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Adaptogenic activity of *Cinnamomum camphora*, *Eucalyptus globulus*, *Lavandula stœchas* and *Rosmarinus officinalis* essential oil used in North-African folk medicine

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Abstract: Depressive anxiety is one of the most emotional disorders in our industrial societies. Many treatments of phobias exist and are based on plant extracts therapies, which play an important role in the amelioration of the behavior. Our study aimed to evaluate the adaptogenic activity of different essential oils provided from local plants: *Cinnamomum camphora* (Camphora), *Eucalyptus globulus* (Blue gum), *Lavandula stœchas* (Topped lavender) and *Rosmarinus officinalis* (Rosemary) on Wistar rats. The adaptogenic activity was evaluated on the elevated plus-maze. The efficacy of the extract (200 mL/kg) was compared with the standard anxiolytic drug Diazepam® 1 mg. Animals administered by the essential oil of *Lavandula stœchas*, *Cinnamomum camphora*, *Rosmarinus officinalis* and *Eucalyptus globulus* showed a behavior similar to those treated with Diazepam®. For groups treated with the following essential oils: *Rosmarinus officinalis*, *Lavandula stoechas* and *Cinnamomum camphora* at a dose of 200 mL/kg, we notice an increase in the time spent on the open arms of the elevated plus-maze and a decrease in time spent on the closed arms of the elevated plus-maze, especially for *Rosmarinus officinalis*, which explains the anxiolytic effect of these plants. We also notice a decrease in the number of entries in closed arms, open arms and the number of passing to the central square. The increase in the number of entries to open arms with *Eucalyptus globulus* essential oil shows a reduction in anxiety behavior in rodents and this shows that these plants have an inhibitory effect.

Key words: Anxiolytic; Adaptogenic; *Lavandula stœchas; Cinnamomum camphora; Rosmarinus officinalis; Eucalyptus globulus;* Essential oil; Elevated plus maze; Wistar.

Introduction

The plants represent the first natural medication to consider toget out of a habitand replace chemical treatment (1). Several phytoresources are already used in Algerian traditional medicine (2). Various studies cite antioxidant, antiradical, anti-Alzheimer, antibacterial and antifungal, bio-insecticide, antilipemic, antidiabetic activities…etc. (3, 4, 5, 6, 7, 8, 9, 10). The herbal treatments, however, are qualified as less effective than those of modern pharmacy (less immediate and less powerful action). Plants offer, in addition to their antidepressant action, anxiolytic, antispasmodic and adaptogenic effects.Different molecules and different natural or artificial substances have anxiolytic effects. Antidepressants used in the treatment of anxiety: generalized anxiety disorder, obsessive-compulsive disorder (OCD) or certain phobias (11). Generalized anxiety disorder is a psychiatric condition, statistically more common in women and young adults (12). An adaptogenic plant is a plant increasing the body's ability to adapt to different stresses, whatever their origins. This concept is attributed to a Russian toxicologist, Lazarev (13), who sought to define in 1947 the type of plant action such as Ginseng (*Panax ginseng* C.A. Mey.). An adaptogenicsubstance generally (non-specific) increases the resistance of the organism to diverse stresses that affect it. An adaptogen exerts a non-specific normalizing action on many organs or physiological functions (14). In traditional Chinese medicine, the notionof "adaptogen" has existed for thousands of years under the concept of "higher tonics" that regulate various functions and increase energy, overall promoting health without treating any specific diseases (15, 16, 17, 18). As various studies (19), have demonstratedthat the concept of an adaptogenic plant corresponds well to plants such as Ginseng (Panax ginseng C.A. Mey.);the Pink stonecrop (*Rhodiola rosea* L.), and *Astragalus* with hanging flowers (*Astragalus* *penduliflorus* Lamk.). Whose action allows to raise (or lower) body temperature or blood pressure, to lose (or gain) weight, stimulate (or calm) the nervous system, the hormonal system and therefore the immune system (20). Adaptogenic plants provide a functional and variable response (modulator/regulator), specific to the needs of the individual. These plants are characterized by a non-specific action on the organism (20). Adaptogens are general regulators of internal functions: they tend to increase the homeostatic capacities specific to our organism, in a permanent search for balance. Among the adaptogenic plants, the best known is the Catnip or Cataire, or "Catswort", or catmint (*Nepeta cataria* L.). Its essential oil has spasmolytic, antiasthmatic properties, by probable inhibition of calcium channels and papaverine-like activity (21). The Catnip produces exceptional effects on cats. It contains a chemical product known as nepetalactone. This monoterpene is known for the supposed triggering of sex pheromones in the cat's brain (22). Other felines like the tiger are also to be sensitive. This plant is a typical example of anxiolytic plants used in veterinary medicine. The essential oil of *Cinnamomum camphora* leaves has anti-inflammatory and antioxidant properties (23, 24). The essential oil of *Eucalyptus globulus* leaves is immunostimulant (25, 26), antioxidant (27), analgesic and anti-inflammatory (28). The essential oil of flowering tops of *Lavandula stoechas*has anticonvulsant, antispasmodic and sedative properties by blocking calcium channels (29). Carnosol, extracted from *Rosmarinus officinalis*, protects dopaminergic neurons (30, 31). The flowering tops of this aromatic plant stimulate memory when inhaled (32). The objective of our study is to test the potential anxiolytic and adaptogenic activities of some medicinal plants in the region of El-Tarf, Algeria, in this case, *Lavandula stoechas*; *Cinnamomum camphora*; *Rosmarinus officinalis* and *Eucalyptus globulus*. We used the Elevated Plus Maze (EPM), which detects anxious behavior (33, 34). The animal activity in the labyrinth and the parameters such as the number of entries and the time spent in the four arms are measured (35).

