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ORIGINAL ARTICLE

Amelioration of neurotoxicity induced by esfenvalerate: impact of *Cyperus rotundus* L. tuber extract

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Abstract

The main objective of this current study was to assess the protective role of *Cyperus rotundus* L. (CR) extract against oxidative stress, neurotoxicity, and inflammation induced by esfenvalerate in rats. The total phenol (TP) and total tannins (TT) were estimated by Folin ciocalteu and total flavonoids were evaluated by aluminum chloride methods. The methanol: acetone: H_2O with ratio 2:2:1 extract of *C. rotundus tubers* was determined antioxidant activity by DPPH, $ABTS^{\bullet+}$scavenging activities, and ferrous chelating, reducing power activities assays. Antioxidant activities of *C. rotundus* tuber extract exhibited 224.25, 191.47, and 218.77 μg/ml against 2,2-diphenyl-1-picrylhydrazyl (DPPH•), and 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS•) radicals and Fe^{2+}-chelating, respectively expressed as IC_{50} while reducing power showed 119.88 μg/ml expressed as EC_{50}. *C. rotundus* tuber extract' analysis showed a presence of several phenolic and flavonoid compounds identified by HPLC. Albino Wistar rats were divided into normal control, *C. rotundus* alone treated esfenvalerate, and treated (*Esfenvalerate* + CR) groups. The dose of *C. rotundus* extract was100 mg /kg BW, while the dose of esfenvalerate was 0.533 mg/kg BW orally. Administration of esfenvalerate decreased the levels of brain reduced glutathione (GSH), and paraoxnase-1(PON-1), and decreased acetylcholinesterase activity along with increasing the levels of brain malondialdehyde (MDA) and nitric oxide (NO), furthermore, increased serum tumor necrosis factor-alpha (TNF-α), adiponectin, and lipocalin-2. On the other hand, treatment with *C. rotundus* extract significantly showed a protective effect against esfenvalerate by ameliorating levels of antioxidant enzymes, acetylcholine esterase, and inflammatory markers. The present study elicited a prophylactic effect of *C. rotundus* against neural damage induced by esfenvalerate in experimental rats.

Keywords *Cyperus rotundus* L. · Esfenvalerate · Acetylcholine esterase · Adiponectin · Lipocalin-2

Introduction

Cyperus rotundus Lynn known as Nagarmotha is an herb that spreads around the world, especially tropics, subtropics, and temperate regions. It also part of *Cyperaceae* family (Shamkuwar et al. 2012). *C. rotundus* is widely used in alternative medicine around the world to treat multiple diseases. It has been shown to have numerous pharmacological activities that include anti-inflammatory and anti-diabetic properties such as antipyretic, analgesic drugs (Singh et al. 2012b), and it may be also a possible resource of naturalistic antioxidants (Bashir et al. 2012).

Egypt is famous for using herbal medicines since ancient times and these medicinal herbs are still reliable treatment sources among the Bedouins and simple popular societies. Verification and proof of the therapeutic effects of *C. rotundus* will be great, especially as it is a safe, natural, and inexpensive source (Hamed et al. 2012). *C. rotundus* tuber extracts main components present in the tubers are polyphenol, flavonoids, saponin, alkaloids, and glycoside where they inhibit free radicals and thus protect the body from infectious and degenerative diseases (Peerzada et al. 2015). They

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can either stop or prevent generations of reactive oxygen. They can either directly scavenge or prevent generations of reactive oxygen species (ROS) (Sayed et al. 2001).

