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Anticonvulsant and GABAnergic Activity of *Nigella Sativa* Oil in Mice

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Abstract

Several experimental studies have described neuroprotective and antioxidant activity of plant extracts and its oil as *Nigella sativa*. The existing study was conducted to investigate the anticonvulsant activity of *Nigella sativa* oil. Fifty five male albino mice were used through three experiments; pentylenetetrazole induced convulsion, maximal electric shock induced convulsion and neurotoxicity tests. Mice were treated with *Nigella sativa* oil 10 ml/kg; using sodium valproate (100mg/kg) and phenytoin sodium (25mg/kg) orally as standard drugs. In pentylenetetrazole induced convulsion, onset of seizure and generalized seizures were measured, beside the gamma aminobutyric acid and antioxidant enzymes levels assessments. In maximal electric shock, mice were observed for hind limb tonic convulsion. *Nigella sativa* oil significantly delayed seizure onset after pentylenetetrazole induced convulsion but had no effect on electric shock induced convulsion. *Nigella sativa* showed a good antioxidant activity, increased the gamma amino butyric acid level in brain, and had neuroprotective effects.

Key words: *Nigella sativa*, Pentylenetetrazole, Maximal Electric Shock, Antioxidant, GABA.

Introduction

Epilepsy is the third most prevalent neurological disorder after stroke and Alzheimer's disease [1]**,** which involves the occurrence of at least one or more epileptic seizures. It affects about 40 million people worldwide [2].Gamma aminobutyric acid (GABA) is a neurotransmitter which able to maintain the inhibitory tone and prevent neuronal excitation. When the balance between inhibitory and excitatory neurotransmission is disturbed, seizures may arise [3].It has been well renowned that functional impairments which occur in central nervous system during epilepsy and seizure cause oxidative damages and lipid peroxidation to brain tissues [4]. Baracskay *et al.* proposed that generalized seizure produces dark neurons which may be prevalent throughout the brain especially in the hippocampus and the pontine reticular formation [5]. Dark neurons are group of neurons that were exposed to shrinkage and destruction such as microtubules or microfilaments cytoskeleton with small dense nuclei inside them [6]

The antiepileptic drugs (AEDs) associated with the need for long-term therapy and undesirable side effects which often render treatment difficult; in addition to at least 30 % of patients are drug resistant [7]; so that searching for new anticonvulsants is vital. Medicinal and aromatic plants have many constituents which have anticonvulsant action and neuroprotective effects without side effects of chemical drugs [8].

Nigella sativa belongs to Ranunculaceae family, is used for edible and medicinal purposes in many countries [9].Many researches demonstrated the active constituents in N. sativa that include thymoquinone (TQ) (30–48%), dithymoquinone, thymohydroquinone and other aromatic components as p-cymene (7–15%), carvacrol (6–12%) and other compounds as 4 terpineol (2–7%), tanethol (1–4%), sesquiterpene longifolene (1–8%), and a-pinene [10]. The fixed oils constitute about

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(32–40%) unsaturated fatty acids. The volatile oil (0.4–0.45%) includes saturated fatty acids. There are as well many nutritional compositions such as vitamins, minerals, carbohydrates, fats, and proteins that include nine essential amino acids [11].Recent studies revealed many pharmacological properties of N. sativa such as antioxidant effect [12], antibacterial effect [13], anti-inflammatory effect [14],cardiovascular protective effect [15], nephro-protective effect [16], hepato-protective effect [17], pneumo-protective effect [18], antidiabetic effect [19]and anticancer effect [20]. Neuro-pharmacological aspects of N. sativa and thymoquinone take big attention in many recent studies which include antianxiety and anti-depressant properties-like effects [21], effects on memory and learning [22], effects on neuro-degenerative diseases like Alzheimer [23], Parkinson disease [24] and Schizophrenia [25]

Therefore, the current experiment was conducted to investigate the anticonvulsant effect of *Nigella sativa* oil against experimentally induced convulsions in mice

Materials and methods

-*Nigella sativa* oil (NSO) was purchased from Harraz for natural and nutritional products, Cairo, Egypt.

Drugs

- Pentylenetetrazole (PTZ) was purchased from Sigma-Aldrich co.

