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The pyrethroid insecticide permethrin confers hepatotoxicity through DNA damage and mitochondria-associated apoptosis induction in rat: Palliative benefits of *Fumaria officinalis*

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Abstract

Permethrin (PER) is a pyrethroid pesticide that is extensively used as an insecticide in world because of its high activity and its low mammalian toxicity. The current study was conducted to investigate the protective action of *Fumaria officinalis* against PER-induced liver injury in male rats. However, HPLC-DAD showed the richness of 6 components in *F. officinalis* (F) including quercetin, ferulic acid, and naringenin which were the most abundant. Total polyphenols, total flavonoids, and condensed tannins were studied by phytochemical screening. In vitro, antioxidant properties showed that *F. officinalis* exhibited the highest DPPH radical, FRAP, and H_2O_2 tests and total antioxidant capacity. Wistar rats were divided into four groups: negative control group (C), positive control group (F) (200 mg *F. officinalis*/kg BW), PER group (34.05 mg permethrin/kg BW), and PER + F group (34.05 mg permethrin/kg BW and 200 mg *F. officinalis*/kg BW). Oral administration of PER led to promote a decrease of body weight and Ca^{2+}-ATPases and Mg^{2+}-ATPases activities and an increase of plasma C-reactive protein level, transaminases, and hepatic ϒ-GT activities as well as hepatic and mitochondrial oxidative stress. An increase in plasma lactate-to pyruvate ratio and a reduction in complexes enzymes I, III, and IV activities were also observed. In addition, histoarchitecture of liver in PER-treated rats showed apoptosis and necrosis as confirmed by DNA fragmentation. *F. officinalis* significantly exerted hepatoprotective effect by modulating hepatic alteration and mitochondrial dysfunction as well as genotoxicity. This effect could be attributed to phenolics compounds such as polyphenols, condensed tannins, and flavonoids.

KEYWORDS

DNA fragmentation, *Fumaria officinalis*, liver, mitochondria, permethrin

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1 | INTRODUCTION

Xenobiotics-like insecticides poisoning induced a high percentage of mortality and morbidity in several countries.[1] Pyrethroids are the synthetic derivatives of natural pyrethrins from the plant *Chrysanthemum cinerariaefoliun*. They are divided into types I and II, depending on the structure of the compound, its action, and symptoms. Type I pyrethroids can cause hyperexcitation, ataxia, and paralysis, while type II pyrethroids provoke hypersensitivity, salivation, and choreoathetosis.[2] Permethrin (PER) is a synthetic type I pyrethroid widely used in different forms in the textile industry, agricultural and public health.[3,4] The main mechanism of PER action is through interference with sodium channels, receptor-ionophore complexes, and neurotransmitters.[5] Some studies have reported that PER increases the risk of severe toxicity like neurotoxicity, genotoxicity, fetotoxicity, cytotoxicity, and hepatotoxicity.[6–9] The generation of reactive oxygen species (ROS) and nitrogen species (NS) is one of the possible mechanisms responsible for PER toxicity through oxidative stress injury, suppression of the antioxidant defense system, and biomolecules damage such as lipids, proteins, DNA.[10] Under normal conditions, body neutralized the oxidative stress by the antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH).[11] Indeed, the liver is the central organ that controls homeostasis. It is a main site of permethrin metabolism and the major target of greater accumulation of metabolites.[12] These perturbations could alter the structure and function of the biological cell.[13] In fact, a direct association between mitochondrial dysfunction and PER toxicity has been demonstrated.[8] Based on both clinical and animal evidence in vitro and in vivo, inhibitory effects have been described for Ca^{2+} channels, ATPases, and complex activities.[6,14] These mitochondrial alterations may be crucial in many aspects of PER hepatotoxicity.

Natural and herbal products have been used in traditional medicine to treat a variety of diseases including hepatotoxicity.[15] Among medicinal plants, *Fumaria officinalis*, known as Fumitory, is one of the medicinal species belonging to the genus Fumaria. This plant is well used for the treatment of different diseases such as laxative, diuretic, choleretic, antispasmodic, chronic eczema, antileprotic, and blood purification activity.[16] These pharmacological properties may be attributed to its high content of polyphenols and flavonoids.[15] Antioxidants have been used as the important protective agents for human health against oxidative stress, currently applied in foods, cosmetics, and pharmacy. To our knowledge, no studies have been conducted to evaluate the in vivo effects of *F. officinalis* against pesticide so far. For this reason, in the current study, we have evaluated the protective effect of *F. officinalis* against hepatic injury and mitochondria dysfunction induced by permethrin. Therefore, we have analyzed oxidative stress in the liver and mitochondria, DNA damage, and histological alterations in the liver in rats.

