academicJournals

Vol. 7(24), pp. 1660-1670, 29 June, 2013
DOI 10.5897/AJPP12.897
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

The neuroprotective role of *Nigella sativa* extract on ciprofloxacin and pentylenetetrazole treated rats

Mona Abdel-Rahman [1], Nadia M. S. Arafa[2*], Manal F. El-khadragy[1], Rami B. Kassab[1]

[1]Department of Zoology and Entomology, Faculty of Science, Helwan University, Ain Helwan, 11795, Cairo, Egypt.
[2]Faculty of Science, Jazan University, Biology Department, Saudi Arabia and National Organization for Drug Control and Research, Giza, Egypt.

Accepted 31 May, 2013

This study aimed to investigate the *Nigella sativa* seed (NS) neuroprotective effect on ciprofloxacin (CFX) antibiotic with suggesting neurotoxic effect in rats through the determination of monoamines levels and acetylcholinesterase (AChE) activity in different brain areas. We used valporic acid as a reference antiepileptic drug and pentylenetetrazole (PTZ), a drug used for induction of epileptic model in rats. The present data revealed that the daily oral administration of NS (350 mg/kg b.wt.) for 14 days caused significant increase in the monoamines contents with no statistical difference in AChE as compare to control values. While the administration of CFX (500 mg/kg b.wt.) and/or PTZ (60 mg/kg b.wt.) was found to produce significant decrease in the concentration of monoamines and the activity of AChE in cerebral cortex, cerebellum, striatum and hippocampus after 7 and 14 days. Moreover, the pre- and post-treatment with NS in CFX and/or PTZ treated rats was found to ameliorate most of the side effects induced by these drugs. It could be concluded that the treatment with the therapeutic dose of CFX 14 days could lead to the development of seizures through the reduction of monoamines level and decreasing the activity of AChE in the tested brain areas. The administration of *N. sativa* pre- and the post treatment to CFX and/or PTZ treated rats were found to ameliorate their side effects. Suggesting that *N. sativa* seeds with antiepileptic activity and its administration could alleviate ciprofloxacin neurotoxicity.

Key words: Ciprofloxacin, Pentylenetetrazole, *Nigella sativa*; monoamines, acetylcholinesterase.

INTRODUCTION

Epilepsy is a common chronic neurological disorders affecting ~1–2% of the population worldwide and characterized by the repeated occurrence of seizures (McNamara, 1999; Blume et al., 2001; Loscher, 2002; Berg et al., 2010). Epilepsy may be developed as a result of the imbalance between excitatory and inhibitory neuro-transmission, alterations in neurotransmitter expression and function (Hirose et al., 2000). Animal models have played an important role for detecting the pathophy-siology of human epilepsies (Avoli et al., 2005). Pentylenetetrazole is considered the most useful experimental model which can reveal the changes associated with epilepsy (da Silva et al., 1998). Pentylenetetrazole (PTZ) exerts its action by binding to the picrotoxin-recognition site and benzodiazepine-binding site of the post-synapticgamma-aminobutyric acid A (GABAA) receptor. Thus, PTZ reduces the effects of endogenous GABA and other inhibitory transmitters, which renders the system in a hyperexcitable state. In the case of a convulsive dose, PTZ induces generalized

*Corresponding author. E-mail: nadianeuro@yahoo.com. Tel: +966 073210869; 0563725278. Fax: +966 073211052.

tonic–clonic seizure activity within seconds (Huang et al., 2001). Also PTZ induced oxidative stress results in disturbance of the antioxidant enzyme status accompanied by neuronal injury and the development of epilepsy in rats (Sharma et al., 2010).

Ciprofloxacin belongs to the class of 4-fluoroquinolone antibiotics a commonly used therapy of many bacterial infections. Its antimicrobial activity is based on the inhibition of bacterial DNA gyrase. Ciprofloxacin have few reports of serious reactions over a period of 15 years of use and more than 340 million prescriptions (Ball et al., 1999; Segev et al., 1999). Ciprofloxacin-associated seizures occur most commonly in patients with special risk factors that may cause accumulation of drug (high doses of the drug, old age, renal insufficiency, drug interactions). Several mechanisms are thought to be responsible, the involvement of gamma-aminobutyric acid (GABA) and excitatory amino acid (EAA) neurotransmission and the kinetics of quinolones distribution in brain tissue are discussed (De Sarro and De Sarro, 2001). Extensive toxicological and biochemical experiments have been performed to explain the central nervous system (CNS) effects observed under therapeutic conditions (Akahane et al., 1993; De Sarro et al., 1999; De Sarro and De Sarro, 2001). Seizure activity is associated with a wide range of local biochemical changes, affecting various neurotransmitters (monoamines, amino acids) (Freitas et al., 2004; Cavalheiro et al., 2006). Green and Halliwell (1997) contributed the excitatory action of ciprofloxacin to its selective antagonistic effect on GABA (A) receptors and proconvulsion activity (Dodd et al., 1988; Kawakami et al., 1997). A number of antibiotics, including ciprofloxacin, have been demonstrated to stimulate the production of reactive oxygen species (ROS) in bacterial cells (Becerra and Albesa, 2002; Albesa et al., 2004). Ciprofloxacin previously reported for induction of oxidative stress in cerebral and hepatic tissues of rat (Gürbay and Hincal, 2004; Gürbay et al., 2007) and DNA damage in astrocytes (Gürbay et al., 2006) and the involvement of oxidative stress in tendenopathy related classic side effect of ciprofloxacin (Pouzaud et al., 2004).

