

## ANXIOLYTIC AND ANTIDEPRESSIVE ACTIVITY OF *NEPETA GRANATENSIS* ESSENTIAL OIL

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### ABSTRACT

The present study was undertaken to investigate the anxiolytic activity of essential oil of *Nepeta granatensis*. The anxiolytic activity of the essential oil (12,5; 25; 37,5; 50 mg/kg), Diazepam (1mg/kg) and Fluoxetine 10 mg/kg standard drugs were assessed in *Balb/c* mice by elevated plus maze (EPM), open field test (OF), and forced swimming test (FST) models. The results showed that the essential oil significantly had increased the number of entries and time spent in the open arm in the elevated plus maze apparatus. Moreover, in the open field a significant increase in number of rearing, and number of squares crossed were shown. The administration of the essential oil had produced a diminution of immobility time of mice exposed to forced swimming test in dose dependant manner. Therefore, *Nepeta granatensis* owned an anxiolytic and anti-depressant properties

**KEYWORDS:** *Nepeta granatensis*, micro-wave, essential oil, elevated plus maze (EPM), open field test (OF), forced swimming test (FST).

### INTRODUCTION

In the last decades, stress remains the most common modern life disorder. These phenomena could be characterised by emotional and physical symptoms and conduct to several mental

and behavioural troubles, including, anxiety and depression.<sup>[1]</sup> Different drug classes are available, despite their side effects. Benzodiazepine was generally the often first line drug used to cure neuropsychiatric illness. However, it was known to lead to dependence and problem of tolerance if it was long term administered.<sup>[2,3]</sup> Research had led to investigate other possible therapeutic targets among others, biomolecules from nature. Some medicinal plants were commonly used for their anxiolytic and anti-depressant-like effect such *Passiflore*, *Valerian* and *Melissa*.<sup>[4,5]</sup> *Nepeta* genus is native from North Africa, Asia and Europe and belongs to the mint family (Lamiaceae).<sup>[6,10]</sup> Indeed, *Nepeta* species have long been used owing to their therapeutic virtues. The survey of literature reveals thereby that *Nepeta* has diuretic, antispasmodic, analgesic, febrifuge, antifungal, antimicrobial effects.<sup>[11, 17]</sup> Furthermore, some studies had reported that *Nepeta* was sedative, relaxant, restorative for nervous and respiratory disorders.<sup>[18,19]</sup> The most of this activity was commonly related to nepetalactone the main constituent of their essential oil. It is also been known that *Nepeta* was used in folk medicine as calming. However, only a few scientific reports had demonstrated that *Nepeta* possessed anxiolytic and anti-depressant properties.<sup>[20,22]</sup> Referring to these data, we aimed to examine the neurobehavioral activity of *Nepeta granatensis* essential oil on animal models.

## MATERIAL AND METHOD

### Plant Material

*Nepeta granatensis* has been collected during the flowering period on July 2011, in specific areas of the Ifran Valley, in the Middle Atlas, to humid climatic stages, and at an altitude of 1500m. The plant were identified with botanist of scientific institute. Voucher specimen RAB 79003 and was deposited in the herbarium of Botany Department of Scientific Institute, University Mohammed V- Rabat, Morocco.

### Preparation of essential oils

The plant was dried in the shadow under ventilations, at room temperature and was regularly turned over. After having coarsely cut the aerial parts of the plant, the essential oil was achieved by hydro distillation by irradiation under microwave fields.<sup>[17]</sup> Subsequently, it was kept in the fridge at 4°C.

### Animals

A quantity of 36 females and male *Balb/c* mice weighting 20-30g for each of the three tests were obtained from the animal experimental center of sciences faculty, university

Mohammed V, Rabat. The tested animals were free to standard feed and water ad libitum, and kept in the same conditions of temperature ( $22 \pm 3^\circ\text{C}$ ), humidity 65-70%. An artificial lighting was used, of 12 h light / 12 h dark cycle, lights on 6:00 a.m. The mice were randomly chosen, divided into 6 groups of 6 mice each and housed in polyethylene cage for at least 5 days before the experiment. They were treated according to the Official Journal of European Community (OJOC) in 1991. The experiment protocol was approved by the institutional research committee, regarding the care and the use of animals for experimental procedures, in 2010, CEE 509.