Pyrethroids inhibit acetylcholinesterase (AChE), affecting both peripheral and central nervous system (CNS). Also, it has non-anticholinesterase impacts, including degeneration of peripheral nerves, immunosuppression, hormonal disturbance, liver damage, alteration in neurotransmitters, and uncontrolled neurobehaviour (Baconi et al. 2013). The basic mechanisms of tissue damage caused by pesticides include enhancement of free radicals and excessive releasing of superoxide radical that increase the hazard of carcinogenesis and massive brain damage (Otitoju et al. 2008). Pyrethroids are types of pyrethrins which are known as derivatives of Chrysanthemum (Soderlund et al. 2002). Pyrethroids are divided into two major categories according to the chemical structure; both types prohibit insects' nervous system (Wang et al. 2006). Type I pyrethroids primarily induce hyper excitement and cramps, while type II generates more complicated side effects, such as epilepsy (Verschoyle and Aldridge 1980). Pyrethroids cause chronic syndromes similar to those of multiple chemical sensitivity including brain and locomotion confusion, degeneration of peripheral nerves, and complete suppression of the immune response (Pascual and Peris 1992). Esfenvalerate (BSI, ISO) is a pyrethroid insecticide used in agricultural and residential purposes, it is known as insecticidal with four active isomers of fenvalerate. It was detected in aquatic environments with toxic consequences in organisms (Wang et al. 2020). Synthetic pyrethroids like cypermethrin act through GABA gated chloride channels (Manna et al. 2005). It is important for living organisms to attenuate the toxicity of ROS through activation of anti-oxidants inside the cells (Güven and Kaya 2005). *C. rotundus* is widely cultivated and used as dietary supplement in the Arabian Peninsula, Spain, east Africa, and many west African countries (Ejoh et al. 2006). It is an upstanding fibrous-rooted permanent plant, 1 to 3 ft. tall and reproduces by rhizomes and seeds (Belewu and Abodunrin 2006). Its fat composition is similar to that of olive plant with 72% unsaturated and 28% saturated fatty acids (Zhang et al. 1996). *C. rotundus* is also rich in phosphorus and potassium (Belewu and Belewu 2007). Extracts of *C. rotundus* used in attenuating progression of cancer, microbial infection, and diarrhea and in treatment of anemia, urinary tract infections, and hypercholesterolemia (Sabiu et al. 2017). Previous reports also revealed *C. rotundus* to be non-toxic, practically safe, and with marked aphrodisiac properties (Oladipipo et al. 2016; Sabiu et al. 2016). Accumulation of pesticides residues and toxic metals in human organisms initiates earnest confrontion to public health; from this light, we aimed to evaluate the impact of *C. rotundus* extract against esfenvalerate induced oxidative stress, neurotoxicity, and inflammation in experimental animals.

Materials and methods

Materials

Chemicals

$ABTS^{\bullet+}$ (2, 2′-azinobis (3-ethylbenzothiazoline- 6-sulfonic acid)), aluminum chloride, BHT: butyl hydroxytoluene, DPPH· (2, 2-diphenyl-1-picrylhydrazyl), Bovine Serum Albumin (BSA),disodium hydrogen phosphate, EDTA (ethylenediaminetetraacetic acid), ferrous and ferric chloride, ferrozine: 3-(2-pyridyl)-5, 6-*bis*-(4-phenol sulfonic acid)-1, 2, 4-triazine, Folin–Ciocalteau reagents, potassium chloride, gallic acid, potassium dihydrogen phosphate, potassium ferricyanide, quercetin, sodium nitrite, sodium carbonate, sodium chloride, trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), and tannic acid were obtained from Sigma Chemical Co.(USA).

Animals

Forty male albino rats weighting (130–170 g) purchased from the toxicology and forensic medicine department, faculty of veterinary medicine, Cairo University. Rats were housed and feed on a standard diet and water freely available. All experiments were done according to the guidance published by national institute of health and ethics committee at Cairo University.

Methods

Tuber material and extract preparation

Preparation and extraction of *C. rotundus* tubers The fine dried powder 500 g of *C. rotundus* tubers was extracted with 1.5 l of solvent mixture (methanol: acetone: H_2O, with ratio 2:2:1, respectively), under shaking using Heidolph Unimax 2010 for 48 h at room temperature (R.T.). Using filter paper (Whatman No.1), the extract was filtered. Residue of plant was extracted two more times using the same solvent mixture. The filtrates were dried at 40 °C under vacuum, dried extract was then disbanded in methanol for further phytochemical and antioxidant analysis and disbanded in distilled water (D.W.) for biological experiment.

Evaluation of total phenolic content Total phenolic (TP) content was evaluated in *C. rotundus* tuber extract as described

previously (Singleton and Rossi 1965). In 25 ml volumetric flask, 1 ml of each fraction was added to 9 ml of D.W., and 1 ml of Folin Ciocalteu phenol reagent was then added to the mixture and shacked for 5 min. After that Na_2CO_3 solution (10 ml of 7% concentration) was added, 25 ml D.W. used for dilution, incubated for 90 min at R.T., the absorbance was read using spectrophotometer (Unicum UV 300) that was set at 750 nm. Sample TP content was evaluated in triplicates and expressed as mg Gallic acid equivalents (GAE)/g extract.

