg, and the vehicle (1% Tween 80, 10 mL/kg) was used for the control group. All treatments were administered orally by gavage once daily in the morning for 28 consecutive days.

2.4.2. *Depression protocol*

Depressive disorder was induced according to the methods described by Ekeanyanwu *et al.*, (2021) and Aryanezhad *et al.*, (2021), with slight modifications. Stressors were applied daily for 28 days, during which the control group received no stimulation. Each week, the order of stressors was changed to avoid repetition of the same stimulus on consecutive days. The applied stressors included: swimming in hot water (40 °C) for 5 minutes, ice water swimming (0 °C) for 5 minutes, cage tilt at 45° for 24 hours, wet cage floor for 24 hours, food deprivation for 24 hours, water deprivation for 24 hours, and tail pinch for 90 seconds.

One hour after the final treatment, all experimental groups—control (non-depressed), depressed (untreated), depressed + EO 20 mg/kg, depressed + EO 40 mg/kg, and depressed + fluoxetine 10 mg/kg—were subjected to neurobehavioral assessments: the Forced Swimming Test (FST) and the Open Field Test (OFT).

2.4.3. *Forced swimming test (FST)*

It is the most widely used test to evaluate the antidepressant activity of a molecule. The apparatus consists of an open cylinder (40 cm in diameter and 60 cm in height), filled with water maintained at 25 °C to a depth of 45 cm. The animal is placed in the cylinder and immobility time is recorded during a 6-minutes session. Immobility is defined as the time the rat spends floating passively in the water, making only minimal movements to keep its head above the surface, during the final 4 minutes of the test. A reduction in immobility time is considered indicative of antidepressant-like behavior in treated rats (Porsolt *et al*., 1977).

2.4.4. *Open field test (OFT)*

In this test, the rats were placed in the center of an open wooden box (60 cm [L] × 60 cm [W] × 40 cm [H]). The bottom of the box was divided into 16 equal square sections, with the four central squares representing the central zone and the remaining 12 outer squares representing the peripheral zone. Upon introduction to a novel environment, rats typically exhibit a tendency to explore the periphery near the walls. In this test, we evaluated the number of entries into the central zone—an indicator that tends to increase with antidepressant treatment—and the number of squares crossed (Chang *et al*., 2021). The duration of the test was 5 minutes.

2.4.5. *Cortisol level*

After completing the behavioral tests, the rats were sacrificed in the morning, and blood samples were collected via cardiac puncture into heparinized tubes to determine the cortisol levels. Cortisol concentrations were measured using an electrochemiluminescence immunoassay (ECLIA) on a COBAS 6000/E411 analyzer (ROCHE).

2.5. Statistical Analysis

All results were expressed as mean ± SD (Standard Deviation). Data were analyzed using one-way ANOVA, followed by Tukey's multiple comparisons test to determine the level of significance between study groups. A $p\text{-value} < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 8.0.2.

3. FINDINGS

3.1. Results of Physicochemical Analysis of EO

The percentage yield of EO extracted was calculated using the following formula:

$$\text{Yield (\%)} = \frac{Mass\ of\ EO\ obtained\ (g)}{Mass\ of\ plant\ material\ (g)} X\ 100$$

The average yield of the yellowish *Artemisia herba-alba* essential oil was 1.15 % (w/w). The physiochemical parameters of obtained EO are presented in Table 1. The physicochemical parameters of the obtained EO are presented in Table 1. The results indicated that the oil had a density of 0.928 and a refractive index of 1.4640. These values fall within the ranges described in the AFNOR standard: 0.900–1.000 for density and 1.4555–1.4788 for refractive index.

Table 1. Physicochemical parameters of *A. herba-alba* essential oil.

Relative density *d (20,20)*	Refractive index ($\dot{\eta}^{20}$)	Hydrogen potential (pH)	Acid index (AI) (mg KOH.g^{-1} EO)
0.928 ± 0.00038	1.4640 ± 0.00028	6.4	2.2 ± 0.00023

Values are the Mean ± SD of three replicates.

3.2. Body Weight of Rats

The body weight of the animals was measured before and after the 28-day of treatment period (Table 2). The body weight of the studied groups showed a non-significant increase $p \geq 0.05$ after 28 days.

Table 2. Body weight (in grams) of rats after 28-day of treatment period.