### Drugs & Chemical

Diazepam DZP, Fluoxetine FLUX, Tween 80, *Nepeta granatensis* essential oil (NGEO). All the doses are expressed in mg/kg body weight and administered by intraperitoneal route i.p with a volume of 10 ml/kg

### Experimental protocol

The six groups had received i.p, 30 min before experiments respectively, 0,05% Tween 80 dissolved in 0,9% saline solution(control group), EO solution to 12,5; 25; 37,5; 50mg/kg (treated group), Diazepam 1mg/kg or Fluoxetine 10mg/kg dissolved in normal saline(standard group)

### Elevated plus maze

The Elevated plus Maze (EPM) test is validated to assess anxiety in rodent models.<sup>[23,26]</sup> The EPM apparatus was made from wood painted in black and composed of two oppositely positioned open arms, and two oppositely positioned closed arms and a central square area. To form a "plus" shaped maze elevated above the floor. Each mouse was put at the centre of the maze, facing one of the open arms. Number of entries and time spent in the open/enclosed arms was recorded for 5min test. Entry into an arm was defined as the animal placing all four paws onto the arm. The mouse behaviour is recorded by means of a video camera mounted above the maze and analysed using a video tracking system. After each test, the maze was carefully cleaned up with a wet tissue paper (10% ethanol solution).

### Open Field

The Open Field test is used to assess general activity levels, locomotors activity, and exploration habits in rodent models of CNS disorders.<sup>[27,28]</sup> The Open field arena used was (45cm x45cm x17cm) made with transparent Plexiglas walls and a black floor. White lines

were drawn on the floor with a marker, dividing the arena to nine equal area squares (15cm x15cm). A central area was drawn of (29cmx29cm). The animal is placed in the right corner of the arena and allowed to move freely about for 5 minutes, while being recorded by a video camera. The video is then analysed, the counting was done manually for the following parameters: number of squares crossed (with the four paws) number of rearing, and time spent in central pre-defined zones. Each mice was returned to its home cage and the apparatus was cleaned with a wet tissue paper (10% ethanol solution).

### Forced Swimming Test

This test is widely used to evaluate the anti-depressant effect in-vivo model.<sup>[29,33]</sup> Mice are individually forced to swim in a Plexiglas cylinder (height 45 cm, diameter20 cm). Which contains fresh water at  $24\pm1^{\circ}\text{C}$ , up to 15 cm for 5min. At first, the mouse swims vigorously in circles, trying to climb the walls .The mouse is considered immobile when it made no further attempts to escape, apart from the movements necessary to keep its head above the water. Thus, the immobility reflected a state of lowered mood in which the animals had lost hope of finding an egress and had resigned themselves to the experimental situation. During the test, the immobility time was recorded using a video camera. Afterwards the test, the mouse was removed and dried, then, returned to its home cage. The water was changed for every animal after each test.

### Statistical Analysis

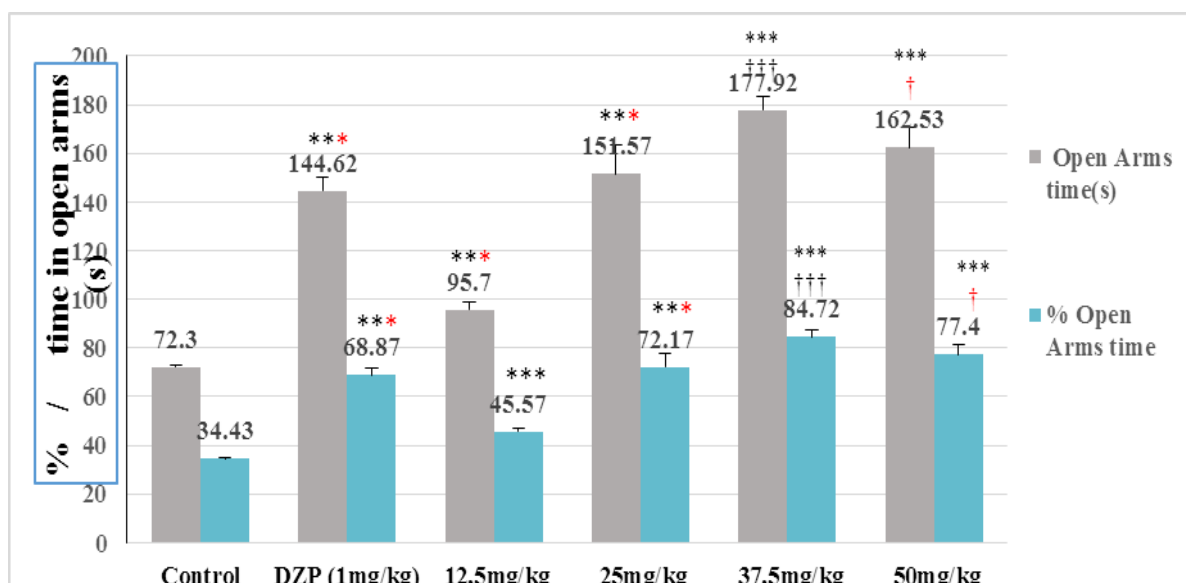
The result obtained were subjected to statistical analysis using one-way Anova followed by Turkey's post hoc test multiple comparisons in Graph Pad Prism 5 ( Graph Pad, San Diego, CA). All the data were expressed as mean  $\pm$  Standard Error of Mean (S.E.M). Differences were considered statistically significant from  $p<0.05$ .