Evaluation of total flavonoid content Total flavonoid (TF) content in *C. rotundus* tuber extract was evaluated according to Zhishen et al. (1999). Briefly, in 10 ml volumetric flask, 1 ml from each of using fraction was mixed with 4 ml D.W. and $NaNO_2$ (300 µl from 5% concentration); after incubation for 5 min, 300 µl from 10% $AlCl_3$ was added. Then, 2 ml of NaOH (1 M) was added and the final volume was completed to 10 ml with D.W. The absorbance was read using spectrophotometer that was set at 510 nm. Samples were evaluated in triplicates and TF was expressed as mg quercetin equivalents (QE)/g extract.

Determination of total tannin content Total tannin (TT) content of *C. rotundus* tuber extract was evaluated according to Polshettiwar et al. (2007). Briefly, 1 ml from each fraction was added to 7.5 ml D.W. Then, 500 µl from folin reagent and 1 ml of sodium carbonate solution (35%) were added; the final volume was then completed with D.W. to reach 10 ml. The absorbance was read against at 775 nm by spectrophotometer. TT was evaluated in triplicate and expressed as mg tannic acid equivalent (TAE)/g extract.

Antioxidant activity

DPPH$^{\bullet}$ radical scavenging assay

The scavenging activity of free radicals was determined (Chu et al. 2000). 0.1 mM DPPH$^{\bullet}$ solution was prepared using methyl alcohol. Five hundred microliters from the prepared solution was then added to different concentrations (50, 100, 150, 200) µg/ml of the extract with shaking, and then incubation for 30 min in dark at room temperature. The absorbance was read at 515 nm against the blank. The scavenging capacity was calculated as follow:

$$\%\text{of scavenging capacity} = ((A_c - A_s/A_c) \times 100).$$

A_c is the absorbance of the control reaction.
A_s is the absorbance of the plant fractions.

Results were expressed as IC_{50} which is the concentration of the plant by µg/ml that scavenges 50% of free radicals.

ABTS$^{\bullet+}$ antioxidant assay

ABTS$^{\bullet+}$ (7.4 mM) was dissolved in D.W. and $K_2S_2O_8$ (2.6 mM) equal volumes of these solutions were mixed, incubated in dark for 12–16 h at R.T. to prepare the working reagent. The solution was diluted (1 ml ABTS$^{\bullet+}$ solution was added to 60 ml methanol); absorbance of 1.1 ± 0.02 at 734 nm was detected using the spectrophotometer (Arnao et al. 2001). One hundred fifty microliters of *C. rotundus* tuber extract from different concentrations (50,100,150,200 µg/ml) were incubated with 2850 µl of ABTS$^{\bullet+}$ solution (freshly prepared) for 120 min in the dark at R.T. The absorbance was detected at 734 nm. Trolox used as a positive control. ABTS$^{\bullet+}$ scavenging activity (%) was calculated as follow:

$$\text{ABTS}^{\bullet+}\text{ scavenging }(\%) = ((A_0 - A_1)/A_0) \times 100.$$

where A_0: ABTS$^{\bullet+}$ absorbance of the control (the entire reaction reagent without sample), and A_1: ABTS$^{\bullet+}$ absorbance in the presence of the sample. The results were expressed as IC_{50} (the concentration (µg/ml) of the plant fraction that scavenges 50% of ABTS$^{\bullet+}$ radical).

Ferrous chelating activity

Ferrous chelating activity was evaluated colorimetrically according to Hsu et al. (2003). *C. rotundus* tuber extract (1 ml) or EDTA solution as a positive control at different concentrations (50, 100, 150, 200 µg/ml) was spiked with 0.1 ml of 2 mM $FeCl_2$-$4H_2O$ and 0.2 ml of 5 mM ferrozine solution and 3.7 ml methanol were mixed in a test tube and incubated for 10 min at R.T. Then, the absorbance was measured at 562 nm. Mixture without fraction was used as the control. A lower absorbance showed a higher ferrous ion chelating capacity. The percentage of ferrous ion chelating ability was calculated as follow:

$$\text{Chelating activity (inhibition\%)} = [(A_c - A_s)/A_c] \times 100.$$

where (A_c): absorbance of the control reaction and (A_s): absorbance in the presence of the plant fractions. The results were expressed as IC_{50} (the concentration (µg/ml) of the *C. murale* fractions that chelate 50% of Fe^{2+} ions).