2 | MATERIALS AND METHODS

2.1 | Materials and reagents

Permethrin (Y0001733) was purchased from Protagri Company. All the other chemicals were of the analytical grade. *F. officinalis* from Parachimic Laboratory (Tunisia) (HEMF001003) specie was used for therapy.

2.2 | Methods

2.2.1 | In vitro studies

Preparation of F. officinalis *extract*

An ethanolic extract of *F. officinalis* was obtained after grinding the *F. officinalis* microspheres using a mortar with 8 ml of ethanol (1.07017) and 2 ml of dimethyl sulfoxide (DMSO) (472301) to obtain 0.25 ml g^{-1}. After centrifugation (EBA 270) at ×4000 *g* for 10 min, the supernatant (crude extract) was kept overnight in a refrigerator.

2.2.2 | Characterization of *F. officinalis* extract

Determination of total polyphenols content

The total polyphenols content was measured according to the Folin-Ciocalteu reagent method of Stintzing et al. (2005)[17] with some modifications. 1 ml of Folin Ciocalteu reagent (F9252) diluted 10 times was mixed with 200 µl of sample for 3 min. Then, 0.8 ml 7.5% Na_2CO_3 (20256-U) was added in a test tube, and the contents were mixed and allowed to stand for 30 min. Absorption at 760 nm was measured in a Shimadzu 300 UV-vis spectrometer (Shimadzu UV-1601) against the blank sample. The results were expressed in mg gallic acid equivalent (GAE)(PHL89198) per gram of extract, occurring within the range of 0.02–0.10 mg used as a standard.

Determination of total flavonoids content

Total flavonoids content was determined spectrophotometry by the method described by Zhishen et al.[18] with some modifications. The sample was mixed with 1 ml of distilled water adding 75 µl of 5% $NaNO_2$ (237213). Five minutes after, 75 µl of 10% $AlCl_3$ (237051) was added in a test tube. Then, 6 min after, 500 µl of 1 M NaOH (72068) was added, and the total was made up to 2.5 ml with distilled water. The absorbance of the mixtures was measured at 510 nm and total flavonoid content was calculated as quercetin (PHR 1488) equivalent from a calibration curve of quercetin.

Determination of condensed tannins

The quantification of condensed tannins was determined by the vanillin method as described by Sun et al.[19] Five milliliters of vanillin reagent (4% vanillin [123-33-5] and 8% HCL [320331] in ethanol) were added to 1 ml of the different concentrations. This reaction was

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then kept in the dark for 20 min at 20°C. The absorbance was measured at 500 nm. The results were obtained in mg of catechin (154234) equivalent per g of dry weight (m CE/g DW).

HPLC-DAD analysis of F. officinalis extract

The identification of phenolic compounds of *F. officinalis* ethanolic extract was carried out using HPLC system (consisting of a vacuum degasser, an autosampler, and binary pump with a maximum pressure of 400 bar, Agilent Technologies) equipped with a reversed-phase C18 analytical column of 4.6 × 100 mm and 3.5 µm particle size (Zorbax Eclipse XDB C18). The DAD detector was set to a scanning range of 200–400 nm. The column temperature was incubated at 25°C. The injected sample volume was 2 µl and the flow rate of mobile phase was 0.4 ml/min. Mobile phase B was milli-Q water consisting of 0.1% formic acid (F0507) and mobile phase A was methanol (179337). The optimized gradient elution was illustrated as follows: 0–5 min, 10%–20% A; 5–10 min, 20%–30% A; 10–15 min, 30%–50% A; 15–20 min, 50%–70% A; 20–25 min, 70%–90% A; 25–30 min, 90%–50% A; 30–35 min, return to initial conditions. Identification analysis rests on the comparison of their retention times with those obtained from the extract. For the quantitative analysis, a calibration curve was obtained by plotting the peak area against different concentrations for each identified compound at 280 nm.

