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Original Article

Chemical Composition and Therapeutic Effects of *Ammodicus leucotricus* Essential Oils on Neurobehavioral Changes in Wistar Rats after Experimental Scorpion Envenomation

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ABSTRACT

Background: Our study consists of a study of the chemical composition of the essential oil administered to a batch of rats undergoing a scorpion sting. Compared with control batches, the nervous state was evaluated by several neurobehavioral tests, namely open classified, dark and light and forced swimming. **Materials and Methods:** Determination of the composition of the essential oil the plant by GC/MS and its protective effect on the nervous system after exposure of rats to scorpions. **Results:** of GC/MS show that the chemical composition of this plant is characterized by the dominance of the natural monoterpenoid agent Perilla aldehyde, with a percentage of 70.12%, followed by Limonene (10.10%), Methyleugenol (5.69%), and alpha-Pinene (5.04%). Other compounds such as Perilla alcohol (1.90%), Beta-Pinene (0.61%), Delta-3-Carene (0.59%), Carvone (0.44%) and Camphene (0.33%) were identified only in a small proportion. The series of tests allowed us to see the onset of a depressive state, as well as a significant decrease in locomotor activity in the bitten rats compared to the controls and the treated batch. This hypolocomotor effect is accompanied by a decrease in the animal's stereotyped behaviours (curiosity, sniffing, biting, and grooming) and muscular tone, which explains the animal's inability to explore the environment. **Conclusion:** The neuroprotective power study confirmed the powerful properties of the plant to improve the symptoms caused by the scorpion sting, as proven by several neurobehavioral tests.

Keywords: Scorpion, Rat, *Ammodicus leucotricus*, Neurobehavioral test.

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INTRODUCTION

Scorpions constitute within arthropods a minor order but of great medical importance. They are naturally fearful and may sting when disturbed or abused. Scorpionism, the pathology of scorpion envenomation, is a problem that rages across five continents. Because of its frequency and seriousness, it is a serious concern for public health on a worrying scale in many countries in North Africa, the Middle East, India and South America.[1]

Epidemiological studies report that more than 5,000 people worldwide die each year.[2] Scorpion stings and envenoming's are common and serious accidents in Algeria, as they are in many other hot countries.

The economic and social consequences are important since this pathology constitutes an emergency, and in general, millions of dinars are spent each year for the purchase of medicines. In addition, hospital expenditure has consequences on the development of the family structure in the event of the sudden death of healthy young children.

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Aware of the importance and severity of scorpion stings and envenomation's, the Saharan population is seeking a cure for medicinal plants such as *Ammodicus leucotricus*.

MATERIALS AND METHODS

Plant

Ammodicus leucotricus

The seeds of the plant *Ammodicus leucotricus* were collected from the Western Sahara region during the month of March 2019. The dried plant material is subjected to steam distillation using the Clevenger device to obtain the essential oil.

Essential oil analysis

A Hewlett-Packard Agilent gas chromatograph (6890 Plus), associated with a Hewlett-Packard Agilent Mass Spectrometer (5973), and an A polar column: 5% Phenyl 95% dimethylpolysiloxane HP-5MS (30 m x 0.25 mm; 0.25 µm) was used to analyze the essential oil. The gas chromatograph was programmed at an initial temperature of 60°C for 8 min, then increased to 250°C at a rate of 2°C/min, isotherm for 10 min. Helium was used as the carrier gas (0.5 mL/min); 0.2 L was injected in split mode (1 hr 13) with a fraction of 1/20; injector and detector temperatures were 250 and 280°C, respectively.

The mass spectrometer was operated in EI mode at 70 eV; ion source temperature, 230°C; MS data was acquired in scan mode at a range of 30 to 500 m/z. The identification of each compound was based on a comparison of its mass spectra with those of the NIST mass spectral library 02 and Wiley 7.

