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THE EFFECTS OF LAVENDER ESSENTIAL OIL AND GALLIC ACID PRE-TREATMENT ON THE NEUROCOGNITIVE ASSESSMENT OF POST-STROKE WISTAR RATS

CHEBBAH FELLA [a*], DJOUINI AMINA [a], AIDAOUI LATIFA [a], LAHMANES NARIMENE [a], RETEM CHAHIRA [a], SMILI CHAIMA [a] AND BAIRI ABDELMADJID [a]

[a] Applied Neuroendocrinology Laboratory, Department of Biology, Faculty of Sciences, University Badji Mokhtar, Annaba 23000, Algeria.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Stroke is a multifactorial, fatal and often disabling neurodegenerative disease in which neurons are degenerated leading to cognitive and muscular problems, there is no curative treatment for this disease; the drugs available on the market offer symptomatic relief with some improvement of daily functions. Thus, phytochemicals with multifactorial efficacy may be promising substances for the treatment of cerebral ischemia and its recurrences that would have been prevented by various plants and plant products. The aim of our study is to evaluate the effect of lavender oil and gallic acid administered orally at doses of 200 mg/kg and 100 mg/kg, respectively, prior to stroke induction by middle cerebral artery occlusion in Wistar rats. The aim is to evaluate their effects on post-stroke sequelae, such as anxiety, exploration and memory (spatial and working), which were quantified and compared between: the control, non- pretreated stroke and pretreated stroke batches. The results indicate a better cognitive-motor recovery on an anxious and exploratory level in the rats pretreated with GA and LEO, while memory capacities are superior in the latter compared to the non-pretreated stroke group. These findings reveal and support the neuroprotective effect of gallic acid and lavender essential oil taken separately or in combination.

Keywords: Stroke; Wistar rats; Gallic acid; Lavender Essential Oil; cognitive-motor recovery.

**Corresponding author: Email: chebbahchaima27@gmail.com;*

1. INTRODUCTION

Stroke survivors with invisible impairments in cognition and depression are particularly vulnerable to poor recovery. In the past, approximately 70% of survivors of acute stroke were limited in their activities and independence due to cognitive deficits or depression [1].

Cognitive impairment and memory loss are common after a stroke; approximately 30% of stroke patients develop dementia within one year of the onset of the stroke [2].

Memory disorders occur after a stroke when a brain region involved in memory function (Papez circuit) has been affected. These problems may not be observed in the first few days after the stroke, especially if they are discreet or if other deficits mask them [3].

The burden of stroke continues to increase, particularly among young adults who also have cardiovascular risk factors; including hypertension, diabetes, obesity and substance abuse [4].

Therefore, post-stroke dementia (PSD), in particular vascular dementia (VD), reflects the vascular risk factors that are primarily correlated with cerebrovascular disease (CVD). Post- stroke cognitive impairment is the progression of CVD that predisposes individuals to the spectrum of vascular cognitive impairment. Thus, understanding the stages of this spectrum is necessary to assess the mental status of post-stroke patients, in particular cognitive dysfunction and memory decline in the period following a stroke diagnosis [5].

Due to research developments, this is achieved through primary prevention, acute and post- stroke care. It allows the control of risk factors through screening, treatment and follow-up [6].

In Africa, for example, 80% of the population relies on traditional medicine for health care [7].

Many efforts have been made to develop beneficial agents from medicinal plants to achieve neuroprotection. Recent studies have shown that supplementation with certain phenolic compounds can prevent or treat brain damage and the ability of phenolics may be related to their antioxidant properties [8].

Flavonoids are cardioprotective [9,10], antihypertensive [11] and some flavones are antiplatelet [12]. All of these metabolites have antioxidant activities and are essential for the recovery of brain injury through their ability to scavenge free radicals and reduce oxidative stress produced after a stroke, through regeneration of brain cells [13]. Several studies in animal models and in human subjects have indeed confirmed the bioavailability of phenols to exert a protective role against oxidative stress and free radical damage [14,15].