Biological activities of F. officinalis extract

DPPH assay. The assay was performed according to Hou et al.[20] with minor modifications. One milliliter of the sample with different concentrations was mixed with 1ml of 0.025 g/ml DPPH (D9132) for 30 min under light protection at room temperature. The absorbance was recorded at 517 nm. Ethanol was used as a blank and vitamin C (A5960) was used as a positive control. The scavenging activity of DPPH radicals (%) was calculated as indicated in the following equation.

$$PI\ (\%) = (1\text{-}[A1/A0]) \times 100 \quad (1)$$

where A0 is the absorbance of the control (distilled water instead of sample solution) and A1 is the absorbance of the sample.

Ferric reducing antioxidant power (FRAP) assay

The assay was performed according to the method described by Oyaizu[21] with some modifications. Different concentrations of the sample were mixed with 2.5 ml phosphate buffer (P5244) (0.2 M, pH 6.6) and 2.5 ml 1% potassium ferric-cyanide (K3Fe (CN)6) (702587). This assay was incubated at 50°C for 20 min. After the incubation period, 2.5 ml of 10% trichloroacetic acid (T6399) was added and the mixture was vortexed. Following centrifugation at 3000 rpm for 10 min, 2.5 ml of the supernatant was mixed with 2.5 ml of distilled water and 0.5 ml of 0.1% $FeCL_3$ (157740). Then, ascorbic acid was used as a positive control as well, and the absorbance was measured at 700 nm. The percentage inhibition of the sample was calculated with the equation (Equation 1).

Evaluation of total antioxidant capacity

Total antioxidant capacity of the samples was measured according to Prieto et al.[22] with some modifications. To obtain dilutions, different concentrations of the sample were prepared in ethanol where each concentration (100 µl) was combined with 1 ml of reagent solution (4 mM ammonium molybdate (277908), 28 mM phosphate buffer and 0.6 mM of H_2SO_4 (258105). The tubes were capped and incubated in a thermal block at 95°C for 90 min. After cooling, the absorbance of each solution was recorded at 695 nm against a blank. However, the negative control contained 1 ml of reagent solution and 100 µl of distilled water, then was incubated under the same conditions as the rest of the samples. Total antioxidant capacity is expressed in mg GAE, which was used as a standard at different concentrations.

Scavenging hydrogen peroxide assay

The hydrogen peroxide scavenging activity was assessed according to the method of Ruch, et al.[23] with minor modifications. To improve effectiveness, the solution of 10 mM H_2O_2 (H1009) was prepared in phosphate buffer (pH 7.4). The mixture contained 10 mM H_2O_2 for different concentrations of the sample. The absorbance of this reaction was measured at 240 nm for 0 and 60 min. Ascorbic acid was used as a standard. The percentage scavenging of H_2O_2 was calculated with equation (Equation 1).

2.2.3 | In vivo studies

Animals and treatment

Male albino Wistar rats weighing at their reception 180 ± 7 g and aged 8 weeks were purchased from the Central Pharmacy in Tunisia (SIPHAT). The animals were housed at room temperature (25°C) with 12 h light/dark cycle and a minimum relative humidity of 50%–60%. They had free access to commercial pellet diet (SNA) and drinking water. Experiments were conducted according to the Ethical Committee Guidelines for the care and use of laboratory animals at Sciences Faculty of Sfax, Tunisia.

Twenty-four rats were randomly divided into four groups of six animals each ($n = 6$) (Figure1).

Control group (C): served as a negative control, received every day corn oil by gavage at the dose of 2 ml/kg BW.

F. officinalis group (F): served as a positive control, rats received by gavage *F. officinalis* extract at a dose of 200 mg/kg and corn oil at a dose of 2 ml/kg BW.[24]

Permethrin group (PER): rats received daily by gavage a dose of 34.05 mg/kg BW of permethrin (corresponding to 1/50 of LD_{50}) dissolved in corn oil.[25]

PER + F group: rats received daily permethrin by gavage at the same dose than PER and group *F. officinalis* at the same dose than F group.

Body weight and food consumption were monitored every day for 7 days. At the end of the experimental period, rats were killed by cervical decapitation to avoid any stress.