Groups	P_0	After 28 days
Control	255 ± 20.35	261.8 ± 18.61
Depressed	246.5 ± 17.25	256.81 ± 7.35
Dep + Standard	255.8 ± 5.06	265 ± 12.19
Dep + EO 20	248.3 ± 11.84	258.3 ± 17.06
Dep + EO 40	248.5 ± 8.8	255.8 ± 7.27

P_0: Initial weight; Dep: Depressed; Standard (Fluoxetine 10mg/kg); EO 20 (*A. herba-alba* essential oil at the dose of 20 mg/kg); EO 40 (*A. herba-alba* essential oil at the dose of 40 mg/kg). No significant difference $p \geq 0.05$ between initial weight and weight after 28 days of treatment for each group. Values are expressed in Mean ± SD (n=5).

3.3. Neurobehavioral Tests Results

3.3.1. *Forced Swimming Test Result*

The results of the Forced Swimming Test (FST) are illustrated in Figure 1. A significant difference ($p<0.0001$) in immobility time was observed between the control group (51± 7.31 seconds) and the depressed group (114.8±4.03 seconds). Depressed rats treated with 20 mg/kg and 40 mg/kg of *A. herba-alba* essential oil, as well as those treated with fluoxetine (10 mg/kg) for 28 days, showed a significant reduction in immobility time—70.75 ± 1.71 seconds, 65.25 ± 1.26 seconds, and 58.75 ± 2.22 seconds, respectively—when compared to the depressed group that received the vehicle (1% Tween 80) ($p<0.0001$). A non-significant difference in immobility time was observed between the group treated with 40 mg/kg EO and the group treated with fluoxetine (10 mg/kg).

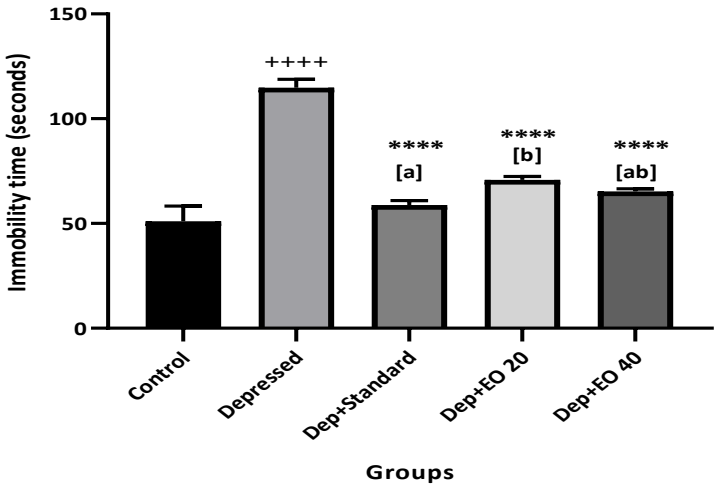

Figure 1. FST results expressed in term of immobility time in seconds. $^{++++}p<0.0001$ shows significant difference compared to the control group. $^{****}p<0.0001$ shows significant difference compared to the depressed group. Columns with different letters indicate a significant difference $p<0.05$. Values are expressed in mean ± SD, (n=5).

3.3.2. *Open field test result*

The results of the first parameter of the Open Field Test (OFT) are shown in Figure 2. Treatment of depressed rats with *A. herba-alba* essential oil at doses of 20 mg/kg and 40 mg/kg for 28 consecutive days significantly increased the number of squares crossed—90.25 ± 10.5 and 101.5 ± 5.45, respectively—compared to the depressed group (70.8 ± 6.02) ($p < 0.05$, $p < 0.001$). A significant difference was also observed between the control group (102 ± 9.8) and the depressed group ($p < 0.0001$), as well as between the fluoxetine-treated group (97.25 ± 5.32) and the depressed group ($p < 0.001$), in terms of the number of squares crossed.