## RESULT

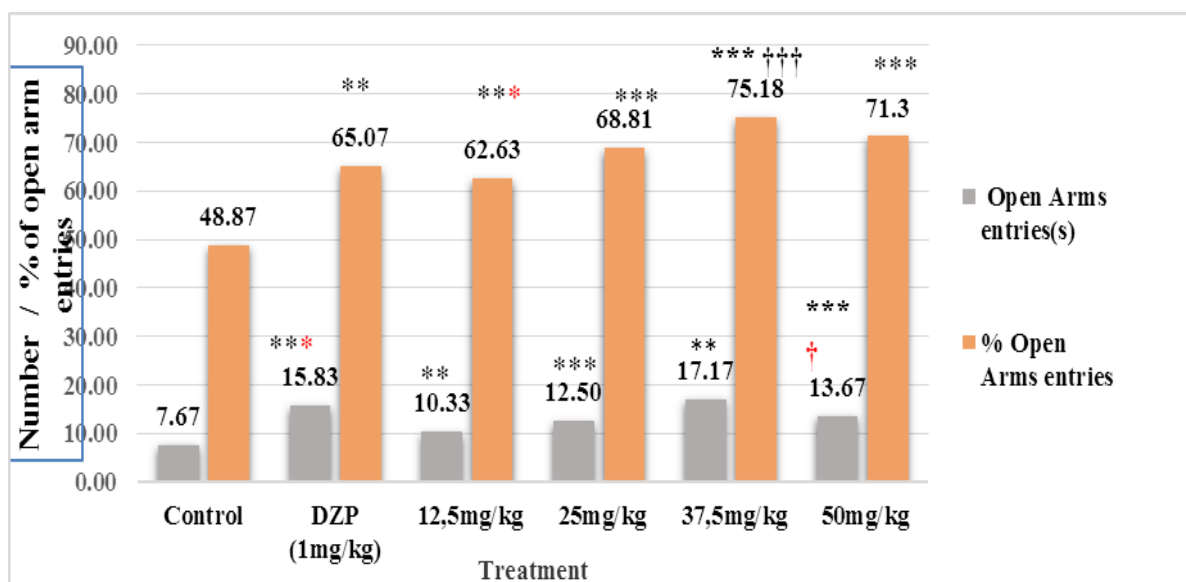
### Elevated plus maze

The intraperitoneal administration of the different doses of *Nepeta granatensis* essential oil 12,5, 25, 37,5 and 50mg/kg in *Balb/c* mice exposed to EPM test showed an increase statistically significant ( $p<0.001$ ) in the percentage and the time spent in open arms as compared to the control group . While the dose 37,5mg/kg ( $p<0.001$ ) and 50mg/kg ( $p<0.05$ ) significantly increase theses parameters as compared to Diazepam (Fig .1). Indeed, the EO has increased significantly ( $p<0.001$ ) the number and percentage of entries in open arm for

all the doses compared with the control group and had the same effect at the dose 37,5 mg/kg as compared to Diazepam (Fig. 2)