Reducing power assay

The reducing power was estimated according to previous method (Kuda et al. 2005).Briefly, *C. rotundus* tuber extract (1 ml) from different concentrations (50, 100, 150, 200)µg/ml was mixed with 2.5 ml from 50 mM phosphate buffer (pH = 7.0) and 2.5 ml from potassium ferricyanide (1%). The mixture was then kept for 20 min at 50 °C. 2.5 ml of trichloroacetic acid (10%) was added to the mixture, centrifuged for 10 min at 4000 rpm. After that, equal volumes (1.25 ml) from

D.W and the supernatant were mixed with 1.25 ml of an 0.25 ml from 0.1 $FeCl_3$ solution (*w*/*v*). The absorbance was detected spectrophotometrically at 700 nm.

HPLC for identification and quantitation of phenolic compounds

HPLC system was used for the identification of flavonoid and phenolic compounds as described by Ben-Hammouda et al. (1995). All using chemicals are HPLC grade and purchased from Sigma (St. Louis, USA) and/or Merck, Shcuchrdt Munich, Germany.

Sample preparation

Dried crude (methanol: acetone: H_2O, with ratio 2:2:1) *C. rotundus* tuber extract (10 mg) was dissolved in methanol (2 ml) and shacked with vortex for at least 15 min and filtrated via 0.2 μm Millipore membrane filter.

HPLC system

Agilent 1100 series equipped with diode array detector set at 280 nm. Twenty microliters of sample was injected onto HPLC via auto-sampler. Reversed phase (RP) column (4.6 × 250 mm × 5 μm) was used for separation.

HPLC conditions

Flow rate of 1 ml/min was used. The mobile phases are consist of A and B: (A) acetic acid/water 0.5/99.5 (*v*/v), pH was 2.65; and solvent (B) acetic acid/acetonitrile 0.5/99.5 (v/v) with gradient elution that was linear starting from A to B along 50 min.

Biological analysis

Experimental design

Forty experimental mature rats were randomly divided into four groups; group (I) was the control group; group (II) were rats that received *C.* rotundus extract; group (III) were rats that received esfenvalerate (0.533 mg/kg b.wt) orally for 65 days based on a previous study by Saeed et al. (2007), who stated that esfenvalerate and deltamethrin have similar LC_{50} and Ogaly et al. (2015) who tested deltamethrin induced brain neurotoxicity at a dose of 0.6 mg/kg b.wt. in rats. Group (IV) were rats that received esfenvalerate in a dose level 0.533 mg/kg b.wt beside 1 ml of *C. rotundus* extract via gastric intubation for 65 days.

Tissue sampling

Rats were sacrificed by decapitation. The brain was taken quickly and washed with iced. Phosphate-buffered saline (PBS) pH was adjusted at 7.4, blotted on filter paper, and frozen at − 80 °C until used.

Tissue homogenate

Frozen brain tissues (1 g) was homogenized in 5 ml buffer, and then centrifuged at 4000 rpm for 10 min at 4 °C. The supernatant was then used for the estimation of different biochemical parameters (Manna et al. 2005; Hussein et al. 2017).

Biochemical analysis

Determination of oxidant and anti-oxidant parameters

Brain homogenates were used for the determination of MDA, NO, and GSH as described by Watanabe et al. (2006), Moshage et al. (1995), and Ellman (1959) respectively.

Determination of paraoxonase activity

Brain paraoxonase activity (PON1) was measured according to Haagen and Brock (1992).

Determination of acetylcholinesterase activity

Brain acetylcholinesterase (AChE) activity was determined using colorimetric kinetic assay according to Ellman et al. (1961).

Determination of tumor necrosis factor-alpha

Brain tumor necrosis factor-alpha (TNF-α) were determined by an enzyme-amplified sensitivity immunoassay (EASIA) according to Seriolo et al. (2006). The kits were purchased from Biosource, Belgium.

Determination of adiponectin

Brain adiponectin was assayed by an enzyme-linked immunosorbent assay (ELISA). Adiponectin was assayed according to Watanabe et al. (2006) and the kit was supplied from Orgenium Laboratories, Finland.

Determination of lipocalin-2

Brain lipocalin-2 levels were determined using Lipocalin-2 Quantikine ELISA kit.

Statistical analysis

Data were expressed as mean ± SE. Data were analyzed using one-way ANOVA using SPSS (Version 16). Duncan's new multiple-range test was used to assess differences between means. A significant difference was considered at the level of $P < 0.05$.