Among them is gallic acid, which is a natural plant triphenol. This compound is widely found in black tea leaves, green tea, apples, grapes, strawberries and pineapples, and is found in a wide range of foods in varying amounts depending on plant species and environmental factors [16].

Gallic acid has been reported to be effective against neurodegenerative diseases [17,18], including Alzheimer's disease, Parkinson's disease, ischaemia and reperfusion, depression and anxiety, as well as its benefits on brain and cognitive function [19]. In fact, GA reduces chronic cerebral hypoperfusionin rats and has a significant protective effect on brain cell viability [20,21].

Complementary medicine, a low-risk, cost-effective and easy therapeutic method, has trivial side effects, aromatherapy being one of its branches [22]. Aromatherapy is an effective treatment for the management ofbehavioural and psychological symptoms of dementia, improving cognitive function, increasing quality of life and improves independence in activities of daily living [23, 24].

Essential oils, known for their therapeutic properties, have been used for thousands of years in millennia in China, India, the Middle East, Egypt, Greece, America and Africa [25].

The essential oil of Lavender officinalis is without doubt an essential oil of aromatherapy, it is obtained from the flowering tops of the lavender plant by complete distillation. In view of the number of existing scientific articles, the essential oil of Lavender officinalis is very probably the most studied essential oil today [26]. Various studies have been conducted on aromatherapy with lavender essential oil on memory [27,28]; but different results have been reported.

The aim of our study is to evaluate the separate effect of the two drugs on the induction of ischemic stroke, surgically produced by occlusion of the middle cerebral artery in Wistar rats, to evaluate the separate effect of gallic acid and lavender essential oil and then the combination of the two taken as prophylactic treatment (by gastric gavage). These virtues are quantified at the cognitive level by evaluating the

skills of memory and exploration skills in post-stroke rats.

The present study aims to identify the invisible disability after stroke and to evaluate the impact of pretreatment with GA and EOL on cognitive rehabilitation.

2. MATERIALS AND METHODS

2.1 Biological Materials

The basic biological material we used was the white rat Rattus rattus of the Wistar strain. Forty male rats from the Institut Pasteur in Algiers (Algeria) were acclimatised to the conditions of our animal house acclimatised to the conditions of our animal house, which is attached to the Biology Department of the Faculty of Natural and Life Sciences (Université Badji Mokhtar University, Annaba, Algeria).

The animals used in this experiment were all of EOPS (Exempt from Specific Pathogenic Organisms) health status. of specific pathogenic organisms) and weighed between 180 and 260g.

2.2 Breeding Enclosure

The animals are housed in translucent polyethylene cages in groups of 8. The cages are are lined with wood shavings and are regularly cleaned with a daily change of bedding.

Prior to any experimentation, the animals are subjected to a two-week period of accommodation under well-controlled conditions.

The animals are acclimatised to a temperature of 25 ± 2°C, , a humidity of 50-70% and a natural photoperiod (12 h darkness/12 h light). They are fed a balanced diet in the form of sticks consisting of maize, barley, milk and vitamin supplements. Drinking water is provided in abundance.

2.3 Experimental Methods

2.3.1 Method of stroke induction in wistar rats

Middle cerebral artery occlusion: In order to avoid performing a craniotomy, an intraluminal middle cerebral artery occlusion model has been developed and artery has been developed and modified by many authors [29,30] The model developed by Koizumi and modified by Longa and his team, remains the most widely used [31]. It is based on the introduction of a monofilament of sufficient diameter monofilament wire with a rounded end through the stump of the external carotid artery to occlude the ostium of the middle cerebral artery.

After consultation with the veterinarian attached to our laboratory, the operating protocol was as follows:

The animals are anaesthetised by intra-muscular injection of the combination of Zolazepam and Tiletamine in the form of hydrochloride (0.1 ml of Zoletil®)., 5 min after the injection the rat loses consciousness and is placed in the operating field on which the instmruments must be kept sterile throughout the procedure, in dorsal recumbency in order to clear the cervical region. The cervical region is incised to expose the right carotid bifurcation, an incision is made in the midline of the neck and the soft tissues are separated. Then the arteries are carefully dissected to locate the right common carotid artery (CCA), the external carotid artery (ECA) and the internal carotid artery (ICA). The internal carotid artery (ICA) is gently separated from the tissues taking care not to damage adjacent vessels or nerves, it is ligated with a 4.0 monofilament and then the insertion of a monofilament of the same thickness via the ECA proximal to the ICA, This positioning results in occlusion of the middle cerebral artery.