Valproate (VPA) is one of the conventional antiepileptic drugs that possess a broad spectrum of antiepileptic activity (Loscher, 1993). Its pharmacological effects involve a variety of mechanisms, including increased GABA-ergic transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage-gated sodium channels and modulation of dopaminergic and serotoninergic transmission (Perucca, 2002). Herbal remedies and alternative medicines are used throughout the world and in the past, herbs often represented the original sources of most drugs (Cooper et al., 2004; Tsao et al., 2005). *N. sativa* Linn., belonging to the family Ranunculaceae, commonly known as black seed or black cumin (Ali and Blunden, 2003), provide a highly nutritional product that has been used extensively as a supplement to help maintain good health and well-being (Cheikh-Rouhou et al., 2008). Several pharmacological properties have been documented such as antidiabetic (Kanter et al., 2004), antibacterial (Kanter et al., 2003), hepatoprotective (Nagi et al., 1999), nephroprotective (Yaman and Balikci, 2010), antitumor (Khan et al., 2003; Salem, 2005; Yi et al., 2008) antiepileptic (Akhondian et al., 2007) and neuroprotective (Ismail et al., 2008; Ezz et al., 2011; Akhtar et al., 2012).

Therefore, the aim of the current work was to evaluate whether the treatment with the therapeutic dose of ciprofloxacin for 14 days can induce convulsions or not and the efficacy of *N. sativa* seeds supplementation pre- or post-treatment to alleviate ciprofloxacin side effects as compared to the effect on PTZ induced seizure model through the estimation of monoamines and the activity of acetylcholinesterase in different brain areas in adult male albino rats.

MATERIALS AND METHODS

Adult male albino rats (Rattus Norvigicus) weighing 140±20 g were used for the experiment purchased from the Egyptian Institution of Serum and Vaccine (VACSERA) Cairo, Egypt. Animals were kept under normal conditions throughout the experiment and allowed to adapt to laboratory conditions for 10 days before the beginning of the experiment. The animal care conformed to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996). Animals had free access to food and water ad libitum throughout the experimental period and were divided into 9 groups (n=24/group) randomly as shown in Table 1.

Drugs

Ciprofloxacin manufactured by Bayer healthcare pharmaceuticals, Germany and *N. sativa* extract was purchased from the Arab company for pharmaceuticals and medicinal plants (MEPACO), Egypt. Pentylenetetrazole was obtained from Sigma-Aldrich, MO, USA while sodium valproate (Depakine) was obtained from Sanofi-aventis, Paris, France.

Tissue sampling

Animals of this study were scarified by sudden decapitation after 7 and 14 days post-treatment, except PTZ group which decapitated after 24 h. Brains were rapidly dissected into four areas of cerebral cortex, cerebellum, striatum and hippocampus and used for the determination of monoamines by high performance liquid chromatography (HPLC) according to Pagel et al. (2000) and previously detailed in Tousson et al. (2012), and acetylcholinesterase (AChE) activity by the method of Ellman et al. (1961) and modified by Gorun et al. (1978).

Statistical analysis

Reported values represent means ± SE. Statistical analysis was evaluated by one-way ANOVA. Once a significant F test was obtained, least significant difference (LSD) comparisons were performed to assess the significance of differences among various treatment groups. Statistical Processor System Support "SPSS" for Windows software, Release 17.0 (SPSS, Chicago, IL) was used.

Table 1. Animals'groups used in the present study.

Group	Treatment daily/duration
Control	Normal saline (P.O)/14 days
CFX	Ciprofloxacin (500mg/kg) (P.O)/ 7and 14 days (Gürbay and Hincal, 2004)
PTZ	Pentylenetetrazole single dose (60mg/kg) (IP) (Quintans-J̊nior et al., 2009)
NS	*Nigella sativa* (350mg/kg) (P.O)/ 7 and 14 days.
NSandCFX	*Nigella sativa* (P.O) as in NS/ 7 and 14 days, followed by ciprofloxacin as in CFX group/ 7 and 14 days.
CFXandNS	Ciprofloxacin (P.O) as in CFX group for 7 and 14 days, followed by *Nigella sativa* as in NS group/ 7 and 14 days.
NSandPTZ	*Nigella sativa* (P.O) as in NS group/ 7 and 14 days, followed by single PTZ (IP) (60mg/kg).
PTZandNS	Single PTZ (IP) (60mg/kg), after 24h received daily *Nigella sativa* (P.O) as in NS/ 7 and 14 days.
PTZandVPA	Single PTZ (IP) (60mg/kg), after 24h received daily valproate (200mg/kg) (P.O)/ 7 and 14 days (Chen et al., 2009).