Results

Chemical analysis

Amount of total phenolics, flavonoids, and tannins content

In this study, the phenols, flavonoids, and tannins present in the extract of *C. rotundus* tubers were shown in Table 1.

Chemical identification of phenolic compounds by HPLC

The individual phytochemical identification of the *C. rotundus* tuber extract shows the presence of phenols and flavonoids. The chemical separation and separation of the HPLC of the *C. rotundus* tuber extract showed the presence of many phenolic compounds such as ellagic coumarin and caffeic acid, as well as flavonoids such as genistein, quercetin, catechin, and rutin (Table 2).

Antioxidant activities

In the present study, *C. rotundus* tuber extract exhibited 50% scavenging activity against the $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ radicals at amount (224.25 and 191.47 μg/ml, respectively) expressed as IC_{50}. This data was compared with reference compounds, BHT (6.33 μg/ml) and Trolox (7.61 μg/ml), respectively. The formation of the ferrous-ferrozine complex is reduced in presences of the *C. rotundus* tuber extract, indicating its chelating activity with an IC_{50} of 218.77 μg/ml as shown in Table 3. The reducing power of *C. rotundus* tuber extract was very strong. The value of ferric reducing antioxidant ability with a value of 119.88 μg/ml in *C. rotundus* extracts as shown in Table 3. The extract could reduce the most Fe^{3+} ions which had a lesser reductive activity than the synthetic standard BHT (11.20 μg/ml).

Table 1 Phenolic (TP), flavonoid (TF), and tannin (TT) contents of *C. rotundus* tuber extract

Extract	TP mg/g DW	TF mg/g DW	TT mg/g DW
C. rotundus	12.33 ± 0.08	9.44 ± 0.03	2.07 ± 0.05

All values are the mean of three replicates ± SD

Table 2 HPLC profile of polyphenolic compounds of *C. rotundus* tuber extract

No.	Phenolic compounds	Concentration (mg/100 g, DW)
1	Ellagic	2.080
2	Genistein	0.158
3	Quercetin	0.742
4	Coumarin	0.678
5	Catechin	0.496
6	Rutin	1.257
7	Caffiec acid	0.662

Biological analysis

Results of this study showed that animals that treated with esfenvalerate have a significant increase in MDA and NO levels, and a significant decrease in GSH and PON-1 activities compared to the control group. On the other hand, the administration of *C. rotundus* significantly decreased lipid peroxidation and increased anti-oxidant markers as shown in Table 4.

In this study, brain AChE levels were significantly reduced compared to the control group as a result of the treatment with esfenvalerate. Administration of *C. rotundus* along with esfenvalerate showed significant increase in brain Ach esterase activity (Table 5).

Table 6 summarizes the inflammatory response induced by esfenvalerate. Our results suggested that esfenvalerate significantly increased brain TNF-α, adiponectin, and lipocalin-2 (LCN-2) levels compared to the control group. *C. rotundus* significantly ameliorate these levels and became close to the control group.

Discussion

Phytochemical compound phenols, flavonoids, and tannins are some of the most common secondary metabolites in the plant kingdom. This group of secondary compounds is of great interest because it is considered a natural anti-oxidant due of its activity to curb free radicals and its ability to chelate different minerals. The antioxidant activity mainly extends to the phenolic compounds present in the plant that have multiple properties as singlet oxygen quenchers, hydrogen donors, and redox properties (Rice-evans et al. 1995). *C. rotundus* tuber extract contains sufficient quantities of phenols, flavonoids, and tannins, which can have many biological effects. These data are in line with those shown by Kilani-Jaziri et al. (2011); Bashir et al. (2012); Imam et al. (2014); Kamala et al. (2018). Also, many phenolic and flavonoid compounds were detected and specified in the *C. rotundus* tuber extract by