After surgery, the incision is closed with a simple suture, the animals are returned to their heated cages and cared for with hydrogen peroxide and Betadine daily.

2.4 Pre-treatment Methods

2.4.1 Gallic acid pre-treatment method

Gallic acid is a phenolic acid not used in its basic state. However, its salts and esters are widely used [32]. It is present in the form of a white or pale yellow crystalline powder, odourless, with an astringent and acidic taste. it is a substance naturally found in walnuts and oak bark, tea leaves, green tea, and other plants. tea leaves, green tea, apple peel, grapes and wine [33].

The GA (3, 4, 5-trihydroxybenzoic acid, C6H2 (OH) 3-COOH, MW = 170/12) was purchased from Sigma-Aldrich® Co, USA; a dose of 100mg/kg was administered by gastric gavage to the affected Wistar rats every day for 10 days at the same time (10:00 a.m. to 5:00 p.m.).

2.4.2 Lavender essential oil pre-treatment method

We used the essential oil of lavender officinalis coming from the lavender cultivated in September 2021 in the national park of Lalla Setti in Tlemcen (north-west of Algeria), hydrodistilled (by steam distillation) from the dried flowering tops. The dose administered was 200 mg/kg [34,35], by gastric

gavage to selected Wistar rats every day for 10 days of pre-treatment at the same time (10 am).

2.4.3 Pre-treatment method with the combination of GA and EOL

For one of our experimental batches, we combined the two previous pre-treatments, namely GA at a dose of 100mg/kg with EOL at a dose of 200 mg/kg; which was administered to the rats concerned by gastric gavage daily for 10 days at a fixed time.

2.5 Behavioural Tests

2.5.1 Object recognition test

The object recognition test (ORT) is particularly useful for studying declarative memory in rodents because it appeals to their natural preference for a new object over a familiar one in a known environment. . Control animals typically spend more time exploring the new object, thus reflecting the use of memory and learning processes. The apparatus for this test consists of a (70cm×70cm×40cm) enclosure, surrounded entirely by 40cm partitions and covered with grey paper to eliminate any external cues from the rat's visual field [36].

In this protocol, the test is divided into 3 phases, containing 4 learning sessions of 3 minutes each, except for the first one which lasts 5 minutes, interspersed with 3-minute intersessions during which the rats are returned to their usual cage.

A training phase: Consisting of 02 sessions, the first allows the rat to explore the empty chamber for 05min.

A spatial memory exploration phase: It consists of 02 sessions of 03min each. The rat is free to explore the space in the presence of the 04 similar objects from the training phase, 1 of which was moved.

2.5.2 Experimental protocol

A working memory assessment phase: Also comprising 02 sessions of 03min each. This time, one of the previous objects is replaced by a new one. The rat is therefore free to explore the space in the presence of 03 familiar objects and one new object.

Between one session and the next, any defecation or urine is collected and between the passage of one rat and the next, the rat is free to explore the space. The device and the objects are cleaned with 70° alcohol, so as to present each rat with an environment.

Table 1. Batching of rats during the experiment

Batchs	Effective	Treatment	Dose
Control lot (C)	8	\	\
batch without pre-treatment (S)	8	\	\
Batch GA	8	+	100mg/kg
Batch EOL	8	+	200mg/kg
Batch GA+EOL	8	+	100mg/kg(GA) +200mg/kg (EOL)

Data processing: The data obtained were entered and processed using GraphPad Prism® software (GraphPad Prism® 9.0.0 (121), Inc, USA).

The results are expressed as mean ± SEM (Standard Error of the Mean).

All measured parameters were processed by a one-way analysis of variance (ANOVA).

All these statistical analyses were followed by a post-hoc test (Dunnett's) when the probability of the outcome was 0.05. After treatment, the results are expressed as bar charts.

