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Original Article

Preventive Effects of Ginger Extract and *Nigella sativa* Oil on Anxiety and Depression Behavior in Wistar Rats Exposed to Mercuric Chloride

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ABSTRACT

Background: Mercuric chloride ($HgCl_2$) is toxic to humans and animals, and usually causes systemic and nerve damage. **Aim:** The aim of this study is to evaluate the neuro-protective effects of two medicinal plants rich in antioxidants against mercuric chloride poisoning in Wistar rats. **Materials and Methods:** This is an experimental study conducted on twenty-five adult rats randomly divided into five groups of five rats each, the untreated control group and the four groups are treated daily with Ginger extract (500 mg/kg/day) and *Nigella sativa* oil (2ml/kg/day) for four weeks. The administration of mercuric chloride (4mg/kg/day) will be from the second week of experimentation to three weeks. **Results:** The results obtained showed by behavioral tests that the administration of inorganic mercury ($HgCl_2$) significantly increases the state of anxiety and depression of rats compared to control rats, while the groups pre-treated with antioxidants can reduce the damage of these behavioral disorders. **Conclusion:** Ginger extract and *Nigella sativa* oil have a very important role in neurobehavioral alterations induced by mercury toxicity.

Key words: Antioxidants, Mercuric Chloride, Anxiety, Depression, Neuroprotection, Wistar Rats.

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INTRODUCTION

Mercury is one of toxic heavy metals. Due to industrial pollution and its deposition in ecosystems, mercury is a widespread pollutant,[1] Elemental form of mercury is a silver metal that exists as a viscous liquid at room temperature. Most people are familiar with the silver liquid in mercury thermometers. Mercury is a naturally occurring metal used in man-made products and processes, and is also emitted into the air from industrial sources. Human exposure to mercury comes from various sources, such as breathing mercury-containing air, using mercury-containing commercial products, and eating fish and seafood containing methylmercury[2] Its exposure can be toxic to the kidneys, stomach and intestines and can also be embryotoxic, increasing rates of miscarriages and stillbirths, and can further increase blood pressure and is neurotoxic sometimes presenting with neuropsychiatric symptoms[3,4] The toxicity of mercury can be prevented by using antioxidant defense mechanisms, including reducing or eliminating reactive oxygen species, free radicals, and heavy metals[5] In herbal medicine, plant organs including: leaves, stems, roots, flowers, fruits and seeds are used as alternative and complementary therapies. Some herbs with neuroprotective properties, including resveratrol, curcumin, ginsenosides, polyphenols, triptolide, etc[6] One of this plantis the *Zingiber officinale*, has been used as a spice for over 2000 years. The high antioxidant activity of ginger is due to the polyphenolic 6-gingerol compounds and its derivatives contained in these roots.[7] Another commonly used plant, *Nigella sativa* is a medicinal herb used for antioxidant activity. In rats, *Nigella sativa* seeds also play an important role in the lack of spatial cognition caused by chronic cerebral hypoperfusion. In addition, *Nigella sativa's* enhanced scopolamine promotes learning and memory deficits, and also reduces the AChE effect and oxidative stress in the mouse brain. The neuroprotective effects of Nigella and thymoquinone (TQ) on various neurological diseases such as Alzheimer's disease, epilepsy, and neurotoxicity have been studied in human and animal models.[8]

The aim of this study was designed to investigate the preventive effect of *Nigella sativa* oil and ginger extract in the improvement of anxious and depressive behavior of Wistar rats exposed to mercuric chloride ($HgCl_2$).

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MATERIALS AND METHODS

Drugs

Mercury II chloride ($HgCl_2$), Purity≥99.5% and Ginger extract used in this research were obtained from (Sigma-Aldrich, St Louis, MO, USA), The *Nigella sativa* oil product by (CAP Pharm, Egypt).

Animals and administration procedure

Healthy male Wistar albino rats weighing 280±15g, obtained from the Pasteur Institute of Algiers, housed in standard polypropylene cages and maintained at an ambient temperature of 23 ± 2°C, a hygrometry of 45-55% and a natural photoperiod. The animals were divided at random into five groups of five animals each, the first group (T), control group, receives no treatment, the second group (M) receives distilled water (1ml/kg/day) for one week (D01-D07) and mercuric chloride (4mg/kg/day) for three weeks (D08-D28), the third group (G+M) receives ginger extract (500mg/kg/day) for four weeks (D1-D28) and mercuric chloride (4mg/kg/day) for three weeks (D08-D28) the fourth group (N+M) received *Nigella sativa* oil (2ml/kg/day) for four weeks (D1-D28) and mercuric chloride (4mg/kg/day) for three weeks (D08-D28) the fifth group (G+N+M) received a ginger extract (500mg/kg/day) and *Nigella sativa* oil (2ml/kg/day) during the whole experiment (D1-D28) and mercuric chloride (4mg/kg/day) for three weeks (D08-D28).All these treatments were administered by gastric gavage.