- Sodium valproate (Depakine 200mg®) was purchased from Sanofi co. (ARE).

- Phenytoin sodium (Phenytin 100mg®) was purchased from Nile co. (ARE).

Animal groups

Fifty five male albino mice of 20-30gm average body weight were taken from Faculty of Veterinary Medicine laboratory house, Zagazig University. All animals were under observation and acclimatization period of 2weeks to laboratory experiment before starting the experiment time and kept in metal cages in good hygienic conditions. The experimental protocol was carried out according to the guidelines approved with the Ethical Committee of Zagazig University (No. ZU-IACUC/2/S/18/2018).

*Anticonvulsant activity of N. sativa against pentylenetetrazole (*PTZ*) induced convulsion in mice*

There were 20 mice divided into 4 groups; 5 mice per each.

Group (1): negative control group received only distilled water 0.2ml p.o for 7days. **Group (2):** positive control group mice received distilled water +PTZ.

Group (3): mice received *Nigella sativa* oil 10 ml /kg orally for 7 days +PTZ [26].

Group (4): mice received sodium valproate 100 mg/kg orally for 7 days +PTZ [27].

At the 7th day, the mice were injected i/p by PTZ (85 mg/kg bwt) [28], the mice were observed for 1 hour after PTZ injection and onset of seizure (sec) and generalized seizure (sec) were recorded.

Biochemical measurement

After 1 hour of PTZ injection the mice were sacrificed by decapitation and the brains were taken and twenty brain specimens sliced up on an ice-cold surface and finally tissues were submitted to GABA measurement by using double antibody sandwich ELISA test according to published reports of Ben-Ari *et al. [*29]. Glutathione peroxidase(GPx) was assayed indirectly according to method of Paglia and Valentine.[30].Superoxide dismutase(SOD) was measured as published reports of Nishikimi *et al*. [31], which is based on the ability of the enzyme to hinder the reducing power of phenazine methosulphate to nitroblue tetrazolium dye. Malondialdehyde as lipid peroxidation marker was estimated using method of Ohkawa *et al. [*32],which depend on the reaction between the tissue malondialdehyde (MDA) and thiobarbituric acid (TBA) in an acidic medium forming thiobarbituric acid reactive product, the absorbance at 534 nm was measured.

Histopathological examination

Twenty brain specimens were preserved in 4% formalin for 72 h and were then administered for histopathological studies [22]**.**

Anticonvulsant activity of N. sativa oil against maximal electric shock in mice

There were 15 mice divided into 3groups; 5 mice per each.

Group (1): control group received distilled water 0.2ml p.o for 7days.

Group (2): mice received *N. sativa* oil 10 ml/kg orally for 7 days [26].

Group (3): mice received phenytoin sodium (25 mg /kg) orally for 7 days [33].

At the 7th day, maximal electric shock was applied (150 mA, 50-60Hz, 0.2S duration) through mouth electrode to induce hind limb tonic extension.

Neurotoxicity test

There were 20 mice divided into 4groups; 5 per each.

Group (1): control group mice received distilled water 0.2ml p.o for 7days.

Group (2): mice received *N. sativa* oil 10 ml /kg orally for 7 days.

Group (3): mice received sodium valproate 100 mg/kg orally for 7 days.

Group (4): mice received phenytoin sodium 25 mg /kg orally for 7 days.

a. Rotarod test

For evaluation of motor coordination rotarod test was performed. Mice were walked on accelerating rotarod which revolves 5-10 rpm for a period of 120 s. The diameter of the rod was 3.2 cm, normally mice able to maintain balance for many minutes, but mice with deficits in motor coordination fall more quickly [34].

b. Mouse forced swim test

According to method of Porsolt *et al*. [35], forced swim test was performed. Mice were placed in a chamber (diameter: 45 cm: height: 20 cm) containing water with height of 15 cm at 25 ± 2 °C. The immobility time through 5min of test was measured. Immobility was allocated when no additional activity was observed further than that required to keep the mouse's head over the water**.**

Statistical analysis

Means and standard error (SE) values of variables were calculated. One-way ANOVA test were used for comparison between different groups for parametric data. Probability values (p) ≤ 0.05 were considered significant [36].