RESULTS

The animal behavior was observed throughout the experimental period diurnally, since it has been recorded that PTZ treated rats developed seizures, these seizures ranged from ear and facial twitching, clonic and myoclonic convulsions with the animal falling on its side and lethal convulsions in some animals. Meanwhile, no seizures were observed in ciprofloxacin treated rats. In addition, no seizures was manifested in pretreated animals with *N. sativa*, while the post treatment with *N. sativa* prolonged the onset of seizures and reduce the duration of seizures in PTZ post treated animals. Data in Tables 2 and 3 represented the mean monoamines (noradrenaline, dopamine and serotonin) and AChE activities values ± SE, respectively, in all tested groups, recording the significance at 0.05 level according to one-way ANOVA. Figures 1-4) represented the percentage change in monoamines levels and AChE activities, respectively, in *N. sativa* seed (NS) and PTZ, PTZ and NS and PTZ and valproic acid (VPA) groups from PTZ group values and NS and ciprofloxacin (CFX) and CFX and NS from CFX group values. In CFX group, the three monoamines decreased significantly throughout the experimental periods as compared to control values, with the exception of no change in striatal noradrenaline level at the 14th day and not statistically different decrease in hippocampus dopamine at the 14th day and cerebellar and hippocampal serotonin at the 7th day of CFX administration. AChE activities decreased significantly as compared to the control value except in cerebellum at 7 days. Pentylenetetrazole administered group showed dramatic significant decrease in monoamines levels as well as AChE activities in all tested areas throughout the two experimental durations as compared to control values. Nigella extract orally administered group (NS) exhibited after 14 days significant increase in noradrenaline and serotonin in both cortex and hippocampus and cortex and striatum dopamine levels increased significantly as compared to the control values. The AChE values recorded in NS group showed no statistically significant difference as compared to control group recorded values. Nigella extract orally administered before and after PTZ i.p administration in group (NS and PTZ) and (PTZ and NS) reflected significant increase in all monoamines levels as compared to that of PTZ group in the tested areas throughout the two tested periods. Also, AChE activities increased significantly in hippocampus at 7 days and in all tested areas at 14 days in NS and PTZ group as compared to the corresponding PTZ group values while AChE activities significantly increased in all areas throughout the two periods in PTZ and NS group except in cerebellum as compared to the corresponding PTZ group values. Valproate treatment after PTZ i.p administration in PTZ and VPA group, recorded significant increase in all monoamines levels and AChE activities in all tested areas throughout the experimental duration as compared to the corresponding values recorded in PTZ group. Also, in PTZ and VPA, cortex and striatum noradrenaline levels at 14th day decreased significantly as compared to their corresponding values in PTZ and NS group. But dopamine increased significantly in cortex throughout the two periods, in cerebellum in 7 days and in hippocampus at the 14th day as compared to values in PTZ and NS group. Results about Nigella extract orally administered as prophylactic before ciprofloxacin administration or administered after ciprofloxacin groups (NS and CFX) or (CFX and NS), respectively, showed significant increase in all monoamines levels throughout the two periods as compared to CFX group values. In the same manner, AChE activities increased significantly as compared to CFX group values except at the 1st duration in NS and CFX in all areas and in cerebellar AChE activity at the 1st duration in CFX and NS group.

DISCUSSION

The study extended to the brain areas as the cortex and hippocampus areas appeared to be important in the expression of early convulsive seizures (Kelly et al., 1999; Ang et al., 2006) in addition to the important functional association between cortical regions and the hippocampus in seizure propagation (Cavalheiro et al., 1991; Kelly et al., 2002). The cortex and hippocampus

Table 2. Effect of *Nigella sativa* extract on monoamines content in brain areas of male rats treated with either pentylenetetrazole or ciprofloxacin for 7 or 14 days.