Behavioral assessment

Open field test (OFT)

The open field test (OFT) is designed to measure locomotion, exploration and anxiety in rats. The device consists of a base surrounded by Plexiglas parapets whose measures are respectively 70 × 70 × 40 cm. The floor is in the form of squares of 10 cm×10 cm in diameter, it has been divided into two areas: central area and peripheral area to which each is 35 cm (Hall, 1934).

Elevated plus-maze test (EPM)

The elevated cross maze is used to measure the degree of anxiety in rodents. The labyrinth raised 50 cm from the ground is composed of four wooden Arms, two open arms (50×10 cm) perpendicularly opposed to two closed arms (50×10 cm) with 40 cm of plexiglass at the high edge. The intersection of the four arms (central platform) measures 10 cm.[9]

Forced swimming test (FST)

The forced swimming test, or Porsolt test, is frequently used to examine depressive behavior[10] The device for this test is aglass aquarium (height: 54 cm; length: 34cm; width: 60 cm) filled with water up to a height of 40 cm from which the rat does not use its lower limbs to stand on the surface or escape, thus subjecting it to forced swimming. The water is regularly maintained at (24±1°C) and is renewed after each experimental session.[11]

Statistical Analysis

Statistical analysis of the data was performed with the software (GraphPad Prism 9.0.0). Data are presented as the mean ± SEM (Standard Error of the Mean). All measured parameters were processed by a one-way analysis of variance (One-way ANOVA) and all these statistical analyses were followed by a *post-hoc* test (Dunnett's test) when a significant difference was determined.

RESULTS

Anxiety tests

Open field test (OFT)

The open field test is performed for 5 min, on the 14th day of experimentation, each animal is placed in the center of the device. Its displacement allows measuring the number of squares crossed as well as the number of rearing.

Statistical analysis of the results shows in Figure 1A a very highly significant decrease in the number of squares crossed by the groups (M; 34.00±1.14), (G+M; 49.20±1.77), (N+M; 42.00±1.51) and (G+N+M; 39.80±3.65) compared to the control group (T; 68.60±2.50). Therefore, a very highly significant increase in the (G+M; 49.20±1.77) group compared with the (M; 34.00±1.14) group.

While in Figure 1B, the results reveal a highly significant decrease in the number of rearingin the group treated with mercuric chloride (M; 9.80±0.58) and a significant decrease of the group (G+M; 12. 00±1.22) compared to the control group (T; 16.20±1.15) with significant and highly significant increases in the (N+M; 14.20±1.15) and (G+N+M; 15.40±0.92) groups respectively compared to the (M; 9.80±0.58) group.

Elevated plus-maze test (EPM)

On the 21st day of experimentation, each rat is placed for 5 min in the central area facing an open arm.

The results obtained in Figure 2A show very highly significant decreases in the (M; 22.40±0.92) and (G+N+M; 32.40±2.65) groups and highly significant and significant decreases in the (G+M; 39.20±3.95), (N+M; 42.60±1.74) groups in the time spent in the open arms compared to the control group (T; 54. 80±4.54), as well as the (G+M; 39.20±3.95), (N+M; 42.60±1.74) groups represent highly significant and very highly significant increases in time spent in the open arms compared with the (M; 22.40±0.92) group, respectively.

In Figure 2B, rats in the (G+M; 213.2±3.73), (N+G; 237.4±2.67) groups show very highly significant decreases in the time spent in the closed arms compared with the rats treated with mercuric chloride (M; 267.4±3.54). In contrast, we found a very highly significant and highly significant increase in the (M; 267.4±3.54) and (G+N+M; 258.6±2.89) group and a very highly significant decrease in the time spent in the closed arms (G+M; 213.2±3.73) compared with control rats (T; 240.2±4.82).