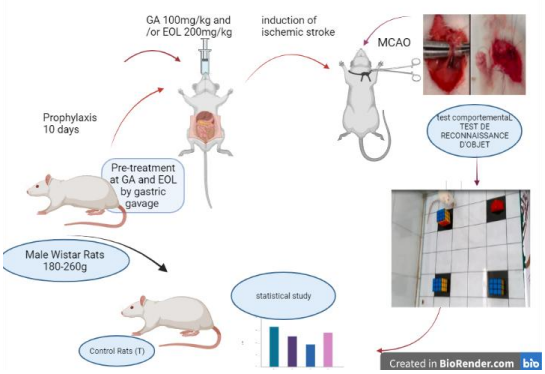

Fig. 1. Protocol experimental

3. RESULTS

3.1 Variations of the Object Recognition Test Parameters

3.1.1 First training session

Fig. 2 shows the locomotion and exploration performance of the first training session of the object recognition test.

Our results show that rats with cerebral ischaemia without pretreatment (Stroke) spend significantly more time in the peripheral zone and less time in the central zone compared to controls (C) (p=0.001) (Stroke: 295.3± 0.88 vs. C: 279.6± 2.29 and S: 4.75± 0.88 vs. C:20.38± 2.29) s, respectively.

These (stroke) batch rats also showed highly significant (p=0.01) locomotor hypoactivity. Compared to controls (C) reflected by the distance travelled (S:208.8 ± 58.41 vs. T: 605.0 ± 52.61) cm.

Rats pretreated with gallic acid show an attenuation of anxiety supported by a decrease in time spent in the periphery (294.5 ± 1.94) s, as well as an increase in the time spent in the center (5.5 ± 1.94) s; with better locomotor activity with a distance travelled of (476.3 ± 85.04) cm compared to the (Stroke) lot.

Rats pretreated with lavender essential oil spent less time in the peripheral zone and more time in the central zone.compared to the (stroke) group and they were more active with a more significant (p=0.05) distance travelled (EOL 504.3 ± 101.8 vs. stroke 208.8 ± 58.41) cm.

Rats in the (GA/EOL) group were less anxious; spent more time in the central than in the peripheral zone compared to those of the (Stroke) group and covered significantly more distance (p=0.05) (GA/EOL: 506.3 ± 89.22 vs. S: 208.8 ± 58.41) cm.