Animal

Scorpion: Leiurus quinquestriatus

The scorpions used in our study belong to the species *Leiurus quinquestriatus* (Figure 1). They were captured in the region of Elabaydh, Algeria. They are large venomous scorpions that measure 80 to 110 mm in length and weigh 1.0 to 2.5 g. They are yellowish in color with brown spots on the V metasomatic segment and sometimes on the carapace and tergites. Tergites I and II have five carinae. The ventrolateral carinae have 3 to 4 rounded lobes, and the anal arch has 3 rounded lobes. Scorpions have 2 eyes on the top of their heads and often 2 to 5 pairs of eyes on the front corners of their heads. It is considered a very dangerous species because its venom is a powerful mixture of neurotoxins, including charybdotoxin. Its bite, although extremely painful, is not normally fatal for a healthy adult. However, young or old people, people with heart disease, or people with allergies are at greater risk.[3]

Wistar rats

The rats were acclimatized in the Saida Biology Department's Animal Department two weeks before the experiments began; they had free access to food and drink; and the animals were divided into four groups. Group I served as a negative control, while Group II was given only essential oil of plant, Group III was exposed to scorpions, and Group IV was exposed to scorpions and then given 0.2 mL of essential oil of plant orally.

Methods

Evaluation of an exploration behavior: open field test

The open field used was a large rectangular open box (90 cm long, 70 cm wide, and 60 cm high), with a black background and brightly lit from above (500 lux). Black lines on the ground delineated tiles (10 x 10 cm).[4]

The open field is a stressful environment for the rat. It is indeed a nocturnal animal, which prefers confined spaces, closed and dimly lit, and is frightened by large spaces, where it goes a little in the center. Each rat was initially placed in one of the four corners of the open field, with its head facing the corner. His behavior was observed for 6 min. Six parameters were measured by the experimenter: Latency (expressed in seconds), which corresponds to the time taken by the rat to exit the four tiles forming the corner, The total number of cells crossed by the rat during the test (6 min), which reflects the locomotor activity, the number of visits to the center's 15 tiles.

The total number of straightening's (animals positioned on their two hind legs, right, balanced in a vacuum or against a wall), The total amount of grooming, the total number of feces. Thus, this test evaluates the exploratory capacities of the rat in a stressful context. The number of tiles crossed and the number of adjustments reflected his exploratory activity and his emotional state. The other parameters are rather indicators of his emotional state.

Depressive type behavior: Forced swimming test

The forced swimming test was initially proposed by Fet V *et al.*,[5] as a test allowing the selection of molecules with antidepressant activity. Rats are placed for 15 min in the room where the test is taking place. The animals are subjected to a forced swim test lasting 6 min. The animals are placed inside a cylinder 20.7 cm in diameter and 39 cm high, in water at 22°C. The time during which the animal actively swims or floats only to keep its head out of the water is measured. After struggling in the water, the animal becomes almost motionless, moving its legs from time to time to stay afloat or regain its balance. This immobility is interpreted as reflecting a "behavioral desperation" that occurs when the animal realizes that it cannot escape.

In this interpretation, immobility is seen as a sign of depression.

The Light / Dark Test for Anxiety

The Light-Dark Test is one of the most widely used tests to measure anxiety behavior in rodents.[6]

Figure 1: *Leiurus quinquestriatus.*

The experimental setup for this test consists of two compartments of the same size (25 cm x 25 cm x 20 cm). One is black and the other white, connected by an opening allowing the animal to move freely from one to the other. The animal is placed in the black compartment with its head facing the wall opposite the entrance to the white compartment. The test starts only after 3 min of exploration of the environment by the rat. The behavior of the animal is observed for 5 min. The parameters measured are the time spent in each compartment.

Statistical analysis

SigmaStat software (SPSS, 3.0, SPSS, Inc., Chicago, IL) was used for the analysis. The data was presented as mean±SD and was evaluated by one-way ANOVA, with Dunnett's *post hoc* test. When appropriate, ANOVA on Rank with Dunn's *post hoc* test was used.