Results

Effect of Nigella sativa oil on PTZ induced convulsions

Convulsions induced by PTZ (85 mg/kg i/p) in mice started by tail twitching followed by generalized tonic clonic convulsions in four limbs. For PTZ group the onset of convulsions were 59.5±0.65 sec, administration of NSO (10 ml/kg) and sodium valproate (100 mg/kg) significantly (P <0.05) delayed the time of onset of convulsions (110.5±0.65 and 119.5±0.64 sec, respectively) compared with 59.5±0.65 sec for PTZ group.

In addition, the delaying generalized convulsion begin for NSO and sodium valproate (266±1.96 and302±0.91sec, respectively) compared with PTZ group for 174.75±2.02 sec (Table1).

Table 1: Effect of NSO delaying onset time of convulsion and generalized time of convulsion after PTZ injection using sodium valproate as standard (M±SE) (n=5).

groups	parameters	
	Onset of convulsion (sec)	Generalized convulsion (sec)
PTZ[1]	59.5±0.65 [c]	174.75±2.02[c]
NSO[2]+PTZ	110.5±0.65 [b]	266±1.96 [b]
SV[3]+PTZ	119.5±0.64 [a]	302±0.91 [a]

1PTZ: pentylenetetrazole (85 mg/kg i/p); 2NSO: *Nigella sativa* oil (10 ml/kg) orally; 3SV: sodium valproate (100 mg/kg) orally as standard anticonvulsant drug.

Means carrying different superscripts in the same column are significantly different at (p<.05).

Effect of Nigella sativa oil on gamma amino butyric acid (GABA):

Administration of PTZ (85 mg/kg i/p) showed significant ($p<0.05$) decrease in GABA level in brain (172.3±10.71µg/g) compared with control group 577.28±47.1µg/g.

Administration of *N. sativa* oil (10 ml/kg) orally and sodium valproate (100 mg/kg) orally for 1week prior to PTZ administration (85 mg/kg) revealed significant ($p<0.05$) increase in GABA level by rate of 293.83±2.7and 430.19±40.51 µg/g, respectively compared with 172.3±10.71µg/g for PTZ treated group (Table2).

Effect of Nigella sativa oil on brain malondialdehyde (MDA) as a biomarker for lipid peroxidation

Administration of PTZ (85 mg/kg i/p) showed significant ($p<0.05$) increase in brain MDA activity (39.35±0.22 nmol/g) compared with 6.51±0.36 nmol/g for control group. Administration of *N. sativa* oil (10 ml/kg) orally and sodium valproate (100 mg/kg) orally for 1week prior to PTZ administration (85 mg/kg i/p) revealed significant ($p<0.05$) decrease in MDA activity (10.8±0.2 and 26.84±0.39 nmol/g, respectively) compared with (39.35±0.22 nmol/g) PTZ group (Table2).

Effect of Nigella sativa oil on brain superoxide dismutase (SOD)

Administration of PTZ (85 mg/kg i/p) showed significant ($p<0.05$) decrease in SOD brain level (4.33±0.19 U/mg) compared with 23.49±0.66 U/mg for control group.

Administration of *N. sativa* oil (10 ml/kg) orally and sodium valproate (100 mg/kg) orally for 1week prior to PTZ administration (85 mg/kg i/p) revealed significant ($p<0.05$) increase in brain SOD level (14.21±0.42and5.05±0.04 U/mg, respectively) compared with 4.33±0.19 U/mg for PTZ group (Table2).

Effect of Nigella sativa oil on brain glutathione peroxidase (GPx) level

Administration of PTZ (85 mg/kg i/p) showed significant ($p<0.05$) decrease in GPx brain level (10.97±0.27 U/g) compared with 33.23±0.66 U/g for control group.

Administration of *N. sativa* oil (10 ml/kg) orally and sodium valproate (100 mg/kg) orally for 1week prior to PTZ administration (85mg/kg i/p) revealed significant ($p<0.05$) increase in GPX level in brain (26.8±0.76 and14.01±0.37 U/g, respectively) compared with 10.97±0.27 U/g for PTZ group (Table2).