Table 3 Antioxidant activities of *C. rotundus* tuber extract

Antioxidant assays	50 μg/ml	100 μg/ml	150 μg/ml	200 μg/ml	
Inhibition %					IC_{50} μg/ml
$DPPH^{\bullet}$	7.66 ± 0.31	13.35 ± 0.12	25.61 ± 0.20	38.08 ± 0.31	224.25 ± 0.49
BHT standard	59.01 ± 0.12	68.56 ± 0.12	77.30 ± 0.23	89.09 ± 0.12	6.33 ± 0.73
$ABTS^{\bullet+}$	10.68 ± 0.15	22.84 ± 0.23	31.00 ± 0.23	42.42 ± 0.47	191.47 ± 2.29
Trolox standard	51.49 ± 0.11	62.12 ± 0.12	76.27 ± 0.24	90.63 ± 0.18	7.61 ± 0.66
Chelating %					IC_{50} μg/ml
Fe^{2+}-chelating	8.23 ± 0.29	17.72 ± 0.21	26.23 ± 0.28	38.10 ± 0.08	218.77 ± 1.27
EDTA standard	58.78 ± 0.15	71.46 ± 0.22	83.72 ± 0.21	93.48 ± 0.08	9.58 ± 0.34
Reading					EC_{50} μg/ml
Reducing power	0.101 ± 0.001	0.221 ± 0.002	0.311 ± 0.002	0.422 ± 0.001	119.88 ± 0.90
BHT standard	0.435 ± 0.002	0.614 ± 0.003	0.803 ± 0.002	1.015 ± 0.002	11.20 ± 0.33

All values are the mean of three replicates ± SD

HPLC. These results were in accordance with Samariya and Sarin (2013) who stated that flavonoids isolated from *C. rotundus* leaf, root, and callus in vitro and in vivo were considerably utilized in traditional medicine and pharmaceutical industries.

Free radicals are produced during the metabolism of both normal and pathological cell. Oxidation processes are necessary to produce energy for many organisms as fuel for the various different biological processes they perform. External chemicals and internal metabolic processes in the digestive system may produce free radicals that are highly reactive, and have the ability to oxidize various biomolecules, leading to cell apoptosis and tissue injury (Mau et al. 2001), due to the multiplicity of the mechanisms of the compounds involved in the formation of the *C. rotundus* tuber extract as antioxidants. More than one method was chosen ($DPPH^{\bullet}$, $ABTS^{\bullet+}$, Fe-chelating, and educing power) to study their biological effects. We have noticed through our study that the *C. rotundus* tuber extract showed remarkable activity in curbing free radicals, both DPPH and ABTS. Our results agreed with the results presented by Hamed et al. (2012) who suggested that mixture of methylene chloride/methanol ($MeCl_2$/MeOH, 1:1) extract of *C. rotundus* in DPPH scavenging efficiency was 222.2 μg/ml. Also, our results of $ABTS^{\bullet+}$ inhibition rate (42.42%) at 200 μg/ml concentration are consistent with the results obtained from Hamed et al. (2012), which found that the $ABTS^{\bullet+}$ inhibition ratio (37.50%) of tigernut (CR). Through the Fenton reaction, the ferrous ion can begin the process of lipid peroxidation and accelerate the formation of peroxides by dissolving lipid hydroperoxides into both free radicals peroxyl and alkoxyl (Halliwell 1991; Fridovich 1995). Ferrous ion produced complex with ferrozine (red-colored). In the presence of chelating agents, the formation of the complex is reduced, and as a result, the formation of the red color is reduced. Accordingly, the chelating effect of the extracts under study can be determined by measuring the rate of color reduction. It is clear from the results obtained in Table 3 the high potential of the *C. rotundus* tuber extract on iron chelates and impeding the formation of the ferrozine and iron complex.

These results correspond to the results obtained from (Nagulendran et al. 2007). For the evaluations of the reducing power ability, the Fe^{3+} to Fe^{2+} transformation was inspected in the presence of *C. rotundus* tuber extract, where we found that

Table 4 Brain oxidant/antioxidant parameters in all groups

Parameters groups	MDA nmol/g tissue	NO mM/g tissue	GSH U/g tissue	PON-1 μmol/g tissue
Control group	103.4 ± 2.4	3.3 ± 0.3	28.0 ± 2.9	23.6 ± 2.6
C. rotundus group	98.7 ± 7.4 [b]	3.0 ± 0.2[b]	31.3 ± 1.9[b]	28.5 ± 2.6[b]
Esfenvalerate group	172.3 ± 7.7[a]	12.1 ± 0.7[a]	12.5 ± 1.3[a]	10.5 ± 1.3[a]
Treated group	124.3 ± 9.6[b]	7.8 ± 0.6[a,b]	19.5 ± 1.0[a,b]	17.8 ± 1.1[b]

Data presented as mean ± SE

Significant p value < 0.05

[a] Significant difference compared to control group

[b] Significant difference compared to esfenvalerate group

n number of rats = 10.