Area / Group	Period (days)	Cerebral Cortex	Cerebellum	Striatum	Hippocampus
Norepinephrine					
Control		0.65 ± 0.01	0.69 ± 0.03	0.32 ± 0.008	0.53 ± 0.03
CFX	7	0.51 ± 0.01[a]	0.54 ± 0.02[a]	0.18 ± 0.01[a]	0.31 ± 0.03[a]
	14	0.47 ± 0.03[a]	0.32 ± 0.01[a]	0.32 ± 0.01	0.20 ± 0.02[a]
PTZ		0.17 ± 0.01[a]	0.14 ± 0.01[a]	0.07 ± 0.01[a]	0.14 ± 0.01[a]
NS	7	0.68 ± 0.03	0.63 ± 0.03	0.32 ± 0.01	0.51 ± 0.03
	14	0.76 ± 0.04[a]	0.69 ± 0.02	0.34 ± 0.02	0.61 ± 0.02[a]
NS & PTZ	7	0.49 ± 0.03[ac]	0.44 ± 0.03[ac]	0.18 ± 0.01[ac]	0.42 ± 0.01[ac]
	14	0.59 ± 0.05[c]	0.53 ± 0.01[ac]	0.20 ± 0.01[ac]	0.49 ± 0.02[c]
PTZ & NS	7	0.54 ± 0.03[ac]	0.49 ± 0.01[ac]	0.19 ± 0.01[ac]	0.30 ± 0.01[ac]
	14	0.60 ± 0.03[c]	0.57 ± 0.01[ac]	0.28 ± 0.01[c]	0.45 ± 0.02[ac]
PTZ & VPA	7	0.57 ± 0.003[c]	0.50 ± 0.02[ac]	0.21 ± 0.01[ac]	0.32 ± 0.01[ac]
	14	0.45 ± 0.01[acd]	0.55 ± 0.02[ac]	0.23 ± 0.01[acd]	0.49 ± 0.02[c]
NS & CFX	7	0.60 ± 0.01[b]	0.75 ± 0.01[b]	0.37 ± 0.01[b]	0.45 ± 0.02[ab]
	14	0.68 ± 0.02[b]	0.81 ± 0.03[ab]	0.35 ± 0.01	0.57 ± 0.02[b]
CFX & NS	7	0.62 ± 0.01[b]	0.71 ± 0.04[b]	0.30 ± 0.01[b]	0.46 ± 0.02[b]
	14	0.66 ± 0.03[b]	0.79 ± 0.03[b]	0.30 ± 0.01	0.50 ± 0.02[b]
Dopamine					
Control		0.35 ± 0.01	0.53 ± 0.01	0.85 ± 0.03	0.79 ± 0.03
CFX	7	0.25 ± 0.01[a]	0.31 ± 0.01[a]	0.58 ± 0.04[a]	0.58 ± 0.03[a]
	14	0.17 ± 0.01[a]	0.31 ± 0.01[a]	0.54 ± 0.05[a]	0.68 ± 0.02
PTZ		0.09 ± 0.01[a]	0.12 ± 0.01[a]	0.32 ± 0.01[a]	0.19 ± 0.01[a]
NS	7	0.33 ± 0.01	0.57 ± 0.01	0.91 ± 0.03	0.81 ± 0.03
	14	0.43 ± 0.01[a]	0.58 ± 0.02	1.05 ± 0.06[a]	0.89 ± 0.02
NS & PTZ	7	0.30 ± 0.01[c]	0.41 ± 0.01[ac]	0.67 ± 0.02[ac]	0.32 ± 0.02[ac]
	14	0.33 ± 0.01[c]	0.46 ± 0.02[c]	0.77 ± 0.04[c]	0.60 ± 0.01[ac]
PTZ & NS	7	0.24 ± 0.01[ac]	0.37 ± 0.01[ac]	0.71 ± 0.01[ac]	0.62 ± 0.02[ac]
	14	0.29 ± 0.01[ac]	0.51 ± 0.01[c]	0.79 ± 0.08[c]	0.72± 0.01[c]
PTZ & VPA	7	0.32 ± 0.01[cd]	0.52 ± 0.01[cd]	0.77 ± 0.03[c]	0.57 ± 0.02[ac]
	14	0.38 ± 0.01[cd]	0.56 ± 0.01[c]	0.80 ± 0.03[c]	0.60 ± 0.02[acd]
NS & CFX	7	0.40 ± 0.02[b]	0.55 ± 0.01[b]	0.74 ± 0.03[b]	0.85 ± 0.02[b]
	14	0.41 ± 0.01[ab]	0.52 ± 0.01[b]	0.85 ± 0.01[b]	0.81 ± 0.02[b]
CFX & NS	7	0.38 ± 0.01[b]	0.48 ± 0.01[b]	0.80 ± 0.02[b]	0.82 ± 0.01[b]
	14	0.33 ± 0.01[b]	0.57 ± 0.05[b]	0.78 ± 0.03[b]	0.79 ± 0.02[b]
Serotonin					
Control		0.53 ± 0.01	0.44 ± 0.01	1.38 ± 0.05	6.40 ± 0.34
CFX	7	0.45 ± 0.02[a]	0.42 ± 0.01	1.19 ± 0.06	4.85 ± 0.15[a]
	14	0.36 ± 0.02[a]	0.43 ± 0.02	0.94 ± 0.02[a]	3.97 ± 0.28[a]
PTZ		0.04 ± 0.01[a]	0.04 ± 0.01[a]	0.40 ± 0.05[a]	0.97 ± 0.08[a]
NS	7	0.56 ± 0.02	0.46 ± 0.01	1.27 ± 0.05	6.89 ± 0.26
	14	0.67 ± 0.02[a]	0.48 ± 0.02	1.42 ± 0.06	8.05 ± 0.18[a]
NS & PTZ	7	0.37 ± 0.01[ac]	0.36 ± 0.02[ac]	0.74 ± 0.05[ac]	5.42 ± 0.29[ac]
	14	0.48 ± 0.03[c]	0.31 ± 0.01[ac]	0.98 ± 0.04[ac]	5.87 ± 0.27[c]
PTZ & NS	7	0.42 ± 0.02[ac]	0.38 ± 0.002[c]	1.09 ± 0.04[ac]	5.28 ± 0.09[ac]
	14	0.46 ± 0.01[c]	0.41 ± 0.01[c]	1.23 ± 0.05[c]	5.97 ± 0.13[c]
PTZ & VPA	7	0.38 ± 0.01[ac]	0.37 ± 0.02[ac]	0.75 ± 0.04[ac]	4.42 ± 0.25[acd]
	14	0.35 ± 0.01[acd]	0.44 ± 0.02[c]	1.06 ± 0.04[ac]	5.38 ± 0.26[ac]

Table 2. Contd.

NS & CFX	7	0.55 ± 0.01[b]	0.49 ± 0.01[b]	1.32 ± 0.04	6.44 ± 0.30[b]
	14	0.57 ± 0.01[b]	0.50 ± 0.01[b]	1.31 ± 0.04[b]	6.04 ± 0.35[b]
CFX & NS	7	0.60 ± 0.02[b]	0.42 ± 0.01	1.19 ± 0.02	6.35 ± 0.11[b]
	14	0.55 ± 0.03[b]	0.46 ± 0.005	1.46 ± 0.04[b]	6.90 ± 0.27[b]

Data expressed as mean ± standard error. n=12. One way analysis performed between groups. Multiple range Duncan test with significance level 0.05. Within the same column superscripts represent significance. a, Control; b, ciprofloxacin (CFX) group; c, pentylenetetrazole (PTZ) group; d, from pentylenetetrazole and *Nigella sativa* (PTZ and NS) group; VPA, valproic acid.

Table 3. Effect of *Nigella sativa* extract on acetylcholinesterase (AChE) activities in brain areas of male rats treated with either pentylenetetrazole or ciprofloxacin for 7 or 14 days.