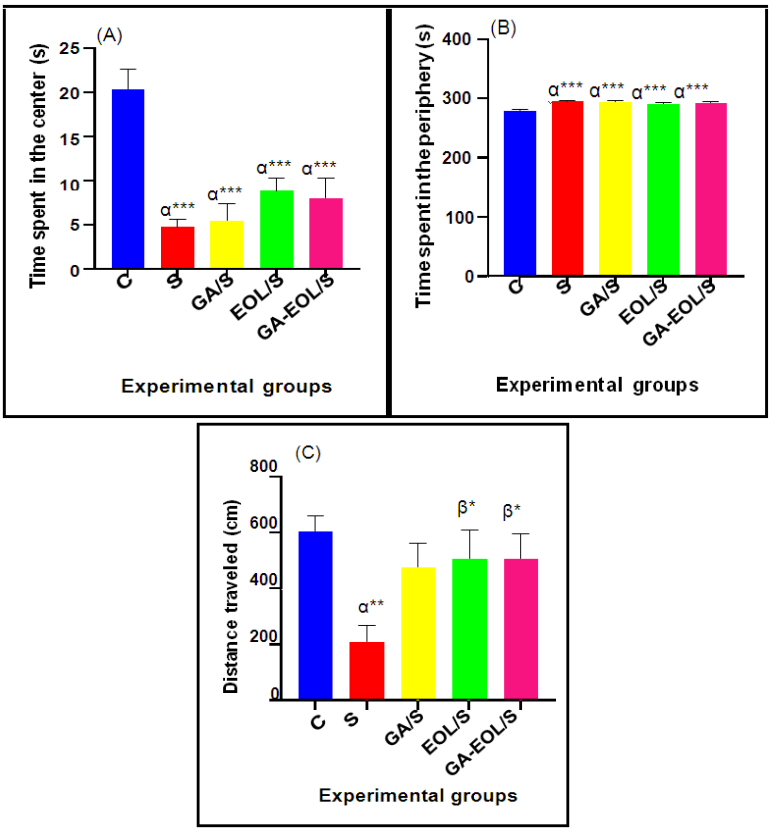

Fig. 2. Bar graph of the parameters of the first training session of the Object Recognition test of rats from the 05 batches (n=40). (A): Time spent in the centre (s),(B): Time spent in the periphery (s), (C): Distance travelled (cm). Expressed as Mean ± SEM. C: Control lot, S: Untreated lot, GA/S: stroke lot treated with Gallic Acid, EOL/S: Lavender Essential Oil treated batch, GA- EOL/S: stroke lot treated with Gallic Acid and Lavender Essential Oil

*α**p=0.01 and α***p=0.001 vs. T; β*p=0.05 vs. Stroke*

3.1.2 Second training session

Fig. 3 shows the locomotion and exploration performance of the second training session of the object recognition test.

The results in graph (A) reveal a difference between the means of the time spent moving around the different corners of the arena in the five batches with a reduction in movement time of all rats with a cerebral ischaemia compared to controls (C: 126.1±3.30) s; they also demonstrate motor skills in the pretreated rats (GA/S: 106.1±3.301; EOL/S: 100.5±3.0; GA-EOL/S: 110.8±5.10) compared to rats from the batch without pretreatment (S: 89.38±3.38). In graph (B), there was a difference in the mean time spent exploring the objects in the arena, with a significant reduction in this time (p=0.05) for rats in the rats (S: 21.38±1.28) s compared to control rats (C: 32.38±4.44) s; as well as a duration of this object exploration was longer for the pre-treated batches (GA/S: 29.13±3.27; EOL/S: 26.50±1.48; GA-EOL/S: 30.75±1.90) compared to the stroke batch.

It should be noted that the means of the GA-EOL /S batches remain higher than those of the other pre-treated batches; they thus showed better locomotor and exploratory performance.

3.1.3 Session of the spatial memory exploration test

Fig. 04 illustrates the spatial memory exploration performance of ratsduring the object recognition test session.

The results in graph (A) reveal a very highly significant difference between the means of time spent in the arena with familiar objects in the five batches (p=0.001); this mean is higher for the (S:stroke) batch compared to the control (85.25±4.82 vs. 50.75±1.81) s; and a contrario it decreases very significantly (p=0.001) for the rats.

Pretreated (GA/S: 20.25±1.84; EOL/S: 27.50±1.86; GA-EOL/S: 26.88±2.01) s compared to those without pretreatment. For graph (B), there was a very highly significant (p=0.001) reduction in the time spent with the displaced object for batch (S) rats compared to control rats (S: 3.37±0.98 vs. C: 11.00±1.30) s; in contrast, pretreated rats spend (GA/S: 10.38±1.56; EOL/S: 11.13±1.15; GA-EOL/S: 13.13±1.42) s compared to rats without pretreatment; with a highly significant difference (p=0.001) for batches pretreated with lavender essential oil alone or in combination.