RESULTS

Hydrodistillation of the aerial part (leaves) of *A. leucotrichus* provided a blue-colored essential oil with a strong aromatic smell. On average, the oil yield was 1.8% (w/w).

The essential oil previously underwent qualitative and quantitative analysis by GC-GC/MS using a gas chromatography mass spectrometry system, which identified 56 chemical components, or 99.98% of the total essential oil, which are listed in Table 1.

Table 1 shows that the essential oil consists mainly of oxygenated monoterpenes (72.02%), including perillal as a major component, and monoterpene hydrocarbons (17.79%), with limonene as the main compound, and methyleugenol, as well as other chemical entities whose abundance rate is quite negligible.

The chromatogram thus obtained, shown in Figure 2, was carefully studied and only molecules with a rather high relative abundance were considered.

The chemical composition of this *A. leucotrichus* species is characterized by the dominance of the natural monoterpenoid agent Perilla aldehyde (peak no. 7), with a percentage of 70.12%, followed by Limonene (10.10%, peak no. 5), Methyleugenol (5.69%, peak no. 10) and alpha-Pinene (5.04%, peak no. 1). Other compounds such as Perilla alcohol (1.90%, peak no. 8), Pentamethylcyclopentadiene (1.29%, peak no. 9), beta-Pinene (0.61%, peak no. 3), delta-3-Carene (0.59%, peak no. 4), Carvone (0.44%, peak no. 6), and Camphene (0.33%, peak no. 2) were identified only in a small proportion.

Evaluation of an exploration behavior: Open field test

The results of this test show that rats bitten in the subjects had a lower number of crossed cells than the control subjects. The observation shows an increase in latency, thus a decrease in the number of crossed cells (horizontal locomotor activity), which is accompanied by a decrease in the defecation number of the "stitched" batch compared to the control group.

The two-factor ANOVA analysis revealed that scorpion exposure resulted in a significant decrease in total number of tiles crossed, righting (p <0.001), and grooming (p <0.05), as well as a significant increase in latency (p <0.01) in the G2 group compared to the control group (G1). These results also show that there is a significant elevation in the number of tiles crossed in the centre (p<0.01), total tiles crossed, righting and grooming (p<0.001) with a significant reduction in latency (p<0.05) in rats exposed to scorpion and treated with the essential oil of the plant (G4) compared to rats exposed to scorpion only (G2). In the same context, the treated rats (G3) showed a significant (p<0.001) decrease in the number of recoveries compared to the controls (G1).

No significant differences in the number of feces were found in any of the groups Figure 3.

Depressive type behavior (forced swimming test)

The recorded results show a significantly (p<0.05) higher Immobility Time (IMT) in the scorpion-exposed rats compared to the control rats (G1). Similarly, statistical analysis showed a significant decrease in TIM (p<0.001) in scorpion-exposed and treated G4 rats compared to G2 rats Figure 4.

Scorpion-exposed rats had a significantly greater immobility time than control rats. The inability to swim is a behavioural despair that proves the depressive effect of envenomation.

Dark and light test

Statistical analysis of this anxiety test shows that rats in group G3 (exposed to the scorpion) showed a significantly (p<0.05) longer stay in the dark compartment than rats in the control group (G1). Thus, this resulted in a significant decrease (p<0.05) in the time spent in the light compartment. While the administration of the plant oils to the rats exposed to the scorpion caused no significant

Table 1: Chemical composition of *A. leucotricus* essential oil.