Area / Group	Period (days)	Cerebral cortex	Cerebellum	Striatum	Hippocampus
Control		15.24 ± 1.11	12.55 ± 0.84	11.85 ± 0.71	17.58 ± 1.00
CFX	7	12.36 ± 0.60[a]	11.38 ± 0.64	9.39 ± 0.34[a]	14.29 ± 0.97[a]
	14	11.75 ± 0.53[a]	9.85 ± 0.44[a]	9.13 ± 0.31[a]	13.14 ± 0.62[a]
PTZ		10.19 ± 0.58[a]	8.59 ± 0.67[a]	7.27 ± 0.24[a]	11.21 ± 0.48[a]
NS	7	13.47 ± 0.90	14.01 ± 0.77	11.14 ± 0.28	18.24 ± 1.22
	14	14.68 ± 0.89	13.58 ± 0.81	12.54 ± 0.97	16.92 ± 0.95
NS and PTZ	7	11.42 ± 0.72[a]	9.65 ± 0.34[a]	8.81 ± 0.16[ac]	13.11 ± 0.89[ac]
	14	13.49 ± 0.65[c]	11.13 ± 0.57[c]	10.91 ± 0.55[c]	15.81 ± 0.71[c]
PTZ and NS	7	12.48 ± 0.49[ac]	9.52 ± 0.48[a]	9.01 ± 0.17[ac]	13.25 ± 0.90[ac]
	14	13.78 ± 0.87[c]	11.72 ± 0.53[c]	11.51 ± 0.38[c]	16.75 ± 0.83[c]
PTZ and VPA	7	12.34 ± 0.85[ac]	10.12 ± 0.33[ac]	9.29 ± 0.13[ac]	14.12 ± 0.78[ac]
	14	13.44 ± 0.85[c]	10.82 ± 0.24[c]	10.79 ± 0.36[c]	16.22 ± 0.81[c]
NS and CFX	7	13.88 ± 0.45	12.22 ± 0.45	10.18 ± 0.23	15.95 ± 0.72
	14	14.16 ± 0.88[b]	12.82 ± 0.65[b]	12.28 ± 0.43[b]	17.25 ± 0.92[b]
CFX and NS	7	14.52 ± 0.67[b]	11.78 ± 0.52	11.47 ± 0.29[b]	16.79 ± 0.86 [b]
	14	14.47 ± 0.71[b]	13.14 ± 0.38[b]	12.52 ± 0.39[b]	15.89 ± 0.91[b]

Data expressed as mean ± standard error. n=12. One way analysis performed between groups. Multiple range Duncan test with significance level 0.05. Within the same column superscripts represent significance, a, Control; b, ciprofloxacin (CFX) group; c, pentylenetetrazole (PTZ) group; d, pentylenetetrazole and *Nigella sativa* (PTZ and NS) group; valproic acid (VPA).

suggested playing a role in inducing convulsions by quinolones (Motomura et al., 1991) and there are direct anatomical connections between the hippocampus and the striatum (Voorn et al., 2004). In addition, there are connections between striatum and hippocampus via the entorhinal and prefrontal cortex (Hyman et al. 1990; Christakou et al., 2004). The sole output of the cerebellum is inhibitory Purkinje cell projections to deep cerebellar nuclei in brainstem. Cerebellar pathways subsequently project to widespread frontal lobe and subcortical structures. The Purkinje cell inhibitory output and widespread cortical projections support the possible role of cerebellar stimulation to reduce epileptogenic activity (Krauss and Koubeissi, 2007). The role of monoamines in epileptogenesis and seizure activity is well documented. Many studies have shown role in unravelling the pathophysiology of human epilepsies (Pitkanen et al., 2006). Pentylenetetrazole provoked clonic convulsions as recorded in Safar et al. (2010). Several studies focus on the role of oxidative stress both as a consequence and a cause of epileptic seizures (Patsoukis et al., 2004; Ilhan et al., 2006). In PTZ group, acetylcholinesterase activities as well as monoamines levels intensely decreased in tested brain areas which is in line with Visweswari et al. (2010) and Chimakurthy and Talasila (2010) results reflecting their roles in the PTZ induced seizure. Paciaa et al. (2001) demonstrated that a marked NE depletion in the temporal neocortex temporal lobe epilepsy (NTLE) patients, this depletion has been shown to enhance the frequency, intensity and spread of seizures (Ferrendelli, 1986; Browning et al., 1989). Chimakurthy and Talasila (2010) found that a decrease in NE levels was observed in the hippocampus and hypothalamus, also a significant decrease in DA levels was observed in the cortex, hippocampus, hypothalamus, and pons in PTZ-treated rats. el-Hamdi et al. (1992)