Table 5 Brain acetylcholinesterase (AChE) in different groups

Parameter groups	AChE (μ mol/SH/g/min)
Control group	750.5 ± 0.2
C. rotundus group	712.5 ± 0.3[b]
Esfenvalerate group	528.3 ± 0.3[a]
Treated group	619.8 ± 1.0[a,b]

Data presented as mean ± SE

Significant p value < 0.05

[a] Significant difference compared to control group

[b] Significant difference compared to esfenvalerate group

n number of rats = 10

the extract had high reductive capabilities. The reducing power of a bioactive compound may serve as a significant index of its potential antioxidant activity. Higher value of absorbance indicated higher reducing power (Sayed et al. 2001). It is clear from the results obtained that the *C. rotundus* tuber extract has a high ability as antioxidant, and this can be due to the presence of phenolic, flavonoids, tannins, and other compounds that have influence mechanisms as antioxidants.

Pyrethroids are widely used insecticides due to their effective influence. However, exposure to high concentration resulting in oxidative damages enhances mitochondrial alteration causing an imbalance between oxidant and antioxidant and neurotoxic effects to human and mammals (Ray 2001). In addition, Hocine et al. (2016) proposed that since disintegration of mitochondrial ATP and Ca^{2+} signaling is the major factors in the evolution of muscle and brain function, the main toxic mechanism of some pesticides intervened by the impairment of both cytoplasmic Ca^{2+} pathway and inducement of mitochondrial ROS.

Our findings showed a marked increase in brain levels of MDA and NO along with a significant decrease in levels of GSH and PON-1. These results are in agreement with the results of Leja-Szpak et al. (2004) who reported that during pythethroid metabolism, degradation of cyanohydrines resulting in formation of cyanides and aldehydes; metabolites that enhance excessive liberation of ROS, increased levels of lipid peroxidation products, and levels of cytosolic calcium which increase the toxic effect (Idris et al. 2012).

In agreement with our suggestions, Shukla et al. (2002) reported that exposure to oxic substances including pesticides induce neurotoxicants modifying the ordinary nervous system activities. Synthetic pyrethroids are considered least toxic and globally account for over 30% of insecticide use (Shukla et al. 2002). In addition, the main pyrethroids neurotoxic propensity mechanism of action is by binding and alteration of the voltage-gated sodium channel balance, resulting in continuous opening of sodium channels. The prolonged exposure to this action potential which destroy locomotor behaviors, severe nervous complications, and consequently death (Soderlund et al. 2002). Esfenvalerate produces its neurotoxicity through the prohibition of AChE and detention of ACh in synaptic gaps and interacts with sodium channels resulting in the production of hyperexcitable conditions (Ray 2001).

Our results showed a significant decrease in brain AChE which is in concordance with previous studies of Singh et al. (2012a) and Wang et al. (2020) who indicated that pyrethroids alters the dopaminergic system via deregulation of neurotransmitter levels and modification of gene expression. Also, Ogaly et al. (2015) and Nieradko-Iwanicka and Borzęcki (2015) reported that pyrethroids enhance the risk of neurodegenerative disorders via inhibition of nerve impulse by altering GABA receptors, nicotinic acetylcholine receptors, glutamate receptors, and suppression of the activity of AChE (16, 17). Gasmi et al. (2017) suggested that the lipophilic nature of pyrethroids enhances the brain toxicity and suppresses the activity of AChE by reducing the acetylcholine binding capacity (Khan et al. 2018).Thus, it is clear that esfenvalerate blocks AChE, fluctuates neurotransmitters, and increases ACh at neuromuscular junctions and the nerve endings (Moustafa et al. 2018).

Romero et al. (2012) showed that pyrethroid metabolites were actually more dangerous than the parent compounds to SHSY5Y neuroblastoma cells. Singh et al. (2016) identified

Table 6 Brain inflammatory markers in different groups

Parameters Groups	TNF-α Pg/g tissue	Adiponectin μg/g tissue	LCN-2 μg/g tissue
Control group	0.03 ± 0.002	3.3 ± 0.2	1.6 ± 0.07
C. rotundus group	0.03[b] ± 0.002	3.3[b] ± 0.2	1.5[b] ± 0.03
Esfenvalerate group	0.09[a] ± 0.005	7.1[a] ± 0.2	2.6[a] ± 0.05
Treated group	0.05[a,b] ± 0.005	5.5[a,b] ± 0.4	2[b] ± 0.10

Data presented as mean ± SE

Significant p value < 0.05

[a] Significant difference compared to control group

[b] Significant difference compared to esfenvalerate group

n number of rats = 10

higher nitrite and lipid peroxide (LPO) levels in the nigrostriatum inducing nigrostriatal dopaminergic neurodegeneration. Pyrethroids inhibit the anti-oxidative activities of brain SOD, CAT, and GPx, and GSH boosting expression of nuclear factor erythroid-2-related factor 2 (Nrf-2) and Nuclear factor kappa B (NF-κB), inducing mitochondrial dysfunction and enhancing apoptotic pathways (Khan et al. 2018).