NO.	Components	RT (min)	Concentration %
1	2-Methylbutyric acid methyl ester	3.8985	0.04
2	α-Phellandrene	8.6709	0.01
3	α- Pinene	9.0252	5.04
4	7-Oxabicyclo[4.1.0]heptane, 3-oxiranyl-	9.4882	0.02
5	Camphene	9.8140	0.33
6	β-Pinene	11.4429	0.61
7	β-Myrcene	12.4488	0.17
8	α-Thujene	13.2204	0.05
9	δ-3-Carene	13.5690	0.59
10	o-Cymol	14.6321	0.12
11	Limonene	14.9865	10.11
12	γ-Terpinene	16.9354	0.02
13	1,3,8-p-Menthatriene	21.4564	0.05
14	1,3-Bis-(2-cyclopropyl,2-methylcyclopropyl)-but-2-en-1-one	22.2451	0.03
15	3-Octyne	22.5595	0.15
16	Dispiro[2.0.2.5]undecane, 8-methylene-	25.4401	0.06
17	(Z)-3-Heptadecen-5-yne	25.8573	0.04
18	4,7,10,13,16,19-Docosahexaenoic acid, methyl ester, (all-Z)-	26.2917	0.03
19	6-Heptenoic acid, 4-methylene-5-methyl-, methyl ester	26.4460	0.03
20	3-Methylcyclohexene	26.6689	0.05
21	2H-Benzocyclohepten-2-one, 3,4,4a,5,6,7,8,9-octahydro-4a-methyl-, (S)-	26.8861	0.05
22	Tricyclo[4.4.0.0(2,8)]dec-4-ene	27.2462	0.06
23	Bicyclopentyl-1,1'-diene	28.7722	0.27
24	1,3,5,5,6,6-Hexamethyl-1,3-Cyclohexadiene	29.1380	0.04
25	1-cyclopropylethynyl-2-methoxy-3,3-dimethyl-Cyclopropane	29.4695	0.03
26	10-(2-oxopropyl)-α-Pinene	29.6238	0.02
27	Propanal, 2-methyl-3-phenyl-	29.9496	0.26
28	Carvone	30.1496	0.44
29	Spiro[2.5]octane-4-methanol, 1,1-dibromo-.alpha.-phenyl-	31.3327	0.14
30	Perilla aldehyde	33.0874	70.12
31	Perilla alcohol	34.1104	1.90
32	(1R*,5R*)-1,5-Dimethylbicyclo[3.3.0]oct-3-en-2-one	34.8420	0.25
33	3,9-Epoxy-p-mentha-1,8(10)-diene	35.3450	0.16
34	m-tert-Butylphenol	35.5564	0.13
35	1-(1,1-dimethyl-2-propenyl)-1-cyclohexene	35.9794	0.10
36	Pentadecanal-	38.5628	0.03
37	1,3-cyclopentadiene, 1,2,3,4,5-pentamethyl-	40.1174	1.29
38	Methyleugenol	40.9804	5.69
39	Thymohydroquinone dimethyl ether	41.9521	0.28
40	2,4,5,6,7,7a-hexahydro-4,7-Methano-1H-indene	42.9008	0.02
41	trans-2-Isopropylbicylclo[4.3.0]non-3-ene-8-one	43.4266	0.03
42	γ-Decalactone	44.8841	0.13
43	γ-Dodecalactone	45.0841	0.10
44	10-12-Pentacosadiynoic acid	45.3927	0.11
45	γ-Selinene	47.7247	0.06
46	Longifolene-(V4)	48.8506	0.02
47	Cycloisolongifolene, 8,9-dehydro-	50.9025	0.14
48	1,4-Heptadiene	51.1025	0.04
49	β-Ethallyl chloride	52.6057	0.04
50	Dehydrosaussurea lactone	53.0115	0.04
51	Isolongifolene, 9,10-dehydro-	53.9316	0.06
52	1H-Cycloprop[e]azulene, decahydro-1,1,7-trimethyl-4-methylene-, [1aR (1a. α.,4a. β.,7. α.,7a. β.,7b. α.)]-	54.5489	0.06
53	δ-Guaïène (α-bulnésène)	54.9776	0.04
54	α-Neoclovene	55.2576	0.09
55	Bicyclo[4.3.1]deca-2,4,7-triene, 2,5,9-trimethyl-, endo-	56.4179	0.08
56	Isolongifolene	57.2352	0.14
	Total identified compounds		99,98