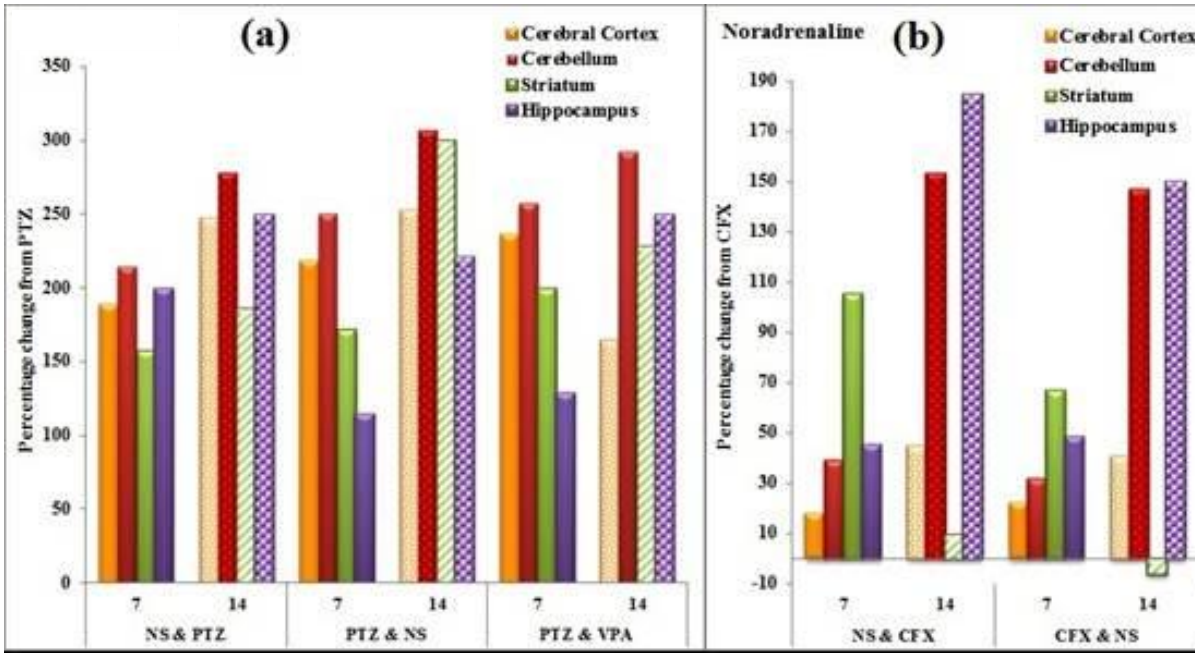
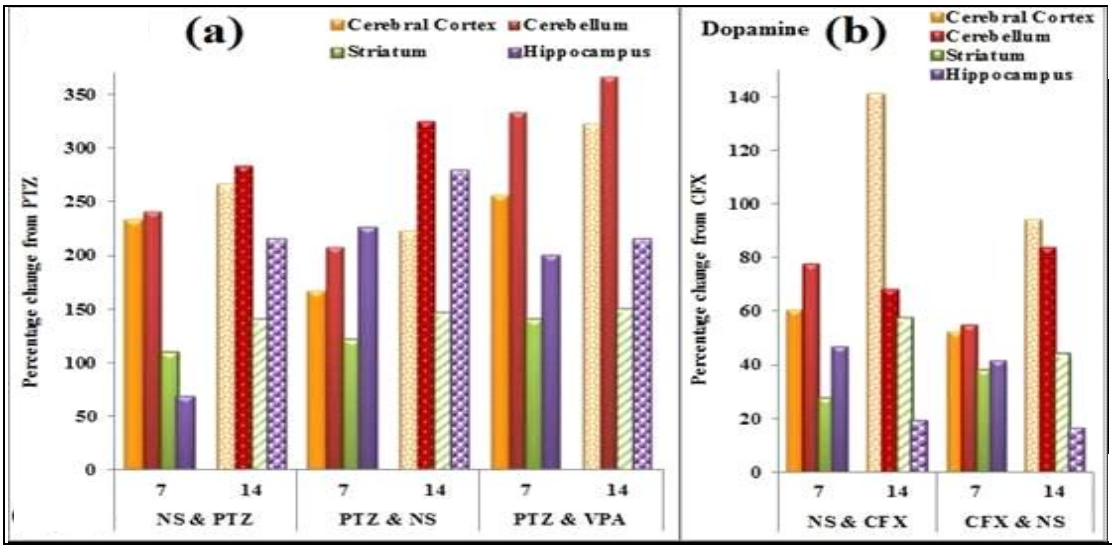


Figure 1. Percentage change of noradrenaline levels in (a) *Nigella sativa* pre-or post-administration to PTZ administered groups (NS and PTZ), (PTZ and NS) and valproate administered post PTZ administration (PTZ and VPA) as compared to the value in PTZ group. In (b) *Nigella sativa* pre- or post-administration to CFX groups (NS and CFX) (CFX and NS) as compared to the value in CFX group.



Figures 2. Percentage change of dopamine levels in (a) *Nigella sativa* pre-or post-administration to PTZ administered groups (NS and PTZ), (PTZ and NS) and valproate administered post PTZ administration (PTZ and VPA) as compared to the value in PTZ group. In (b) *Nigella sativa* pre- or post-administration to CFX groups (NS and CFX) (CFX and NS) as compared to the value in CFX group.

found that the tissue levels of DA concentration were markedly reduced in the cerebral cortex and striatum of PTZ treated rats. Serotonin is a well-recognized modulator of cortical excitability which reduces susceptibility to seizures. In a model of generalized epilepsy, a decrease in serotonin concentration, synaptosomal 5-HT uptake, and tryptophan hydroxylase activity (measured in vivo and in vitro) in most regions of the forebrain and in selected regions of brainstem rat brain tissue was recorded (Statnick et al., 1996). It has been demonstrated

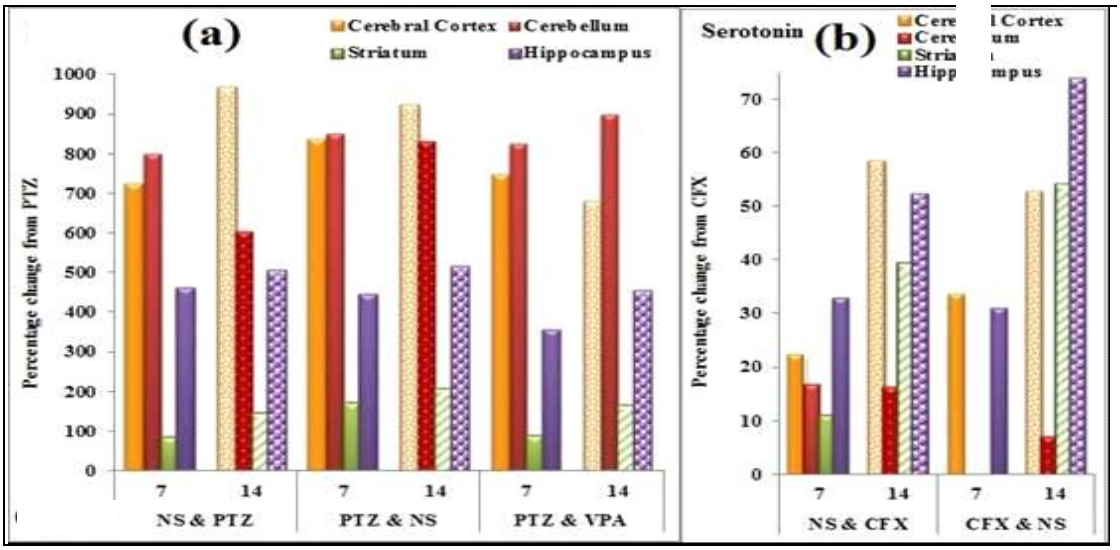


Figure 3. Percentage change of serotonin levels in (a) *Nigella sativa* pre-or post-administration to PTZ administered groups (NS and PTZ), (PTZ and NS) and valproate administered post PTZ administration (PTZ and VPA) as compared to the value in PTZ group. In (b) *Nigella sativa* pre- or post-administration to CFX groups (NS and CFX) (CFX and NS) as compared to the value in CFX group.