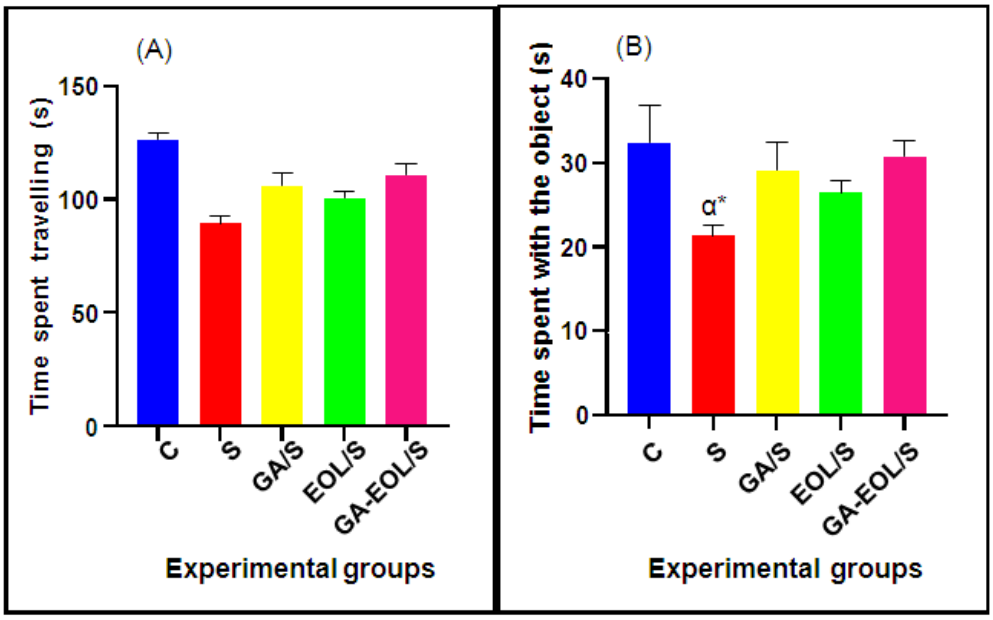

Fig. 3. Bar chart of the parameters of the second training session of the Object Recognition test of the rats of the Object Recognition test of rats from the 05 batches (n=40). (A): Time spent moving (s), (B): Time spent with objects (s). Expressed as Mean ± SEM. C: Control lot, S: Untreated lot, GA/S: stroke lot treated with Gallic Acid, EOL/S: Lavender Essential Oil treated batch, GA-EOL/S: stroke lot treated with Gallic Acid and Lavender Essential Oil

α p=0.05 vs. C*

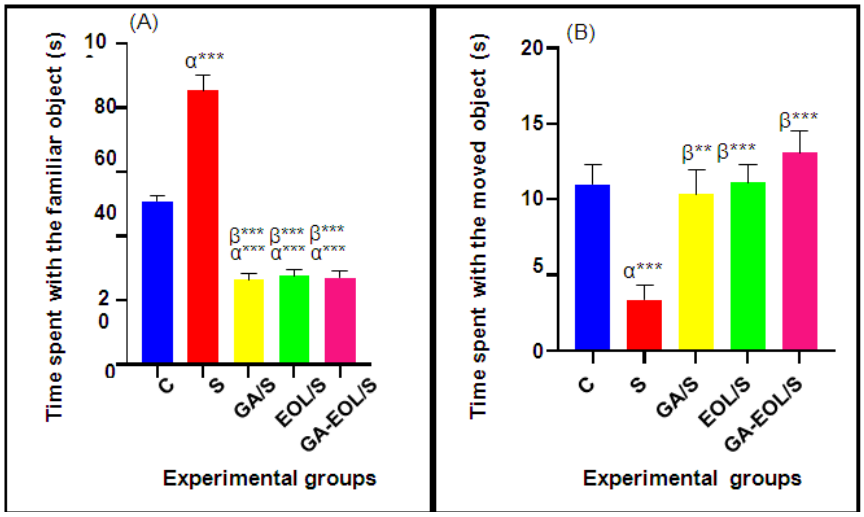

Fig. 4. Bar graph of the parameters of the spatial memory assessment session in the object recognition test (A): Time spent with the familiar object (s), (B): Time spent with the moved object (s). C: Control lot, S: Untreated lot, GA/S: stroke lot treated with Gallic Acid, EOL/S: Lavender Essential Oil treated batch, GA-EOL/S: stroke lot treated with Gallic Acid and Lavender Essential Oil