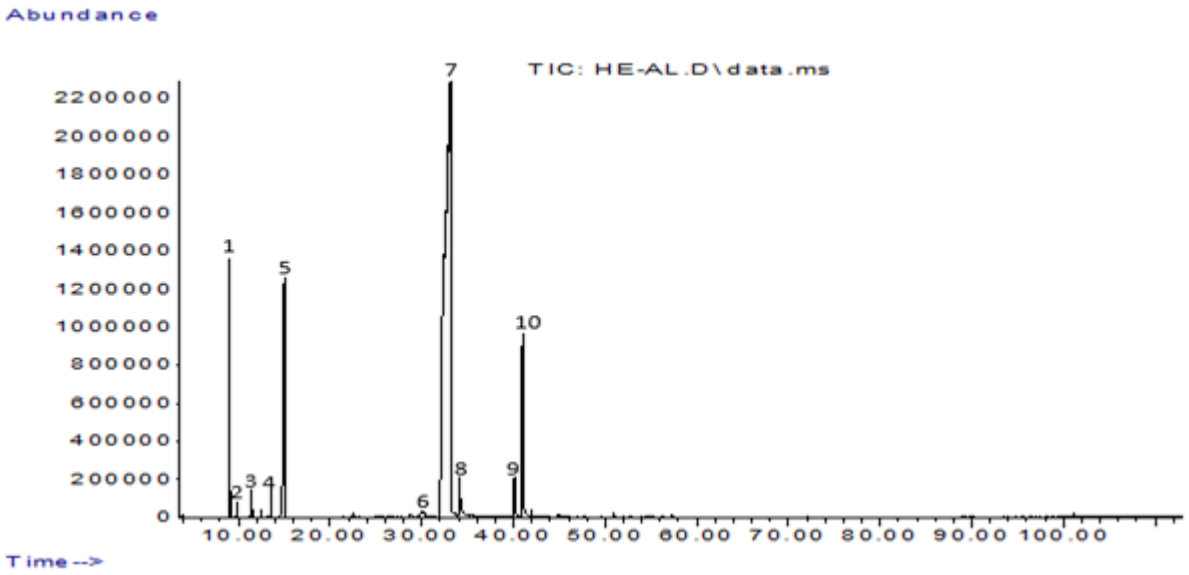

Figure 2: Gas chromatogram of*A. leucotricus* essential oil.