Table (2): Effect of NSO on GABA, MDA, SOD and GPX levels after administration of PTZ using SV as standard, (M±SE) (n=5)

Groups	parameters			
	GABA[1] (µg/g)	MDA[2] (nmol/g)	SOD[3] (U/mg protein)	GPX[4] (U/g)
Control	577.28±47.1 [a]	6.51±0.36[d]	23.49±0.66 [a]	33.23±0.66 [a]
PTZ[5]	172.3±10.71 [d]	39.35±0.22[a]	4.33±0.19 [c]	10.97±0.27 [d]
NSO[6]+PTZ	293.83±2.7 [c]	10.8±0.2[c]	14.21±0.42 [b]	26.8±0.76 [b]
SV[7]+PTZ	430.19±40.51[b]	26.84±0.39[b]	5.05±0.04 [c]	14.01±0.37 [c]

1GABA: gamma aminobutyric acid; 2MDA: malondialdehyde; 3SOD: superoxide dismutase; 4GPX: glutathione peroxidase; 5 PTZ: pentylenetetrazole (85 mg/kg i/p);

6NSO: *Nigella sativa* oil (10 ml/kg) orally for 7days; 7 SV: sodium valproate (100 mg/kg) orally for 7days as standard anticonvulsant drug. Means carrying different superscripts in the same column are significantly different at ($p<.05$).

Histopathological findings

Brain sections from mice administered PTZ (85 mg/kg i/p) illustrated degenerated or dark neurons peculiar among the hippocampus cells and represented about 15-20 % (Figure 1A). While brain section from mice NSO (10 ml/kg) orally for 7 days and at the 7th day received PTZ (85 mg/kg i/p) showed hippocampal cells of the brain were mostly normal except a few neuronal cells which not exceed 0.5% of the cells, the affected cells showed mild degenerative changes (Figure 1B). The brain section from mice treated with SV (100 mg/kg) orally for 7 days and at the 7th day received PTZ (85 mg/kg i/p) showed almost normal hippocampus cells (Figure1C).