*α***p=0.001 vs T; β**p=0.01 and β***p=0.001 vs. T.*

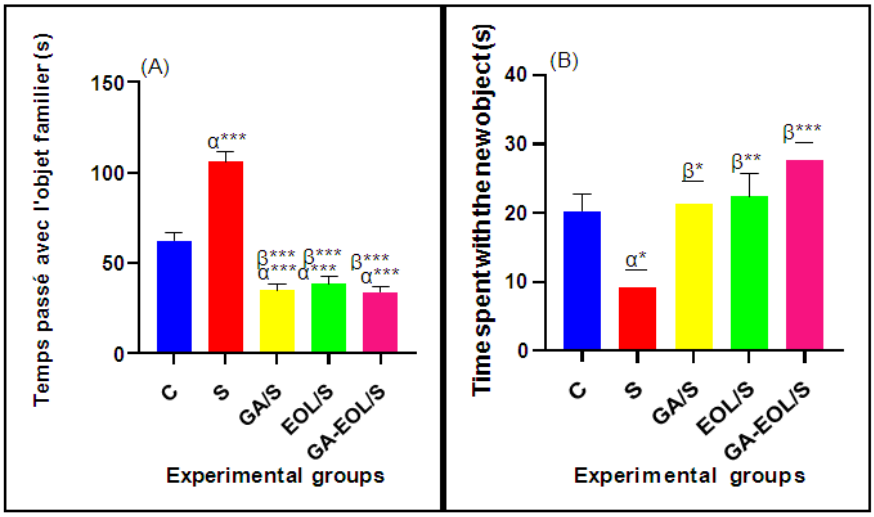

Fig. 5. Bar chart of the parameters of the working memory evaluation session in the(A): Time spent with the familiar object (s), (B): Time spent with the moved object (s).C: Control lot, S: Untreated lot, GA/S: stroke lot treated with Gallic Acid, EOL/S: Lavender Essential Oil treated batch, GA-EOL/S: stroke lot treated with Gallic Acid and Lavender Essential Oil

*α**
*p=0.05 and α***p=0.001 vs. C ; β**
*p=0.05, β**p=0.01 and β***p=0.001 vs. Stroke*

3.1.4 Working memory test session

Fig. 5 illustrates the performance of the rats during the working memory exploration during the object recognition test session.

Our results show a highly significant difference between the means of the time spent in the arena with the familiar object for all batches with cerebral ischaemia compared to the control batch (p=0.001), thus reflecting a longer duration for the (Stroke) batch (S: 106.10±5.48 vs. C: 62.38±4.32) s; as opposed to the other (GA/S: 34.75±3.47; EOL/S: 38.68±3.63; GA-EOL: 33.75±2.87) s, where the rats are less interested in the latter, reveals a significant difference (p=0.05) between the mean time spent with the novel

object for rats without pretreatment compared to controls (S: 9.25±2.13 vs. C: 20.25±2.51) s and found to be significantly decreased; in contrast the pretreated rats spend significantly more time with the new object (GA/S : 21.38±2.66 ; EOL/S: 22.38±3.38; GA-EOL/S: 27.75±2.53) s compared to the (stroke) rats; while that this duration is all the more important as the pre-treatment contains lavender essential oiL.

4. DISCUSSION

The analysis of the classical variables obtained in the first training session in the object recognition arena; consisting of letting the rat freely explore this arena in the absence of objects; reports significant differences between the means of the time spent in the peripheral zone of stroke rats without pretreatment compared to control rats (Stroke: 295.3±0.88 vs. C: 279.6±2.29).

These rats from the (stroke) batch also showed highly significant (p=0.01) locomotorhypoactivity compared to the controls (C) reflected by a lower distance travelled (S: 208.8±58.41 vs. C: 605.0±52.61) cm.

Stroke rats pre-treated with gallic acid and/or lavender essential oil anxiety supported by a decrease in time spent in the periphery, as well as an increase in periphery, as well as an increase in time spent in the center; with improved locomotor activity expressed by a significant distance travelled.
This is in agreement with what has been reported in the literature; namely that cerebral ischaemiaimpairs cognitive functions involved in learning and memory[37], and that certain substances such as gallic acid have anxiolytic effects [38], and antidepressant [39] effects in the animal models, and lavender essential oil has been shown to have similar effects effects[40,41].

In our series, the results of the second training session, in which the rat was allowed to explore the arena in the presence of four similar objects, showed a reduction in the time taken to all rats with cerebral ischaemia compared to controls (C: 126.1±3.30) s; they also show motor skills in the pretreated rats (GA: 106.1±3.30; EOL: 100.5±3.0; GA/EOL: 110.8±5.10) compared to rats in the non-pretreated (S: 89.38±3.38).