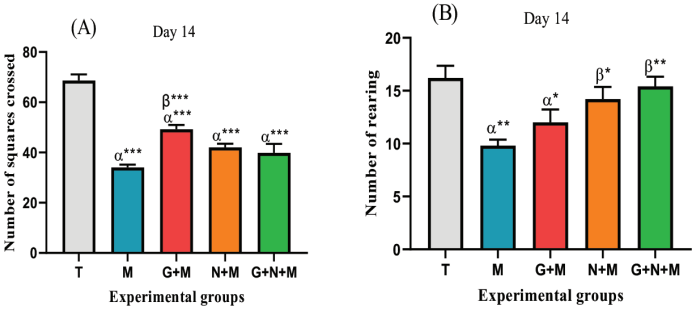

Figure 1: Anxiety-related behavior of rats in the open field test (OFT) on day 14 of the experiment (*n*=05).
(A): Number of squares crossed; (B): Number of rearing
Significance was defined as a *p*-value less than 0.05 (*p<0.05; **p< 0.01; ***p< 0.001)
α: Comparison with control group (T)
β: Comparison with the group treated with mercuric chloride ($HgCl_2$) (M)

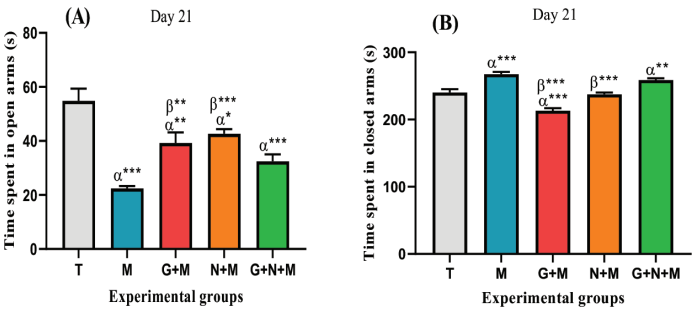

Figure 2: Anxiety-related behavior of rats in the elevated plus-maze test (EPM) on day 21 of experimentation (*n*=05).
-(A): Time spent in open arms (s); -(B): Time spent in closed arms (s)
Significancewas defined as a *p*-value less than 0.05 (**p*<0.05; ***p*< 0.01; ****p*< 0.001)
α:Comparison with control group (T).
β: Comparison with the group treated with mercuric chloride ($HgCl_2$) (M).

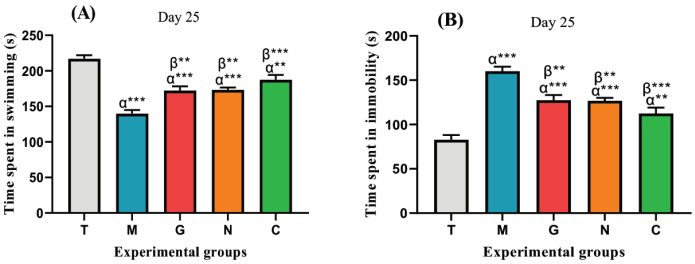

Figure 3: Depression-related behavior of rats in the forced swimming test (FST) on day 25 of the experiment (*n*=05).
(A): Time spent in swimming (s); (B): Time spent in immobility (s)
Significance was defined as a *p*-value less than 0.05 (**p*<0.05; ***p*< 0.01; ****p*< 0.001)
α: Comparison with control group (T).
β: Comparison with the group treated with mercuric chloride ($HgCl_2$) (M).

Depression test

Forced swimming test (FST)

On the 24th day of experimentation the rats are placed individually in the aquarium of the forced swimming test for 15 min, this phase serves to induce a mental depression (depressant session), 24 hr later (25th day) a second session lasting 5 min was performed, during which, the times of immobility and swimming.

In this test, the time of swimming decreased very highly significantly in the rats of (M; 139.6±5.33), (G+M; 172.2±6.11) and (N+M; 173.2±3.33) groups and highly significantly of (G+N+M; 187.4±6.86) group compared to the control group (T; 217.0±5.07). Therefore, rats in the (G+M; 172.2±6.11), (N+M; 173.2±3.33) (G+N+M; 187.4±6.86) groups had a longer swimming time than that of rats in the (M; 139.6±5.33) group (Figure 3A).

In addition, the immobility time of rats was very highly significantly increased in the (M; 160.0±5.16), (G+M; 127.4±5.80), and (N+M; 126.8±3.33) groups and highly significantly increased in the (G+N+M; 112.4±6.70) group compared to the control group (T; 82.80±5.21). In addition, immobility time was significantly shorter in the experimental groups compared with the (M; 160.0±5.16) group (Figure 3B).