In addition, Sharma et al. (2014) reported that although esfenvalerate behave as a fast-acting neurotoxin in insects, it usually causes toxicity to the nervous system via continuous alteration of sodium passing through nerve membrane channels causing repetitive nerve impulses which may induce oxidative stress; hence, there is a possibility of excessive generation of ROS.

Recently, it was suggested that adiponectin receptors including AdipoR1, AdipoR2, and T-cadherin stimulating p38-MAPK, PPARa,AMP-activated protein kinase, and NF-κB are commonly expressed in different parts of the brain; thus, AdipoRs is concerned in neurodegenerative process and neurological disease such as multiple sclerosis, epilepsy, and ischemic stroke (Thundyil et al. 2012).

Another interesting protein which is involved in the transport of small hydrophobic molecules, cellular apoptosis, migration, and differentiation is LCN2 (Goetz et al. 2002); thus, it is involved in many diseases (Cruz et al. 2012).

Our results showed that esfenvalerate exposure increased plasma levels of TNF-α, adiponectin, and LCN-2. These results were in the same line with Wennberg et al. (2016) who found that the serum adiponectin is positively correlated to the levels of amyloid. Also, Jin et al. (2014) indicated that LCN2 is involved in brain damage, neuronal cell apoptosis, stimulation of neurotoxic glial, boosting neuro-inflammation, alteration of blood-brain barriers (Jin et al. 2014), and induction of chemokine in CNS (Lee et al. 2009) via binding to brain 24p3R (LCN2 receptor) (Bi et al. 2013).

Dietary nutrients with antioxidant properties are of great significance in the pathogenesis of many disorders related to free radical damage (Owen et al. 2000). Therefore, the research regarding the use of the antioxidant-rich ingredients in food production takes a special interest.

This study evaluated the effect of *C. rotundus* extract against neurotoxicity induced by esfenvalerate in experimental rats.

Anti-oxidants (enzymatic or nonenzymatic) are the defense line against ROS; it promotes the chain reactions before critical damages occurred (Al-Omar et al. 2004).

In this study, oral administration of *C. rotundus* extract caused enhancement of GSH, PON-1, and brain AChE activities besides reducing TNF- α, adiponectin, and lipocalin-1. These results indicated that C. rotundus extract acts to attenuate the oxidative stress, neurotoxicity, and inflammation due to its high content of phytochemical compounds including saponin, flavones, tannins, and terpenes in addition to unsaturated fatty acids (Kilani et al. 2005a; Kilani et al. 2005b).

Previous studies supported *C. rotundus* extract as a treatment of gastrointestinal, inflammatory, and infectious diseases mainly due to their powerful antioxidant characteristics (Bahi and Necib 2014).

Seo et al. (2001) reported that GSH has a marked effect in scavenging free radicals. Thus, prohibiting antioxidant activities accumulate H_2O_2 and lipid peroxidation products. In this regard, it was found that *C. rotundus* extract flavonoids are able to prevent releasing of oxidants, suppress inducible nitric oxide synthase (iNOS) mRNA expression, and conserve the cell membrane integrity (Zommara and Imaizumi 2017).

Hussein et al. (2011) and Hussein et al. (2016) recommend dietary unsaturated fatty acids and phenolic compounds to play a role in protecting risk against inflammation in many diseases including diabetes and hepatitis. The alcoholic extract of *C. rotundus* not only proved anti-oxidant properties but also marked anti-inflammatory response against proliferative stages of inflammation in experimental studies (Saarbrücken 2010).

Conclusion

Oxidative stress and inflammation are involved in esfenvalerate neurotoxicity. Treatment with *C. rotundus* attenuated inflammatory response, oxidative stress, and protection against neural damage induced by esfenvalerate due to its high contents of phenolic compounds.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical clearance Prior ethical clearance for experimentation was approved by the National Research Centre (NRC), Giza, Egypt. In all the experimentation, the ethical care and treatment of the animals were conducted as per the guidelines laid down and following the regulations of the ethical committee of NRC.

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