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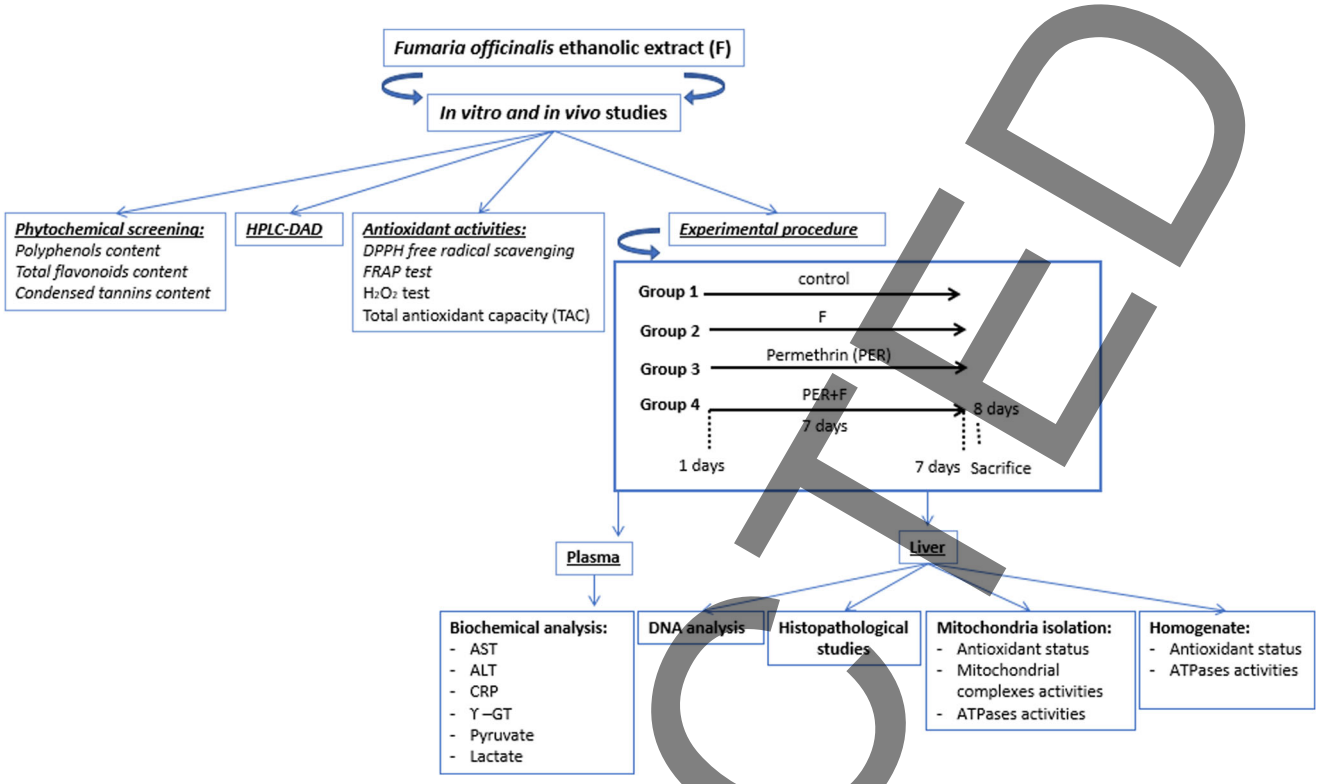


FIGURE 1 Schematic illustration in vitro and in vivo studies.

Blood, collected into heparined tubes, was centrifugated at 3000 g for 15 min for collection of plasma and frozen at −80°C. Livers were quickly excised, rinsed with ice saline solution (0.9%) (P3813), and weighed. Some liver samples were used for mitochondria isolation, the other ones for biochemical analysis. Other portions for histological studies and for qualitative assay of DNA by agarose gel electrophoresis.

Hepatic homogenates were prepared using 1 g of liver which was homogenized with Tris-buffered saline solution (TBS, pH 7.4) using an Ultra Turrax homogenizer (T25, Germany) (Z732346) and centrifuged at 9000 g (4°C, 20 min). The supernatant was collected and frozen at −20°C until biochemical analysis.

Liver mitochondria were isolated from the differential centrifugation procedure according to Hoppel et al.[26] In brief, liver slices of 1 g were homogenized using a Potter-Elvehjem homogenized (T0566) with a loose-fitting Teflon pestle. Nuclei and cells debris were removed by centrifugation at 600 g for 10 min at 4°C. Mitochondria were separated by centrifugation of supernatant at 7000 g for 10 min at 4°C. Mitochondrial pellet was washed with 2 ml of isolation buffer (100 mM-saccharose [107687], 50 mM KCl [60142], 50 mM Tris [GE17-1321-01], and 5 mM EDTA [E9884], pH 7.4) by resuspension and centrifugation at 3500 g for 10 min at 4°C. Finally, the mitochondria were stored in ice-cold at −80°C.