It should be noted that the means of the GA/EOL lots remain higher than those of the other pretreated batches, and thus they showed better locomotor and exploratory performance.

Once the training phase is over, the ORT takes on its full meaning by tackling the exploration of memory, all the more so as the exploration of memory, first of all spatial, by moving objects; if one of the objects is replaced by a completely different one, the replaced by a totally different one, a non-stressed rat will notice the new object and will sniff it significantly more than the other object, which it will have recognised; in contrast, a stressed rat will not do this [42].

According to the parameters of the spatial memory exploration session, our results reveal a highly significant difference between the means of time spent in the reveal a very highly significant difference between the means of time spent in the arena with familiar objects across the five batches (p=0.001); this mean is higher for the (stroke) batch compared to the control (85.25±4.82 vs. 50.75±1.81) s; and a contrarioit decreases very significantly (p=0.001) for pretreated rats (GA: 20.25±1.84; EOL: 27.50±1.86; GA/EOL: 26.88±2.01) s compared to those without pretreatment (stroke).

Our results also show a very highly significant (p=0.001) reduction in time spent with the displaced object for the batch rats (Stroke) compared to the control rats (Stroke: 3.37±0.98 vs. C: 11.00±1.30) s; in contrast, pretreated rats spend significantly more time sniffing the moved object (GA: 10.38±1.56; EOL: 11.13±1.15; GA/EOL: 13.13±1.42) s, compared to rats without pretreatment; with even more highly significant (p=0.001) for batches pretreated with lavender essential oil alone or in combination.

These results are supported by numerous studies that highlight the role of GA in the improvement of long-term potentiation indices of the hippocampus and consequently memory functions, as well as in the improvement of inflammatory parameters and, therefore support its neuroprotective effect [43]; notably in prevention of memory deficits [44]. Chronic administration of GA at a dose of 100mg/kg for 10 days, significantly restores spatial memory.

As for lavender essential oil, studies highlight its promising effects on improving learning and updating impaired memory [45]; one study suggests that the essential oils of both lavender species, rich in linalool and linalyl acetate, act as an anxiolytic and antidepressant and improve spatial memory deficits.

Our test concludes with a session exploring working memory, which is the introduction of a new object; the results of the NRT show a highly significant difference between the means of time spent in the arena with the familiar object for the all batches with cerebral ischaemia compared to the control batch (p=0.001); thus reflecting a longer duration for the

(stroke) batch; as opposed to the other pre-treated batches, where the rats were less interested in the familiar object [46].

There was also a significant difference (p=0.05) between the mean time spent the new object for the rats without pretreatment compared to the controls, which was found to be the pretreated rats spend significantly more time with the new object than with the controls.

With the new object compared to rats in the (stroke) group, although this time is greater the more the pre-treatment contains lavender essential oil, and that it is significantly Significantly greater when combined therapy is used (p=0.001).

This is in agreement with the aforementioned data from the literature, which highlights the beneficial effect of GA in the learning and memory functions, as well as the promising effect of EOL on the latter.

5. CONCLUSION

Our study on Wistar rats with stroke via middle cerebral artery occlusion pretreated with lavender essential oil occlusion of the middle cerebral artery pretreated with lavender officinalis essential oil (*Lavandula officinalis*) and/or gallic acid at doses of 200mg/kg, 100mg/kg, respectively; highlights their effectiveness on post-stroke cognitive recovery. We were able to determine by measuring the anxiety, locomotor and cognitive aspects the protective effect of activity of pre-treated rats in the object recognition test compared to untreated ones.

Our results highlight the promising effect of gallic acid and lavender essential oil on the neurobehavioural and locomotor sequelae; these pretreatments anxiety, increased locomotor activity, thus shedding light on the ability to the spatial and working memory abilities of pretreated stroke rats compared to stroke rats without pretreatment.

ETHICAL APPROVAL

All experiments were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23), revised 1996.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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