Materials and Methods

Biological material

Wistar Rat

The Wistar ratswere bought from Pasteur Institute of Algiers with an average weight of 250g ± 50g. They were bred under standard laboratory conditions. The rats used are divided into batches of five individuals each.

Plant material

As part of our experiment, we were interested in some plants from the El-Tarf region in Algeria. These plants are known for their adaptogenic activities. They were collected in March 2017 and then dried for two weeks at a standard laboratory temperature, protected from light and moisture. Studied plants are Camphor Tree (*Cinnamomum camphora* (L.) J. Presl); Blue Gum (*Eucalyptus globulus* Labill.); Topped Lavender (*Lavandula stœchas* L.) and Officinal Rosemary (*Rosmarinus officinalis* L.).

Neurological drugs used as standard

The diazepam® was used as a positive control. Diazepam® is a medicine from the benzodiazepines family. It is used for its anxiolytic, sedative, anticonvulsant properties, and as a hypnotic. Like all the molecules belonging to the benzodiazepine family, the diazepam® also has muscle relaxant and amnesic properties. Diazepam® has a high bioavailability (80-100%) and has a rapid onset of action (half an hour by oral route). This rapid action is explained by the high liposolubilityof diazepam®. This last point justifies its use in the epileptic crisis; it also partly explains its diverted use, the effect being intense and rapid. This fast action also determines an increased risk of addiction (36). Among its therapeutic uses, diazepam® is used in the treatment of neurovegetative symptoms associated with dizziness (37), the treatment of alcohol withdrawal symptoms, opiates and benzodiazepines (38), treatment of tetanus (39), treatment of seizures (40) and prophylactic treatment of oxygen toxicity during hyperbaric oxygen therapy (41).

Extraction of essential oils

The dried plants out of light for two weeks are then used for the extraction of their essential oil. Each plant is placed in a hydrodistillation of Clevenger type. The extraction takes approximately 3 hours. Essential oils are, collected and stored in glass ampules, protected from light and air, at a temperature equal to 4-6 °C until their use in the experiment.

Experimental device

Used device

The Elevated Plus Maze (33, 34) is used to measure the degree of anxiety. The Elevated Plus Maze has two closed and two open arms (without walls). This cross-shaped device is elevated 50 cm above the ground.It consist of four (04) arms (L = 50 cm × W = 10 cm) opposite two by two.Two of these arms are closed by walls of 50 cm high, while two others are open and surrounded by rods of Plexiglas 0.5 cm high. The arms are connected by a central platform (10cm × 10cm). Rats are placed in the center of the device, facing an open arm, and left free to explore for 5 minutes (300 sec). This device is topped with a video camera to record the behavior of the animal during the test period. An animal exploringwith open arms will be described as being “not very anxious” and an animal that remains confined in the closed arms of the device will be described as being “anxious”. During this test, the measured variables are Time to center (Sec); Time in the open arms (Sec); Time in the closed arms (Sec); Entries into the open arms; Entries into the closed arms; Entriesto the center.