Biochemical analysis

Aspartate aminotransferase (AST, 7D81-21,304410/R1) and alanine aminotransaminase (ALT, 7D56, 304663/R02) activities, C-reactive protein (CRP, ab99995), Ɣ-Glutamyl transpeptidase (Ɣ -GT, 20021), lactate (ref K627-100), and pyruvate (K609-100) levels were scored spectrophotometrically using commercial diagnostics kits according to manufacturer's recommendations (Abbott Park, Architect/Aeroset).

Protein quantification

Protein content was determined using the method of Lowry et al.[27]

Assessment of the pro-oxidant and antioxidant status in liver and mitochondria

Estimation of thiobarbituric acid reactive substances (TBARS) level. Lipid peroxidation in hepatic and mitochondrial homogenates was estimated colorimetrically at 532 nm as described by Esterbauer and Cheeseman.[28] The amount of TBARS level was calculated and expressed by using an extinction coefficient of 156.105 mM^{-1} cm^{-1} of MDA-TBA adduct.

Estimation of protein carbonyl (PCO) level. Protein carbonyl (PCO) level was measured spectrophotometrically at 370 nm according to the method of Reznick and Packer.[29] Result was expressed as µmoles/mg of protein.

Estimation of protein oxidation products (AOPP) level. AOPP levels were estimated using the spectrophotometrically method described by Witko and Nguyen.[30] Absorbance was measured at 340 nm and expressed as µmol/mg protein.

Nitrite oxide. Nitrite oxide (NO) in hepatic and mitochondrial homogenates was assayed colorimetrically following the stable product NO as described by Green et al.[31] The reaction mixture containing equal volumes of homogenates tissues and Griess reagent

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(1% sulfanilamide [33626] reacted in 5% H_3PO_4 [345245]). 0.1% naphthyl-ethylenediamine (N9125) was added and the absorbance was read at 540 nm using $NaNO_2$ (S2252) as standard. Data were expressed as nmol/mg protein.

Antioxidant activities

Superoxide dismutase (SOD) activity was assayed by the method described by Asada et al.[32] Absorbance was measured at 580 nm. Units of SOD activity were expressed as U SOD/mg protein.

Catalase (CAT) activity was estimated using a spectrophotometric method according to Aebi,[33] following the decomposition rate of hydrogen peroxide at 240 nm. CAT activity was calculated in terms of µmol H_2O_2/mg of protein.

Glutathione peroxidase (GPx) activity was measured according to Flohé and Günzler.[34] The absorbance was measured at 340 nm and defined as µmol of GSH/mg protein.

Estimation of GSH, nonprotein bound (NPSH) thiol group, and vitamin C levels

The nonenzymatic level of glutathione (GSH) was determined using the protocol described by Ellman[35] modified by Jollow et al.[36] Absorbance was monitored at 412 nm. Results were expressed as µmol/mg protein.

Nonprotein bound (NPSH) thiol groups were determined according to the method of Sedlak and Lindsay.[37] The reaction mixture was measured at 540 nm and results were expressed as µmol/mg protein.

Ascorbic acid (vitamin C) concentrations were estimated spectrophotometrically by following the developed color of DNPH (dinitrophenylhydrazine) (152803) and sulfuric acid as performed by Jagota and Dani.[38] Data were expressed as ng ml^{-1}.

Mitochondrial enzyme activities determination

Complex I (NADH ubiquinone reductase) activity was measured spectrophotometrically at 37°C in hepatic mitochondria by monitoring the oxidation of NADH at 340 nm as described by Malgat et al.[39]

Complex III (Ubiquinol-cytochrome *C* reductase) activity was determined by monitoring the reduction of cytochrome c at 550 nm using the method of Malgat et al.[39]

Complex IV (Cytochrome *C* oxidase) activity was measured by evaluating the oxidation of reduced cytochrome C as used by Malgat et al.[39] with some modifications. Eighty micrometers solution of reduced cytochrome *C* (C3483) in 50 mM KH_2PO_4 (P5379) (pH 7) was preincubated for 3 min at 37°C. The reaction was initiated by adding the 20 µg homogenate and the absorbance was read at 550 nm for 1 min.