DISCUSSION

In this study, a decrease in the number of squares crossed and the number of rearing was observed in the mercuric chloride groups compared to the control group in the open field test, as we observed that the rats treated with mercuric chloride spent more time in the closed arms and less time in the open arms compared to the control rats in the elevated plus-maze test, which means that the subchronic treatment with mercuric chloride (4mg/kg) triggers a state of anxiety in these animals. This is consistent with the results found by[12] where the results obtained in open field test (OFT) also indicate that mercury can cause anxiety because we measured an increase in the number of crossing squares and time at the periphery compared to activity and time at the center. In fact, the longer the time spent on the periphery of the open field, the higher the anxiety level. This indicates that the mice treated with mercuric chloride are more anxious than control animals in open field test. In this study, in addition to open field test (OFT), we also tested the anxiety effect of mercuric chloride on mice through other behavioral tests, such as the elevated plus-maze test (EPM), This is undoubtedly one of the most widely, used animal models in contemporary anxiety preclinical research[13] In rats pretreated with ginger extract (500 mg/kg) and *Nigella sativa* oil (2 ml/kg), show significant increases in OFT variables were found to correspond to those in control rats. In the EPM test, rats a higher time spent on the open arms and a lower time in closed arms compared to rats treated with mercuric chloride. The effect of herbs in reducing depression and anxiety may be related to the effects of herbal ingredients[14] Ginger extract exerts anti-anxiety effects in anxious behavior models, which may be caused by increased serotonin synthesis, and affects tryptophan metabolism and distribution in a manner similar to antidepressant drugs[15] Ginger and its active constituents may influence central nervous system5-HT metabolism and function by various actions, e.g., by enhancing its synthesis, decreasing its degradation or release and/or blocking its receptors[16] We can conclude that ginger extract can reduce anxiety.[17] There might have some decrease of anxiety due to the effect of *Nigella sativa* on several neurotransmitters-like 5-hydroxytryptamine (5-HT) and gamma amino butyrate (GABA). Accordingto Perveen*etal.,* (2009) *Nigella sativa* increases the level of 5-HT and thus decrease anxiety. Thymoquinone in *Nigella sativa* might also decrease nitric oxide and reverse decreased brain GABA content and give anxiolytic effect[18] Several studies indicate that anxiety and depressive disorders are not heterogeneous disorders, but rather share many common symptoms and pathogenic mechanisms[19] Also, a number of studies have evaluated the effects of inorganic mercury in the central nervous system and reported the presence of behavioral dysfunctions, in particular the anxiety and depression[20,21] In the current study, the forced swimming test (FST) indicates depressive behavior in rats treated with mercuric chloride. Pre-treatment with ginger extract and *Nigella sativa* alone and in combination enhanced swimming time, thereby reducing the immobility time in rats in FST, indicating antidepressant-like activity of this antioxidants. In depression studies, monoamine neurotransmitters such as serotonin (5- HT), noradrenaline (NA) and dopamine (DA) play an important role in mediating depressive behaviors.[22] It has been well proven that swim/immobility influences serotonergic signaling in brain, resulting into increase synaptic transmission which ultimately leads to change in response from immobility to swimming and climbing in FST.[23] Ginger is used for the treatment of various conditions, including atherosclerosis, migraine headaches, rheumatoid arthritis, high cholesterol, ulcers and depression. 6-gingerol, isolated from ginger rhizome oil affected neurotransmission in the snail and possessed neuroprotective effects in rodents.[24,25] However, true mechanism of antidepressant effect of the Ginger is still unknown but behavioral parameters in forced swimming test confirmed potential

antidepressant effect as serotonergic agents.[26,27] The antidepressant effect of thymoquinone (active constituent of *Nigella sativa*) by increasing 5-HT concentrations which in turns modulate/down regulate the swim or hanging stress induced serotonergic dysfunction. The synaptic enhancement of monoamine level, predominantly 5-HT, is the key pharmacological mechanism of the anti-depressant effect. In view of these results, it's suggested that ginger extract and *Nigella sativa* oil alone and in combination have powerful anxiolytic and antidepressant properties.[28]

CONCLUSION

The present study demonstrated the adverse effects of mercuric chloride ($HgCl_2$) which induced anxiety and depression reflected in the decrease in the number of climbs and the number of squares crossed by rats in the open field test and an increase in time spent in the closed arms, On the other hand, a decrease in the time spent in the open arms in the elevated plus-maze test, and a higher significant difference in the period of swimming and immobility in rats treated with mercuric chloride compared to control rats in the forced swimming test. The pretreatment with ginger extract and *Nigella sativa* oil alone and in combination allowed to decrease the state of anxiety and depression of the rats as it is shown by the returns of the parameters of the behavioral tests to their normal levels close to the control rats, and exerts preventive effects against behavioral disorders induced by mercuric chloride and open an interesting research pathway to study the mechanisms of action of these antioxidants on neurobehavioral effects of toxic heavy metal.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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