Test description

The test creates an approach-avoidance conflict between the rodent's natural desire to explore and its fear of open spaces (which put him in front of predators). Anxiety is measured by the time the animal spends exploring the “open” arms. It can be concluded thatthe more anxious an animal is, the less time it will spend in open arms. Montgomery (33) describes in 1955 the aversion of rodents to empty space and height during sessions of free exploration from a familiar environment. On this basis, Handley and Mithami (42) developped the EPM, which will be quickly validated in the rat (43) and then in the mouse (44), as a device for measuring anxiety in rodents.The validation of the EPM as a device for measuring anxiety in rodents is based on behavioral, physiological and pharmacological criteria.

Intraperitoneal injection

The intraperitoneal injection is done by holding the animal head down (thus the organs descend by gravity), in a 45° angle, and by inserting a bevel needle upwards into the lower right face of the abdomen. Animals were withdrawn and checked for the absence of blood or urine (if blood or urine appears, we withdraw the needle and start again). The injected volume of essential oil was 200 µL/kg for the rat.After injection, animals were let rest for five minutes before beginning any manipulation.

Statistical methods

All statistical analyses were performed with the R program (version 2020). GG-plot 2 library was used to assess boxplots for time spent on arms. Whereas, Principal Component Analysis and Cluster dendrogram were used to differentiate between essential oil activities.

Results

Effect of injectionof essential oils on time spent on open and closed arms

Below the graph (Figure 1), representing the behavior of the rats subjected to essential oil-based treatmentvs control and diazepam®.We notice a very highly significant difference in the behavior of rats in their movement and the time spent on open arms and closed arms.

We note that the time spent on open arms is variable from one essential oil to another.The majority of oils used show a state of relaxation in the behavior of rats.As below the graph, representing the behavior of rats subjected to the *Eucalyptus globulus*-based treatment, we notea very highly significant difference in the behavior of rats in their displacement and the past time on open arms and closed arms. We notice also for *Lavandula stoechas* a very highly significant difference in the behavior of rats in their displacement and the past time on open arms and closed arms. *Rosmarinus officinalis* induceda very highly significant difference in the behavior of rats in their movements and the time spent on open arms and closed arms. The greatest relaxation in time spent on open arms is observed for *Eucalyptus globulus* followed by *Lavandula stoechas* with significant differences compared to the used control. Most of the used oils have a shorter time spent on open arms compared to the standard diazepam®. The most significant relaxation in the time spent on the central square is observed for the *Cinnamomum camphora*, followed by *Eucalyptus globulus* with significant differences compared to the used standard diazepam®.

Concerning closed arms, the majority of the used oil shows astate of relaxation behavior of rats. The most important relaxation in time spent in open arms is observed for the *Cinnamomum camphora* followed by *Lavandula stoechas* and then *Eucalyptus globulus* with significant differences compared to diazepam®. Finally, the central square shows a state of relaxation in the behavior of rats. The most significant relaxation in the time spent on the central square is observed for the *Eucalyptus globulus* followed by the *Cinnamomum camphora* with significant differences compared to the standard used.

Effect on the number of transition to closed arms of the device

We also notice that the number of transition to open arms is highly variable from oil to another. Half of the used oils show a state of relaxation in the behavior of rats, relaxation observed by the increase in the number of transitions towards open arms compared to positive white. The highest value is observed for *Eucalyptus globulus*followed by *Cinnamomum camphora* with significant differences compared to the used standard diazepam®.

The Principal Component Analysis (Figure 2) demonstrates also that the major part of rats behavior is correlated with the time passed on the closed arms, and that this is partially depending on the weight of animals. The more they are younger, the more they exhibit a relaxing response to the injection of essential oils. We also see that the only parameter with opposite evolution is the time passed on the closed arms and the number of entries to-and-from the closed arms. The increase in the number of entries to open arms with *Eucalyptus globulus* essential oil shows a reduction in anxiety behavior

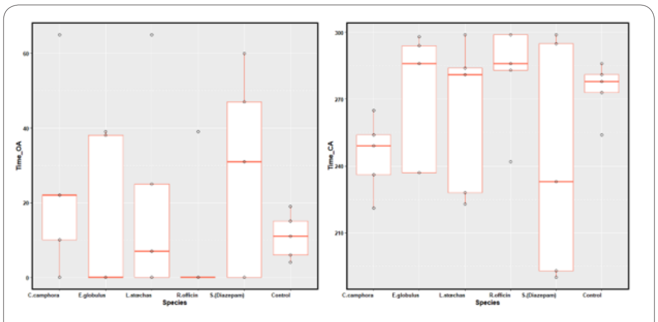

Figure 1. Time spent on Open Arms (OA)vs Closed Arms (CA) for the fourth essential oils.