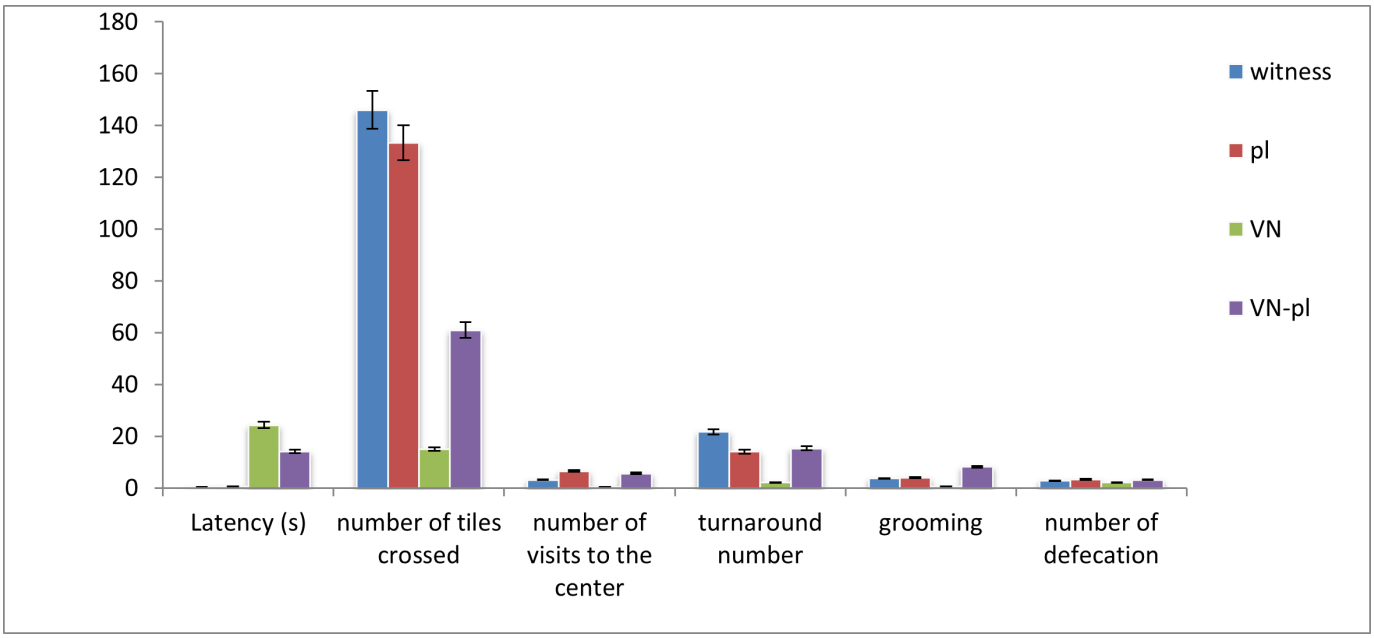

Figure 3: Results of open field test.

change (p>0.05) in the time spent in each of the light and dark compartments (Figure 5).

DISCUSSION

The plant is also used for the treatment of allergy symptoms.[7,8] It is also used against coughs, as an emmenagogue, and against anorexia.[8] In the form of an infusion, the fruits of *A. leucotrichus* are used for the treatment of heart palpitations.[9] A recent study by Hammiche V, *et al.*,[10] reports that some populations in Morocco use the fruits of *A. leucotrichus* for the treatment of lung cancer in the form of powder mixed with honey and administered orally.

Another study revealed the protective effect of A's aqueous extract of fruits against urolithiasis tested *in vitro*. High inhibition percentages have been reported.[11]

The plant is used in decoction for the treatment of diabetes and digestive tract fever, especially in children.[12]

Very few phytochemical studies have been reported on *A. leucotrichus*. Indeed, the study conducted by Muckensturm B, *et al.*,[13] on the ethereal fraction of the fruits of this species revealed the presence of several compounds, namely: ammolactone, limonene, perillaldehyde, hydroxyperillaldehyde, methyl-perillate, borneoleole angelate, and decalactone.

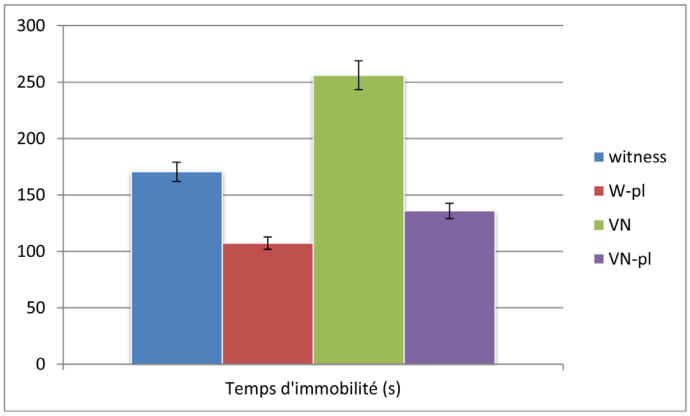

Figure 4: Results of the swimming test.

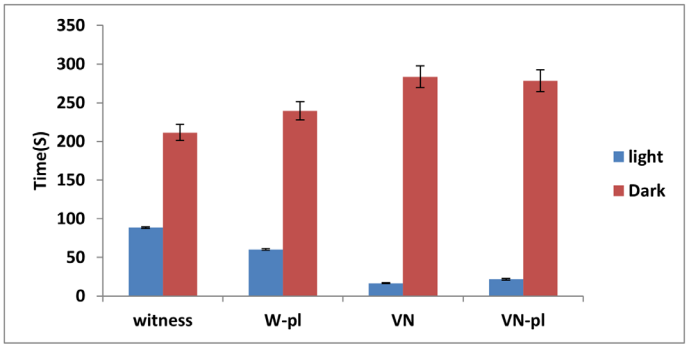

Figure 5: Results of Dark and Light test.