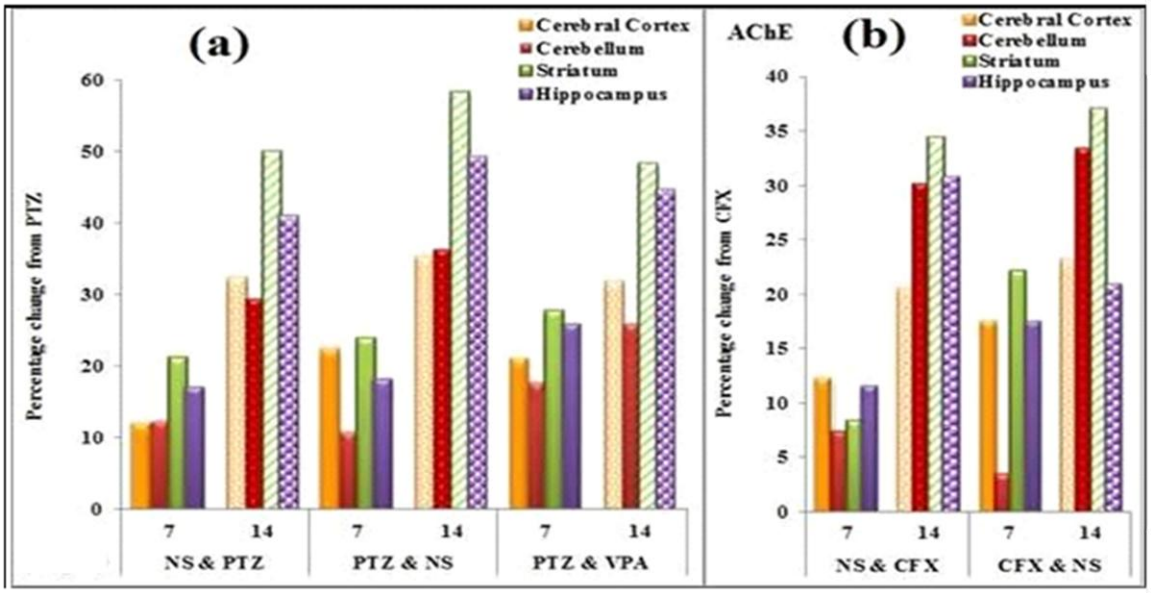


Figure 4. Percentage change of AChE in (a) *Nigella sativa* pre-or post-administration to PTZ administered groups (NS and PTZ) (PTZandNS) and valproate administered post PTZ administration (PTZ and VPA) as compared to the value in PTZ group. In (b) *Nigella sativa* pre-or post-administration to CFX groups (NS and CFX) (CFX and NS) as compared to the value in CFX group.

that the reduction of brain serotonin concentrations leads to an increase in seizure susceptibility in animal models of epilepsy (Wenger et al., 1973; Lazarova et al., 1983). In vivo microdialysis experiments have confirmed the increased release of NE during seizures in normal animals, in addition, changes in NE synthesis and release that occur after seizures may affect the rate and severity of recurring seizures. So, the decrement in the content of the studied neurotransmitters in the present study may be due in part to increase in their release or turnover. The impairment of the brain redox status after PTZ administration reflecting oxidative stress involved in seizure formation previously reported (Hosseinzadeh and Parvardeh, 2004; Silva et al., 2009; Safar et al., 2010).

Ciprofloxacin administration in a less vigorous extent as regard with PTZ results also decreased the acetylcholinesterase activities and monoamines levels in the investigated brain areas which support the proconvulsant effect of the quinolones previously discussed in Smolders et al. (2002) and Rawi et al. (2011). Ciprofloxacin may decrease the threshold of epileptogenic activity (Agbaht et al., 2009) where, ciprofloxacin induced seizures in healthy patients (Darwish, 2008). Extensive toxicological and biochemical experiments have been performed to explain the CNS side effects observed under therapeutic conditions (Stahlmann and Lode, 1999; Rawi et al., 2011). Bidziński et al. (1998) concluded that there is a functional interaction between brain serotonin and GABA systems, due to the effect of serotonin depletion in GABAA receptor down-regulation. Quinolones was found to have a Mg+2 chelating properties which led to prolong opening time of the calcium ion channel, thus increasing intracellular Ca+2 ions concentration (Davies and Maesen, 1989; Stahlmann et al., 1997), this increase in intracellular Ca+2 ions concentration led to the rupture of the vesicles in the presynaptic terminals and increase the release of the neurotransmitters (Bullock et al., 1995), as a result the content of catecholamine is decreased. This is in agreement with the present results where the administration of CFX caused a decrease in monoamines concentration in different tested brain areas which may lead to the initiation of seizures. Also data recorded about monoamines in the tested antibiotic may be a supplement data to the previously mentioned seizure inducing activity of quinolones (Moorthy et al., 2008; Agbaht et al., 2009). The results of Rawi et al. (2011 and 2011a) suggested a shift in the balance of antioxidant markers towards the oxidative stress in cortex, hippocampus and striatum through elevation in malondialdehyde, nitric oxide contents and superoxide dismutase enzyme activity and reduction of glutathione, glutathione peroxidase and Na+, K+, adenosine triphosphatase enzymes activity. The effect tested through histopathological examinations showed focal gliosis, hemorrhagic areas in cerebral cortex and neuronal degeneration, oedema and astrosytosis in hippocampus. Also focal gliosis with congested blood vessels in striatum in ciprofloxacin treated rats under dose equivalent to the human therapeutic onewas noted. Recently, Abdel-Zaher et al. (2012) suggested that elevation of brain glutamate levels with consequent oxidative stress and increase in the expression and activity of brain inducible NO synthase may play a pivotal role in ciprofloxacin-induced convulsive seizures. Delgado-Escueta (1984) demonstrated that the increased activity in noradrenergic, dopaminergic, and serotonergic systems are believed to reduce cortical excitability and decrease seizure activity.