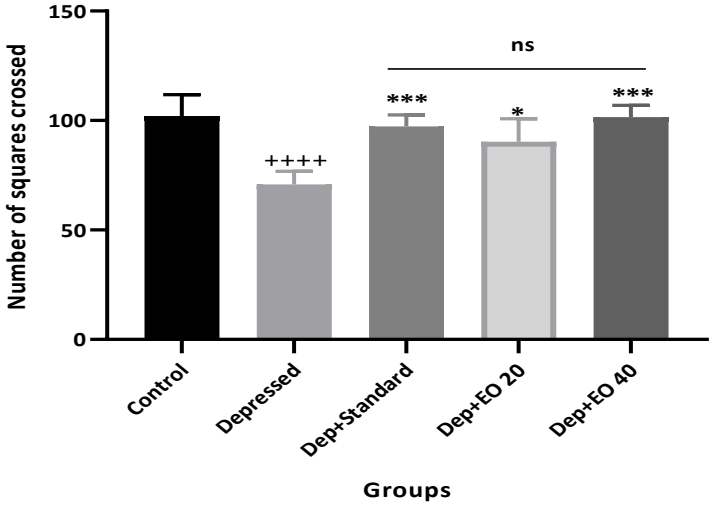

Figure 2. OFT data in terms of the number of squares crossed by rats. $^{***}p<0.001$ and $^{*}p<0.05$ show significant difference compared to the depressed group. $^{++++}p<0.0001$ shows significant difference compared to the control group. ns: non-significant difference $p\geq0.05$. Values are expressed in mean ± SD, (n=5).

In the second parameter of the OFT (Figure 3), treatment with *A. herba-alba* essential oil at doses of 20 mg/kg and 40 mg/kg resulted in a significant increase in the number of visits to the central squares—11.25 ± 0.96 and 12.25 ± 0.96, respectively—compared to the depressed group (3 ± 1) ($p < 0.001$, $p < 0.0001$). A significant difference ($p < 0.0001$) was also observed in comparison to the depressed group and the fluoxetine-treated group (13 ± 0.82). This increase

reflects behavioral improvement and is considered a positive indication of antidepressant activity.

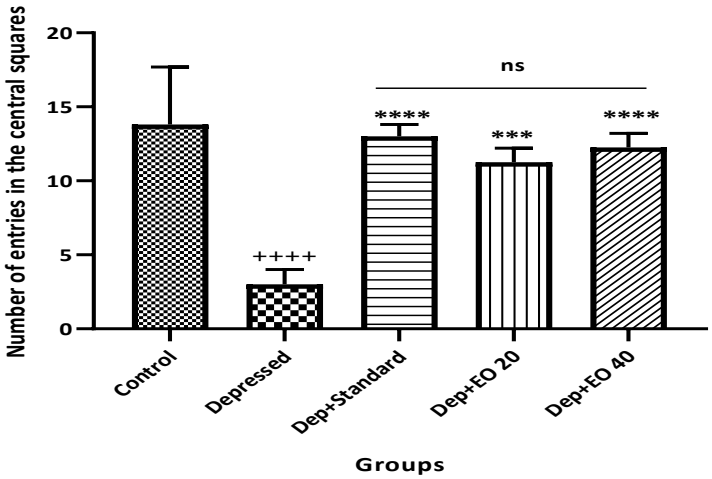

Figure 3. OFT results in terms of the number of entries in the central squares. $^{****}p<0.0001$ and $^{***}p<0.001$ indicate a significant difference compared to the depressed group. $^{++++}p<0.0001$ indicate a significant difference compared to the control group. ns: non-significant difference $p\geq0.05$. Values are expressed in mean ± SD, (n=5).

3.4. Result of Blood Cortisol Level

The cortisol level results are represented in Figure 4. Cortisol levels were significantly elevated in the depressed group (68.91 ± 1.32 nmol/L) compared to the control group (49.14 ± 2.59 nmol/L) ($p < 0.001$). Oral administration of *A. herba-alba* essential oil at the dose of 40 mg/kg and Fluoxetine at the dose of 10mg/kg for 28 days, significantly reduced cortisol levels to 55.05 ± 2.27 nmol/L and 54.68 ± 6.15 nmol/L, respectively, compared to the untreated depressed group *($p < 0.01$)*. A decrease in cortisol level was also observed in the group treated with 20 mg/kg of essential oil (60.16 ± 1.28 nmol/L), which was statistically significant compared to the depressed group ($p < 0.05$).