The GC-MS examination of the essential oil is mostly described by monoterpene hydrocarbons (78%), followed by oxygenated monoterpenes (20.1%). The major compounds are γ-terpinene (33.6%), sabinene (32.0%), and thymol methyl oxide (15.7%). Dillapiole was the only phenylpropanoid detected and was tracked down in leftover sums. Past examinations feature an exceptionally high substance fluctuation in *Crithmum maritimum* Medicinal ointment based upon the district of Portugal where the plant is gathered. Medicinal ointments from plants gathered in São Pedro de Moel and Costa da Caparica contain γ-terpinene and sabinene as the fundamental mixtures, which is as per our outcomes. Be that as it may, an unpredictable concentrate acquired by supercritical liquid extraction from plants gathered in Figueira da Foz is rich in dillapiole.[14]

Considering the substance fluctuation of this species,[15] featured the presence of two particular chemotypes for *C. maritimum* rejuvenating balm with respect to how much dillapiole there was.

One with high measures of dillapiole (15–47%) (chemotype I) and the other with extremely low measures of dillapiole (0–6%) (chemotype II). The essential oil detailed here has a place in chemotype II, which is the most normal chemotype in Portugal, as announced by Pateira.[16]

Other substance profiles have been additionally distinguished in *C. maritimum* from various starting points. For sure, the medicinal oils from plants acquired in Croatia, Turkey and Italy[17-20] have been accounted for as being well-off in limonene Furthermore, phelandrene has been found in extremely high concentrations in the medicinal ointment made from *C. maritimum* in Turkey.[21]

In the same experimental series, a battery of neurobehavioral tests was selected to assess the state of anxiety, exploration of locomotor activity, and memory to estimate stress status in rats exposed to Scorpio.

Indeed, through the open field tests we recorded only the bite induced in rats a locomotor hypoactivity during the first 6 min of experience, this change in environmental exploration can be explained by fear of the new environment.[22] Or the action of venom on the dopaminergic transmission system, which results either in a decrease of the synthesis and release of the neurotransmitter in the synaptic cleft, or by inhibition of the postsynaptic D2 receptors, which explains the decrease in the activity of exploratory and behavioral These findings are consistent with the work undertaken by WHO (2004), which reports that triadimefone decreased locomotor activity by inhibition of synthesis and release of dopamine in the synapse.[23,24]

Moreover, the learning and memory abilities of the animals were evaluated through the Y-maze test. Our results revealed that the percentage of spontaneous alternation is significantly high. This learning deficit is well correlated with the neuropathological results (the loss of pyramidal cells in the hippocampus.[25] The results found by Pateira L, *et al.,* Marongiu B, *et al.,*[26,27] that the alternation deficit for this test observed in rats whose hippocampus is injured is due to disturbances of memory and rather short-term memory.

CONCLUSION

Scorpionism in Africa is a very poorly known reality that is nevertheless considered a public health problem in several countries, in particular Algeria. The lack of knowledge of this problem is due to a combination of ignorance, including the composition of sub-Saharan scorpion fauna, the distribution and density of dangerous species, and the frequency and severity of scorpion stings in Saharan regions. So far, only the presence of *Leiurus quinquestriatus* and its involvement in fatal accidents have been documented. The specific treatment (serotherapy) is to be implemented as quickly as possible. Symptomatic treatment aims to calm the pain in mild cases and to maintain vital functions in serious cases. The work we have done makes an original contribution to the study of the biological activities of the *Ammoudocaus leucotricus* plant.

The neuroprotective power study confirmed the powerful properties of the plant to improve the symptoms caused by the scorpion sting, as proven by several neurobehavioral tests, namely open field, labyrinth, and forced swimming.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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