Estimation of Ca^{2+} and Mg^{2+} ATPase activities

Ca^{2+} and Mg^{2+} ATPases activities in liver and mitochondria were measured spectrophotometrically using the methods of Hejrken and Pan[40] and Ohinishi et al.[41]

Histopathological studies

Liver tissue was fixed in bouin solution (HT101128) for 48 h, embedded in paraffin (107150), cut (4–6 µm), and then stained with hematoxylin (GHS316)-eosin (HT110116) solution (H&E) and examined under light microscopy at ×400 magnification.

Qualitative assay of DNA fragmentation by agarose gel electrophoresis

Total genomic DNA was isolated from 50 mg of liver tissues using the method described by Kanno et al.[42] Then, 5 µl of RNase A (RNASEA-RO) at 20 mg ml^{-1} were added and incubated for 15 min allowing degrade all cellular RNAs. The DNA was evaluated and then analyzed by electrophoresis on agarose gel. The quality and quantity of DNA were assayed spectrophotometrically at 260/280 nm. Migration time was one hour at 100 mV. After observation under UVP BIODOC-ITTM system, the profiles of different samples were compared.

2.3 | Statistical analysis

All values were expressed as means ± standard deviation. One-way analysis of variance was used from multiple comparisons using SPSS for Windows (vers. 18). Differences were significant considered at $p < 0.05$.

3 | RESULTS

3.1 | Phytochemicals analysis

The total polyphenols content of *F. officinalis* was found 41.48 ± 0.24 mg GAE per g dry weight followed by the total flavonoids and condensed tannins content of 27.26 ± 0.64 mg QE/g DW and 14.44 ± 0.3 mg CE/g DW, respectively.

3.2 | Identification of phenolic compounds in *F. officinalis*

Figure 2 and Table 1 exhibited the HPLC identification of the major phenolics compounds of *F. officinalis*. A total of six monomeric phenolics were explored, including two flavonols (quercetin and kaempferol), one flavanone (naringenin), and three hydroxycinnamic (caffeic acid, rosmarinic acid, and ferulic acid). Naringenin, quercetin, and ferulic acid are the major components found in this extract.

3.3 | Antioxidant activities

The *F. officinalis* extract exhibited a remarkable antioxidant activity. Thus, 50% of scavenging concentration on DPPH radical (0.02 ± 0.001), FRAP (0.01 ± 0.00), and H_2O_2 (0.14 ± 0.00) were higher than those of vitamin C (IC_{50} = 0.014 ± 0.00, 0.01 ± 0.00 and 0.02 ± 0.00 mg/ml, respectively). The total antioxidant capacity of *F. officinalis* extract indicated a greater scavenging activity with 258.79 ± 8.59 mg GAE/g dry weight. Data are repeated three times.