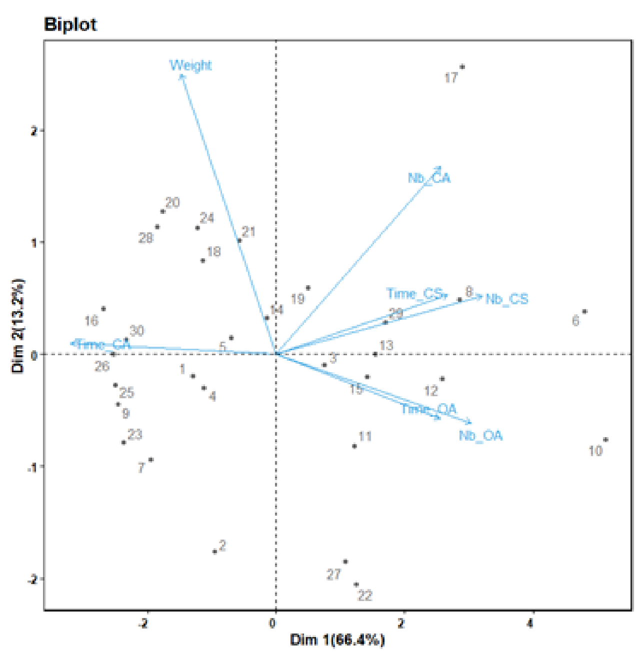

Figure 2. Principal Component Analysis. OA: Open Arm; CA: Closed Arm; CS: Central Square.

in rodents.

The cluster dendrogram (Figure 3) indicates that the essential oils of *Eucalyptus globulus*, *Lavandula stœchas* and *Rosmarinus officinalis* have an anxiolytic effect at different levels but are less correlated than *Cinnamomum camphora* with the Diazepam® induced behavior. *Cinnamomum camphora* essential oil exhibit the effect of the inhibitor observed. In another hand, *Rosmarinus officinalis* is the most tonic one on the opposite side of *Cinnamomum camphora*.

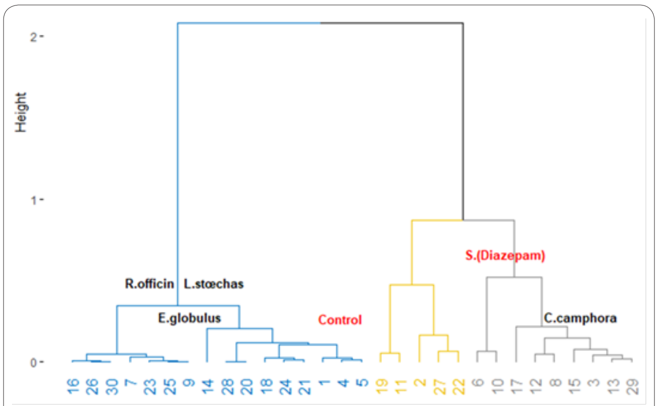

Figure 3. Dendrogram of hierarchical cluster analysis showing the relationship between four essential oils and their anxiolytic effects.

Discussion

Diazepam® is used as an anxiolytic standard and has been frequently used in behavioral pharmacology as a reference compound for a potentially anxiolytic substance (45, 46, 47). As expected, the diazepam® produced significant increases in time spent in open arms and the number of entries into the open arms relative to negative controls not receiving treatment. The decrease in aversion to the open arm is the result of an anxiolytic effect expressed by an increased number of open arm entries and the time spent on them. For the treated batch with the essential oil of *Cinnamomum camphora* at a dose of 200 µL/kg, we note an increase in the time spent in open arms compared to that recorded in rats treated with diazepam®. This shows also an anxiolytic effect of the essential oil of *Eucalyptus globulus*. The increase in the number of entries with closed, open arms and the central square may be due to a tonic effect of *Eucalyptus globulus*.

Concerning the treated groups with *Rosmarinus officinalis* essential oil, *Lavandula stoechas* and *Eucalyptus globulus* at a dose of 200 µL/kg, we note an increase in the time spent in open arms and a decrease in time spent in closed arms.This especially concerned *Eucalyptus globulus* among the four tested essential oils, which explains the anxiolytic effect of these plants. We also note a decrease in the number of entries in closed arms, open arms and the number of passing in the central square; this shows that these plants have an inhibitory effect on rats.