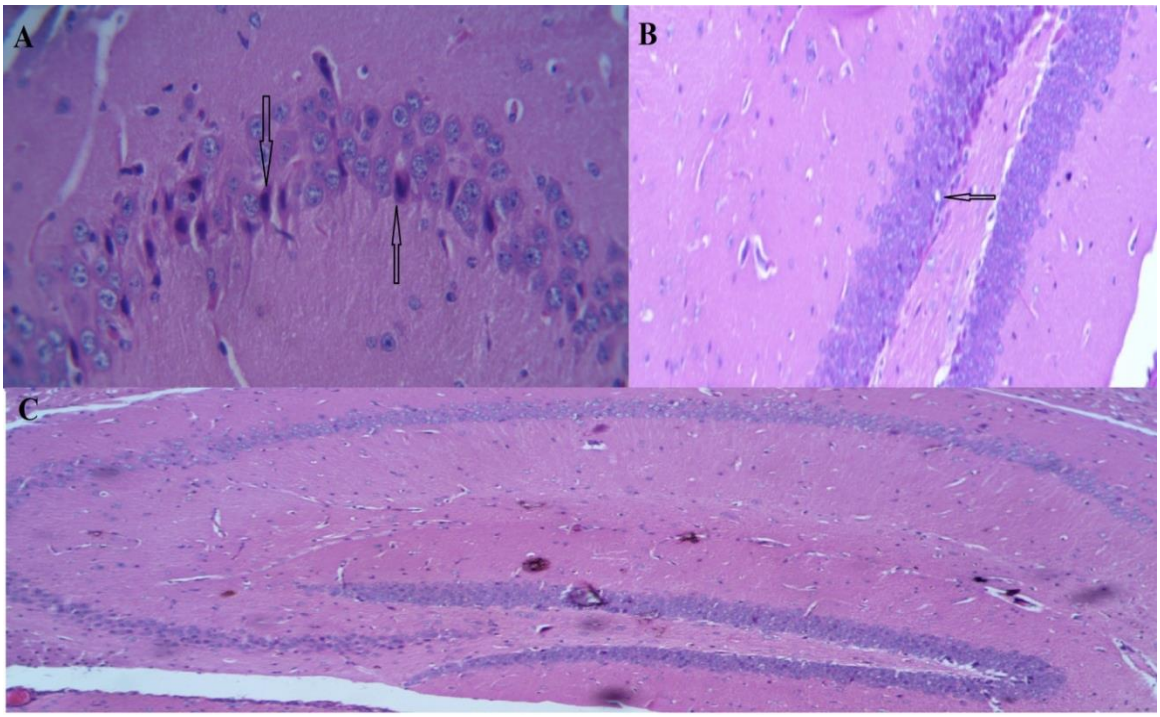

Figure (1): H&E stained mice brain (hippocampal slices) (A) pentylenetetrazole group showing dark neurons among the hippocampus cells represented about 15-20% X400. (B) *Nigella sativa* group showing normal hippocampal cells except a few neuronal cells (0.5%) showing mild degenerative changes (arrow) X 400. (C) Sodium valproate group showing normal hippocampus cells X 200.

Anticonvulsant activity of N. sativa oil against maximal electric induced convulsions

Administration of *N. sativa* oil (10 ml/kg) orally and phenytoin sodium (25 mg/kg) orally for 1week then application of maximal electric shock revealed that the current electric power provoked tonic extension of the hind limbs in control mice completely (0% protection). *N. sativa* oil has no significant protection from hind limb extension caused by maximal electric shock which was 20%only protection in comparison with phenytoin sodium protection which was 80% of mice.

Neurotoxicity tests

A. Rotarod test: Administration of *N. sativa* oil (10 ml/kg) orally and sodium valproate (100 mg/kg) orally for 1week caused no significant ($p<0.05$) effect on the latency to fall off the rotarod compared to the control respectively 164.5±0.65 and 166.25±0.85 sec compared with control group 175±2.04sec.

Phenytoin sodium 25 mg/kg significantly decreased the latency to fall off the rotating rod 61.5±1.55sec compared with control one 175±2.04sec (Table3)

B. forced swim test: Administration of *N. sativa* oil (10 ml/kg) and sodium valproate (100 mg/kg) orally for 1week caused no significant ($p<0.05$) effect on swimming behavior of mice and didn't affect the immobility time of mice 125±1.78 and 132.5 ±1.96 sec, respectively compared with control group110.25±1.65sec.Phenytoin sodium (25 mg/kg) significantly decreased swimming activity of mice and increased immobility time of mice 229.75±2.48 sec compared with 110.25±1.65sec for control group (Table3).

Table (3): Effect of NSO, sodium valproate and phenytoin sodium on rotarod test and forced swim test, (M±SE) (n=5).

Group	Rota rod test (sec)	Forced swim test (immobility time)sec
control	175±2.04 [a]	110.25±1.65 [d]
NSO[1]	164.5±0.65 [b]	125±1.78 [c]
SV[2]	166.25±0.85 [b]	132.5±1.96 [b]
Phenytoin sodium[3]	61.5±1.55 [c]	229.25±2.48[a]

1 NSO: *Nigella sativa* oil (10 ml/kg) orally for 7days; 2 SV: sodium valproate (100 mg/kg) orally for 7 days; 3 phenytoin sodium (25 mg/kg) orally for 7days. Means carrying different superscripts in the same column are significantly different at ($p<.05$)

Discussion

Pentylenetetrazole (PTZ) is a tetrazol derivative [37] that specifically used in seizure tests as a method of evaluating the excitability of the central nervous system and GABA activity [38]. PTZ is a non-competitive GABA antagonist of the gamma amino butyric acid (GABA) A receptor complex [39].

The present study observed that intra peritoneal injection of PTZ (85mg/kg) induced onset of convulsion within less than 1minute and strong myoclonic convulsions which come in agree with Deyn *et al*. [40] observation. Our results were in agreement with Ilhan *et al. [*27] that *N. sativa* oil 10ml/kg orally for 1week delayed time of convulsion onset**,** delayed generalized convulsion and weakened myoclonic convulsions.

Oxidative stress plays an important role in pathogenesis of epileptic seizures [41], and free radicals level increase has been reported during seizures [42].

Similarly, in the present study, we observed an increase in MDA levels and a reduction in glutathione peroxidase and superoxide dismutase in the brain of animals subjected to PTZ-induced seizure. The mice pretreated with *N. sativa* oil (10 ml/kg orally 7days) showed reduction in brain MDA level and elevation of glutathione peroxidase and superoxide dismutase levels. Consistent with this finding, some studies reported strong antioxidant activity for *N. sativa* [43].