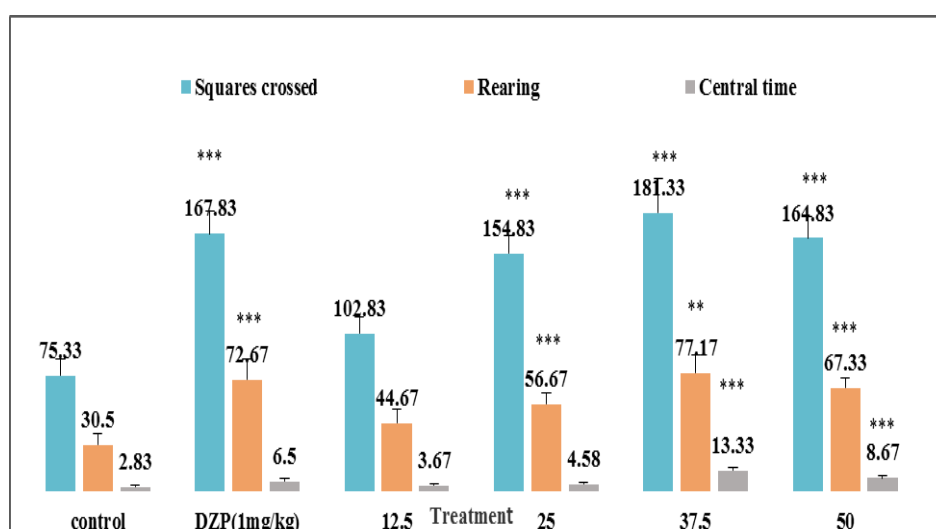
**Fig. 1:** Effect of NGEO and the standard drug Diazepam on time and percentage of time spent in open arms in EPM test on mice. Values are means  $\pm$  SEM from 6 animal in each group \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  versus control † $p < 0.05$ , †† $p < 0.01$ , ††† $p < 0.001$  versus standard group



**Fig. 2:** Effect of NGEO and the standard drug Diazepam on number and percentage of entries into open arms in EPM test in mice. Values are means  $\pm$  SEM from 6 animal in each group \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  versus control † $p < 0.05$ , †† $p < 0.01$ , ††† $p < 0.001$  versus standard group

### Open Field

The treated mice with the NGE0, when compared with the control group, had shown no significant difference in the crossing and rearing at 12,5mg/kg. However a significant increase were recorded at the doses of 25, 37,5 and 50 mg/kg and in Diazepam group. On the other side, comparing to the standard group no significant effect on the mice mobility was shown at those NGE0 doses excluding only the 12,5mg/kg group where a significant decrease was recorded  $p < 0.001$  in the number of squares crossed and  $p < 0.05$  in the rearing frequency. The time spent in the central area of the open field paradigm has no significant differences between the NGE0 groups at 12,5 and 25mg/kg as compared to the control group, and 12,5, 25mg/kg even 50mg/kg as compared to the Diazepam group. Conversely, a significant ( $p < 0.001$ ) increase was recorded at 50 and 37,5mg/kg as compared to control and at 37,5 when compared to Diazepam. A slight decrease was also found at the 50mg/kg as compared to 37,5 mg/kg ( Fig 3)

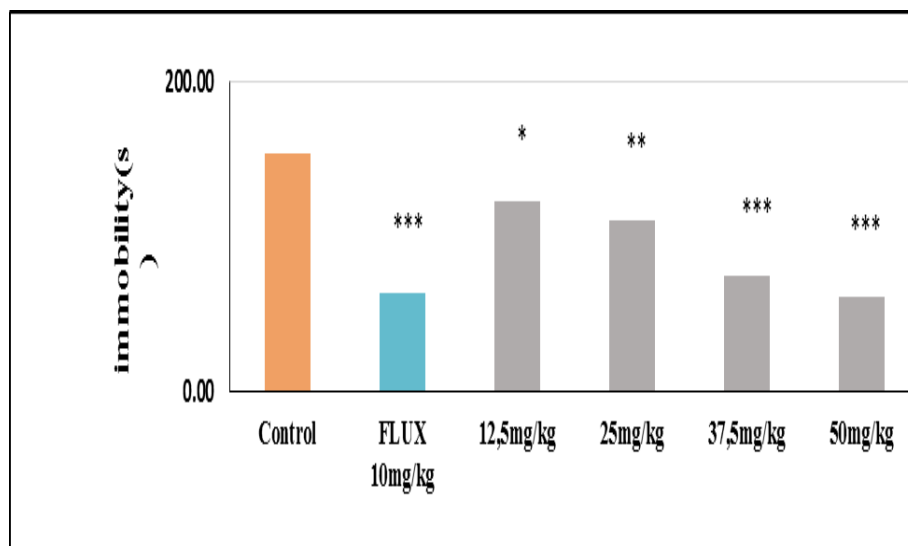


**Fig. 3: Effect of NGE0 and the standard drug Diazepam on frequency of rearing, total of squares crossed and time spent in the centre area in second in the open field test on mice for 5min .Values are means  $\pm$  SEM (n=6) \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  versus control † $p < 0.05$ , †† $p < 0.01$ , ††† $p < 0.001$  versus standard group**