Chemical analysis of *Cinnamomum camphora* Essential Oil demonstrated its richness of monoterpenoids. Chemical studies have reported the presence of several monoterpenoid compounds in the essential oil of *Cinnamomum camphora*, primarily; β-pinene, β-thujone, limonene and also linalool are reported to have antidepressant activity. The mechanism involved in the pathogenesis of depression is monoamine deficiency. Certain biological monoamine like NA and 5-HT, dopamine especially decreases in NA and 5-HT causes depressive episodes in patients suffering from depression which makes their life miserable. The currently available drug therapies focus on increasing the availability of NA and serotonin which centers on the inhibition of MAO. It has been established that the shortening of immobility time in the forced swimming and the tail suspension tests depends mainly on the enhancement of central 5-HT and catecholamine neurotransmission. Early evidence of a role for noradrenaline in depression came from the discovery that drugs, either causing or alleviating depression, acted to alter the noradrenaline metabolism. Furthermore, depletion studies carried out in treated and untreated patients indicated a role for serotonin and noradrenaline in depression. It has been recently shown that the regulation of α2-adrenergic receptors may be the major mechanism of this model. The results indicate that essential oil of *Cinnamomum camphora* may have an antidepressant-like effect and the immobility time observed in the test reflected a state of lowered mood or hopelessness in animals, thus, this animal model is the most widely used tool for preclinical screening of putative antidepressantagents. The FST shows a strong sensitivity to monoamine alterations and is a very specific cluster of stress-induced behaviors that are not related to depression symptoms in humans, but which are nonetheless exquisitely sensitive to monoaminergic manipulations. It also provides a useful model to study neurobiological and genetic mechanisms underlying stress and antidepressant responses (48).

The present study was designed to evaluate the adaptogenic activity of some plants from the Northeastern area of Algeria, especially *Lavandula stœchas* (Topped Lavender), *Cinnamomum camphora* (Camphor), *Rosmarinus officinalis* (Rosemary) and *Eucalyptus globulus* (Blue gum). The tests were conducted *in vivo* on Wistar rats raised under standard laboratory conditions. The anxiolytic activity was evaluated on the elevated plus-maze (Plus Maze Test). The effectiveness of the essential oil extract (200 µL/kg) was compared to the standard anxiolytic drug Diazepam® (1mg). Animals administered with *Lavandula stœchas* essential oil, *Cinnamomum camphora*, *Rosmarinus officinalis* and *Eucalyptus globulus* showed behavior close to those of the positive control group treated with diazepam®. The results showed that the essential oils of these plants considerably increased the time spent in the open arms of the elevated cross with an increase in the number of movements in the open arms for *Eucalyptus globulus*. The treated group with *Eucalyptus globulus*essential oil at a dose of 200 mL/kg, notes an increase in the time spent in open arms compared to that recorded in rats treated with diazepam®, this proved an anxiolytic effect of *Eucalyptus globulus*. The increase in the number of entries in closed and open arms rather than the central square may be due to a tonic effect of *Eucalyptus globulus*. For groups treated with the following essential oils: *Rosmarinus officinalis*, *Lavandula stoechas* and *Cinnamomum camphora* at a dose of 200 mL/kg, we notice an increase in the time spent on the open arms and a decrease in time spent on the closed arms of the elevated plus-maze,especially for *Rosmarinus officinalis*, which explains the anxiolytic effect of these plants. We also notice a decrease in the number of entries in closed arms, open arms and the number of passingto the central square; this shows that these plants have an inhibitory effect. We concluded that the essential oils of *Eucalyptus globulus*, *Lavandula stœchas*, *Cinnamomum camphora, and Rosmarinus officinalis* have an anxiolytic effect at different levels with an inhibitory effect for *Lavandula stœchas*, *Cinnamomum camphora, Rosmarinus officinalis* and tonic one for *Eucalyptus globulus*. A detailed analysis of the composition of essential oil would allow a better understanding of the molecules involved in these adaptogenic and anxiolytic phenomena of the plants used in our experimental setting. All of these results open up tracks to better explore the mechanisms of action of essential oils in plants and to push the investigation further with other devices, such as that of forced swim, in order to verify with more rigor of the presented results above.A detailed analysis of the composition of essential oil would allow a better understanding of the molecules involved in these adaptogenic and anxiolytic phenomena of the plants used in our experimental setting.

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Disclosure Statement
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

Author's contribution
Authors contributed equally to this paper.

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