Moreover, it has been implicated in the onset and perpetuation of many seizure disorders, many experimental procedures designed to increase monoaminergic activity have proven to posses antiepileptic properties (McIntyre and Edson, 1989; Yan et al., 1995). The seizure induction through the assumption about the pharmacological treatments that lowering monoamine levels in the brain generally increase the susceptibility to seizures, while treatments that increase monoamines decrease the susceptibility (Kiyofumi Kobayashi and Akitane Mori, 1977). In animal models, treatments that increase serotonin decrease seizure susceptibility. Conversely, decreasing serotonin function increases seizure susceptibility (Bagdy et al., 2007). According to unanimous opinion, elevated levels of NE, 5-HT, and DA in the brain exert an anticonvulsant activity (Starr, 1996; Jobe et al., 1999). It was previously reported that the efficacy of antioxidants lies in the management of convulsive disorders (Sudha et al., 2001; Ilhan et al., 2005). The data about sodium valproate as established anticonvulsant drug is mediated by alteration in monoamine levels in rat brain areas (Baf et al., 1994; Löscher and Hönack, 1996; Ichikawa and Meltzer, 1999) as the enhancement of monoaminergic transmission reduced seizure threshold (Wahnschaffe and Loscher, 1991; Wada et al., 1993). This may be explained through valproate mechanism via activation of monoamine oxidase (MAO) the key enzyme that degrades a number of monoamine neurotransmitters as recently cited by Wu and Shih (2011). Also valproate post PTZ administration revealed antioxidant potential (Safar et al., 2010). The present study revealed that, the pre- and post-treatment with *N. sativa* alleviate the changes in monoamines (NE, DA and 5-HT) and the activity of AChE in PTZ and CFX treated rats in most investigated brain areas throughout the experimental days, these findings reflect the potent antiepileptic efficiency of *N. sativa* as suggested by Guha et al. (2005), Ilhan et al. (2005) and Ezz et al. (2011), where, Ilhan et al. (2005) reported that the neurotransmitter receptor-mediated activity may be involved in the mechanism of action of *N. sativa* oil in preventing PTZ kindling seizures. Moreover, the pre administration of *N. sativa* restored the AChE activity in cerebral cortex, cerebellum and hippocampus in propoxur-treated rats (Mohamadin et al., 2010). Furthermore, studies carried out by Perveen et al. (2008 and 2009) stated that the administration of *N. sativa* oil increased the 5-HT, tryptophan levels and decreased levels of 5-HIAA in the rat brain suggesting a decreased 5-HT turnover supporting its anti-anxiety effect, these may explain the increase in monoamines content in the present study. Thymoquinone, the major constituent of *N. sativa* seeds prolonged the onset of PTZ-induced seizures and reduced the duration of myoclonic seizures and postulated thymoquinone anticonvulsant activity in the petit mal epilepsy through an increase in GABAergic tone (Hosseinzadeh and Parvardeh, 2004). O'Donnell et al. (2010) stated that the inhibition of AchE leads to a build-up of extracellular ACh and a series of toxic consequences including hypersecretion, tremor, convulsion/

seizure,coma, and death. In addition, the findings of de Sales et al. (2010) reported that seizures caused a decrease in AChE activity, expecting that the constant inhibition of this enzyme by seizures might increase ACh levels. In addition to the antioxidant effect of *N. sativa*, oil and thymoquinone have been demonstrated to prevent oxidative injury during cerebral ischemia-reperfusion injury in rat (Hosseinzadeha et al., 2007) and in a rat model of subarachnoid hemorrhage (Ersahin et al., 2011). Abdel-Zaher et al. (2011) results provided evidence about the therapeutic potential of *N. sativa* oil in tramadol tolerance and dependence through blockade of nitric oxide overproduction and oxidative stress induced by the drug.

From the aforementioned study results, it could be concluded that the treatment with ciprofloxacin for 14 days can behave to a lesser extent like PTZ side effects by decreasing the content of monoamines; this may be due to the increase in their release or turnover, the activity of AChE is also decreased which may lead to a build-up of extracellular Ach and a series of toxic consequences including tremor and seizures. On the other hand, the administration of *N. sativa* pre- and the post treatment to PTZ and CFX treated rats were found to ameliorate their side effects suggesting that *N. sativa* with antiepileptic activity and its administration could alleviate ciprofloxacin neurotoxicity.

ABBREVIATIONS

GABAA, Gamma-aminobutyric acid A; **PTZ**, pentylenetetrazole; **EAA**, excitatory amino acid; **CNS**, central nervous system; **ROS**, reactive oxygen species; **VPA**, valproate; **AChE**, acetylcholinesterase; **NS**, *N. sativa* seed; **CFX**, ciprofloxacin; **MAO**, monoamine oxidase.

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