GABA is the main inhibitory neurotransmitter in the central nervous system. Reducing neuronal excitability all over the nervous system is its principal role and also responsible for the regulation of muscle tone [44].

N. sativa oil (10 ml/kg) orally for 1week increased the brain GABA level more than PTZ group, this result comes hand by hand with Raza *et al*. [45] results who suggested that the main mechanism of *N. sativa* as anticonvulsant is raising brain GABA level.

In this study, we found that pentylenetetrazole (85 mg/kg i/p) only one shot induced degeneration or dark neurons peculiarly among the hippocampus cells which represented about 15-20%. Similar observation was recorded by Baracskay *et al.* [5] who noted the presence of dark neurons after epilepsy and seizure induced by PTZ injection. Our result showed that administration of *N. sativa* oil (10 ml/kg) orally for 1 week before PTZ administration (85 mg/kg i/p) protected the hippocampal cells of the brain which appeared mostly normal except a few neuronal cells which didn't exceed 0.5% of the cells showed mild degenerative changes (dark neurons). These results are compatible with

Seghatoleslam *et al*. [22] who revealed that *N. sativa* oil prevented appearance of dark neurons due to PTZ – induced seizures in all hippocampus regions.

Mice receive an electrical stimulus of sufficient intensity to induce maximal seizures of their hind limbs, with tonic extension as the endpoint of the test [46].*N. sativa* oil 10ml/kg bwt p.o wasn't able to prevent hind limb extension and failed to protect all mice from seizures, so *N. sativa* oil should not use in tonic clonic epilepsy (grand- mal epilepsy)

After application of the rotarod and forced swim test, the results revealed that *N. sativa* oil has no neurotoxic effect on mice and didn't induce any disturbance in motor coordination and there weren't any changes in swimming behavior as control group. This result is in agreement with the results of Perveen *et al.*, [47] who approved that *N. sativa* oil has neuroprotective effect and can improve mice performance for the neurotoxicity tests.

Conclusion

It could be concluded that *N. sativa* oil has anticonvulsant activity in petit-mal epilepsy and can't be used in grand-mal epilepsy. *N. sativa* has antioxidant and neuroprotective properties with apparently no neurotoxic effect.

Conflict of interest

The authors declare that they have no conflict of interests.

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الملخص العربي

التأثير المضاد للتشنجات و التأثير علي مستوي الجابا لزيت حبة البركة علي الفئران

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وصفت العديد من الدراسات التجريبية التأثير الواقى للأعصاب ومضاد الأكسدة للمستخلصات النباتية وزيوتها مثل حبة البركة. أجريت الدراسة الحالية لتقييم النشاط المضاد للتشنجات لزيت حبة البركة. تم استخدام خمس وخمسون من الذكورالفئران. وكانت التجارب على التشنجات المحدثة معمليا بحقن مادة البنتيلينتترازول ,استخدام الصدمة الكهربائية القصوى واختبارات السمية العصبية. عولجت الفئران بزيت حبة البركة (١٠ مل / كجم) عن طريق الفم؛باستخدام فالبوريت الصوديوم (١٠٠ مجم / كجم) وفينيتوين الصوديوم (٢٥ مجم / كجم) عن طريق الفم كعقاقير قياسية.في التشنجا ت المستحثة بالبنتيلينتترازول،بمقياس وقت بداية التشنجات العصبية والتشنجات الكلية للفئران، بجانب تقييم حمض الجابا والأنزيمات المضادة للأكسدة. في الصدمة الكهربائية القصوى،لوحظ التشنجات فى لأطراف الخلفية للفئران . زيت حبة البركة ادى الى تأخير بشكل ملحوظ بداية التشنجات المستحثة بالبنتيلينتترازول ولكن لم يكن له تأثيرعلى التشنجات المحدثة بالصدمة الكهربائية القصوى . وأظهرزيت حبة البركة تأثير قوي كمضاد للأكسدة،وزيادة مستوى حمض الجابا في انسجة المخ والجيد أنه لا يؤدى إلى تسمم عصبي على الفئران.