### Forced swimming test

Treatment with NGE0 had produced in a dose dependence manner a diminution of immobility time. That was significant ( $p < 0.05$ ) at 12,5mg/kg, ( $p < 0.01$ ) 25mg/kg and  $p < 0.001$  at high doses 37,5 and 50 mg/kg compared to control group. The standard drug Fluoxetine also had the same effect and reduced significantly ( $p < 0.001$ ) the immobility time. When

compared to the standard group, mice treated with the low doses 12,5 and 25 mg/kg had indicated a significant increase  $p < 0.01$  in time of immobility. On the other hand, no significant difference was observed at the high doses 37,5 and 50mg/kg (Fig4)



**Fig. 4:** Effect produced by the i.p administration of different doses of the EO from *Nepeta granatensis* and Fluoxetine on the immobility time of *Balb/c* mice exposed to the swimming forced test .The values are Means  $\pm$  SEM (n=6) \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  versus control

## DISCUSSION

The prevalence of the mental illness over the world is one in four people at a given moment in their life.<sup>[34,35]</sup> Due to the serious side effect of drugs used until now, a need of a strong knowledge of alternative based on medicinal plant in the anxiety and depression treatment has become increasingly important.

Recently we have reported the analgesic activity of *Nepeta granatensis*<sup>[36]</sup> essential oil and we have highlighted the observation of a sedative effect and a calming behaviour in mice mainly at the dose 50mg/kg. This finding encouraged us to study the psychopharmacological effect of NGEEO on the CNS. Behavioural assessment on rodent's model is a common way to the identification of meaningful response units and their controlling variables for the aim of comprehending and altering human behaviour. *Balb/c* had known to be emotional and anxious strain mice.<sup>[37,42]</sup> In the present study, we investigated anxiety and depression because there is a comorbidity between the two disorders, using relevant tests on *Balb/c* mice.<sup>[43]</sup>



Elevated plus maze is an approach –avoidance conflict test used to assay mice anxiety behaviour.<sup>[44]</sup> A naïf anxious mouse prefers enclosed spaces and explores less a height and bright space because of his fear. Increase in time spent and the entry frequency in open arm reflect an anxiolytic activity of drugs. Noting that, the standard drug, Diazepam, a benzodiazepine agonist, at 1mg/kg, will push to an increase in the time and the number of entries in open arms without alteration of spontaneous locomotors activity or yielding to a sedative effect.<sup>[45]</sup> The administration of different doses of the EO exhibited a similar anxiolytic effect that was well marked at the dose 37,5mg/kg.

In the open field test, the increase of time spent in the central zones of the paradigm had clear demonstrated the anxiolytic activity of NCEO. Besides, the treated mice showed an increase in rearing and the number of squares crossed that revealed a locomotors activity like the mice receiving Diazepam. The mice upon open field were subjected to the anxiolytic effect without leading to a central nervous depression. At high dose 50mg/kg a slight decrease in both results of EPM and open field tests appeared related to the beginning of a sedative action of the essential oil previously mentioned by others reports.

Despite the widespread of mental disorders that are mostly associated with bouts of depression or anxiety, the real causes of these diseases remain unknown. The GABAergic, noradrenergic (NA) and serotonin (5-HT) system are involved in anxiety. Benzodiazepine drugs including Diazepam act on GABA, an inhibitory neurotransmitter, increase the inhibitory processes in the cerebral cortex and inhibits excessive neuronal excitability. It is therefore, probable that the anxiolytic effect shown by NCEO is due to an activation of GABA transmission.<sup>[46]</sup> A mice exposure to a stressful situation such the forced swimming test give a validated assessment of depression behaviour. Furthermore, it is a rapid assay to prove imputing antidepressant activity of novel compounds. In the FST, mice cannot escape out of the cylinder, will experience a feeling of hopelessness similar to human inability to cope with stressful situation that he cannot manage. Fluoxetine, a SSRI (inhibitor of the reuptake of serotonin), presents anti-depressant properties and is characterized by its ability to reduce time to immobility in the forced swim test.<sup>[47]</sup> Even there, the NCEO had significantly decreased the time spent immobile by mice in a dose dependant way that have reached ( $60,83 \pm 8,5$  s) at 50mg/kg accompanied by a prominent increase of swimming period. That will suggest the effect of NCEO on the depression behaviours.



**CONCLUSION**

Hence, the data of the present strongly support the conclusion that essential oil of *Nepeta granatensis* exhibit both of anxiolytic effect benzodiazepine-like and give a response like to the SSRI anti-depressant effect. Meanwhile, the motor skills may be maintained in contrast to the usual drugs. Further study seems requisite to reveal if the major constituent nepetalactone was the main responsible of this activity or it might be in reason of a synergy between all essential oil constituent.

**Conflict of interest:** Authors declare no conflict of interest.

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