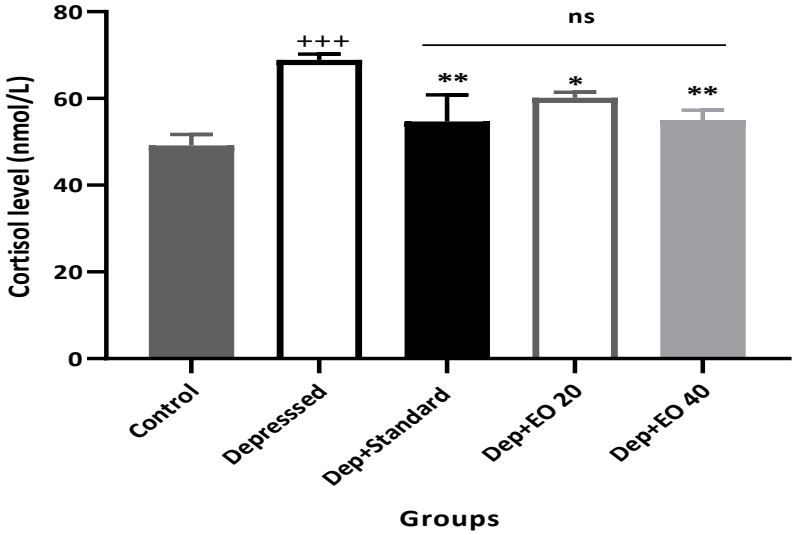

Figure 4. The results of the dose of cortisol (nmol/L). $^{+++}p<0.001$ indicate a significant difference compared to the control (undepressed). $^{*}p<0.05$ and $^{**}p<0.01$indicate a significant difference compared to the depressed group. ns: non-significant difference $p\geq0.05$. Values are expressed in mean ± SD, (n=5).

4. DISCUSSION and CONCLUSION

Depression is a global mental disorder that affects both physical and mental health. Some secondary metabolites, particularly essential oils derived from herbal medicines, can easily cross the blood–brain barrier and exert antidepressant effects with low toxicity and minimal side effects (Zhang *et al*., 2021). In this context, oral administration of essential oil at doses of 20 mg/kg and 40 mg/kg for 28 days in depressed animals resulted in a significant reduction in immobility time in the Forced Swimming Test (FST). The findings of this study are consistent with those of Akbaba *et al*. (2018), who reported that essential oil extracted from the aerial parts (stem, leaves, and flowers) of Achillea biebersteinii, a species in the same family as *A. herba-alba*, enhanced memory formation and reduced anxiety- and depression-like behavior. Moreover, the present results align with those of Khan *et al*. (2016) and Mahmoudi *et al*. (2009), who demonstrated that extracts from the whole plant of Artemisia indica Linn and the aerial parts of Artemisia absinthium (both belonging to the same genus as the plant used in this study) significantly reduced immobility time in the FST.

Several studies have isolated and identified the constituents of essential oils responsible for their antidepressant effects. Cioanca *et al.*, (2016) and Akbaba *et al.*, (2018) demonstrated that camphor and 1,8 cineol reduced depressive behavior by decreasing immobility time in the Forced Swimming Test in a dose-dependent manner. Similarly, Abbasi-Maleki & Maleki (2021) reported that α-thujone reduced immobility time in a manner comparable to fluoxetine (20 mg/kg). These compounds are part of the chemical composition of the essential oil studied and represent its main active constituents.

In our study, the observed improvement may be attributed to the presence of bioactive compounds in the essential oil that exhibit potent antidepressant effects. The antidepressant action of essential oils may involve several mechanistic pathways including selective serotonin reuptake inhibition (Ahangar *et al*., 2011), reduction of corticosterone levels (Ali *et al*., 2017), and modulation of the GABAergic system (Diniz *et al*., 2019).

Excessive secretion of cortisol is commonly observed in patients suffering from depression (Lee *et al.,* 2014). In this study, a significant increase in cortisol levels was observed in rats subjected to the depression protocol compared to normal rats, indicating that elevated cortisol is a biomarker of depression in rats. The results demonstrated that oral treatment with *A. herba-alba* essential oil at doses of 20 mg/kg and 40 mg/kg for 28 days significantly reduced cortisol levels compared to untreated depressed rats. These findings are consistent with previous studies, which confirmed that certain extracts and essential oils from medicinal herbs can significantly lower cortisol levels (Ayuob *et al*., 2017; Sentari *et al*., 2019).

In conclusion, the *A. herba-alba* essential oil demonstrated a significant antidepressant effect in an animal model of depression. The tested doses of 20 mg/kg and 40 mg/kg significantly reduced depressive behaviors compared to the untreated depressed group. The antidepressant effects observed at these doses were comparable to those produced by fluoxetine at 10 mg/kg. However, the precise mechanisms underlying the antidepressant effects of *A. herba-alba* essential oil are not yet fully understood. Therefore, further studies are warranted to identify the specific active compounds and to elucidate their mechanisms of action.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors. **Ethics Committee Number**: CHU-Sidi Bel Abbès – Ref. No: N°9 / February 8, 2024.

Authorship Contribution Statement

Lallia Amara: Methodology, Processing, Data analysis, Interpretation, and Writing. **Mohamed Zairi:** Writing, Analysis and Final approval. **Amine Achemaoui:** Methodology and Validation. **Samira Meziani**: Supervision and final approval. **Abbassia Demmouche**: Supervision and final approval.

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