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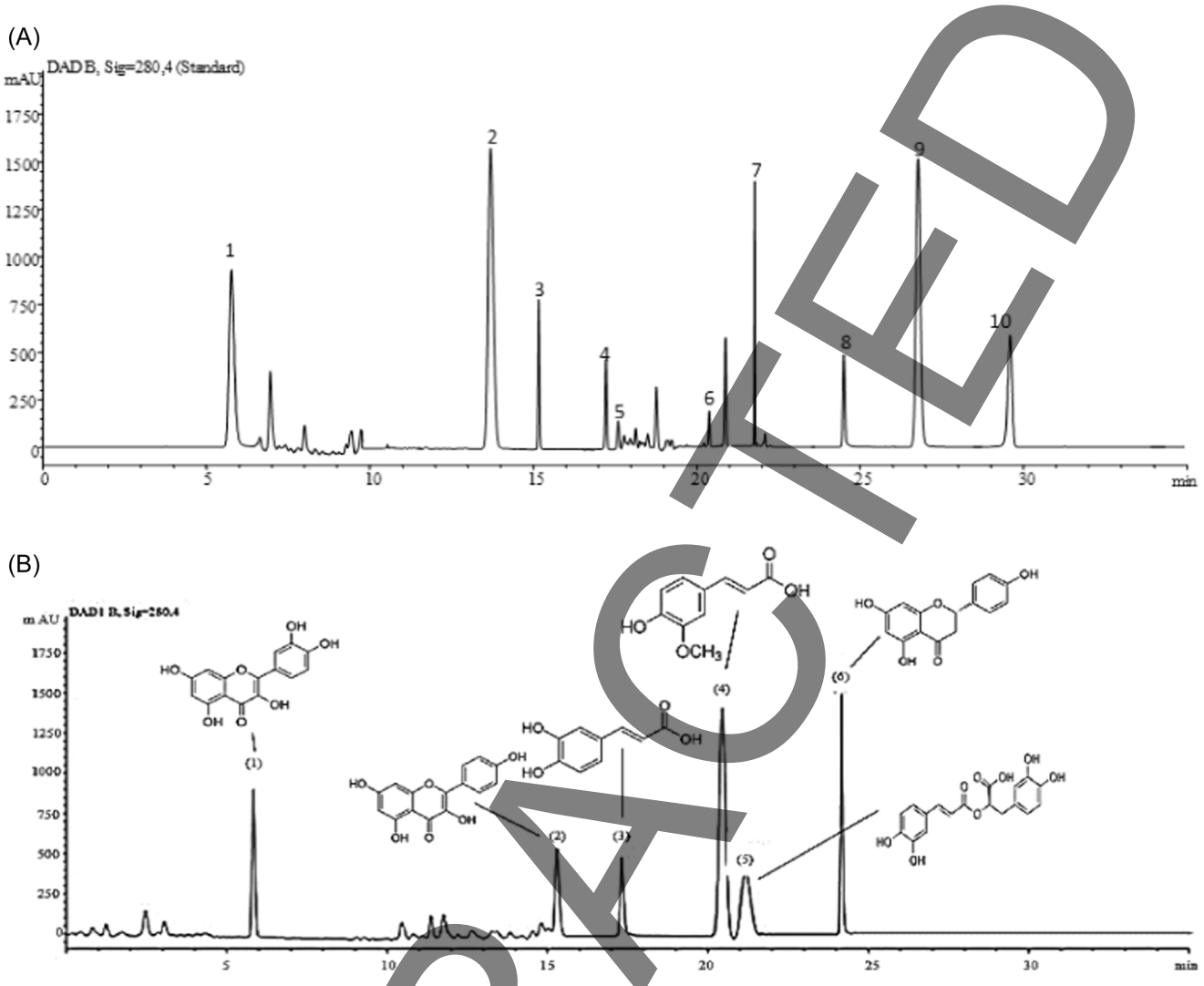


FIGURE 2 Chromatographic profiles acquired at 280 nm of the standard mixture (A) and *Fumaria officinalis* (B). The identified compounds were: (1) quercetin; (2) Kaempferol; (3) caffeic acid; (4) ferulic acid; (5) rosmarinic acid; (6) naringenin.

3.4 | Effects of permethrin on food intake, body, absolute, and relative liver weights

Food intake and body weight were decreased, while absolute and relative liver weights were significantly increased in PER-treated rats as compared to controls groups (Table 2). However, administration of *F. officinalis* to PER-treated rats improved body and liver weights when compared to those of PER group.

3.5 | Biochemical evaluation

The effects of PER, F, and their combination on some biochemical parameters in plasma and liver tissues were represented in Table 3. Results indicated that PER caused a significant reduction in hepatic AST and ALT activities and CRP level with a significant increase of YGT activity as compared to control groups. In addition, plasma transaminase activities and CRP level were increased in PER group. Cotreatment of PER with *F. officinalis* restored these parameters (Table 3).

TABLE 1 Identification of phenolic compounds present in the chromatogram of *Fumaria officinalis*

N° peak	Identification	Concentration (mg/g extract)
1	Quercetin	4.23
2	Kaempferol	3.05
3	Caffeic acid	2.87
4	Ferulic acid	5.14
5	Rosmarinic acid	2.17
6	Naringenin	5.78

Our results showed in PER-treated rats that plasma lactate level and lactate to pyruvate ratio were significantly increased, while pyruvate level was decreased when compared to normal values (Table 3). Coadministration of *F. officinalis* in PER-treated rats induced a significant reduction in lactate decomposition associated with the rise in pyruvate level compared with permethrin group.

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TABLE 2 Food intake, body, absolute, and relative liver weights

Group	C	F	PER	PER + F
Food intake[a]	17.51 ± 2.47	19.00 ± 3.80	13.70 ± 1.04**	21.56 ± 4.31*,###
Body weight[b]	213.32 ± 3.80	213.00 ± 3.84	163.90 ± 8.73***	203.00 ± 1.73*,###
Absolute liver weight[b]	4.85 ± 0.27	4.17 ± 0.51	6.72 ± 0.75***	5.12 ± 1.35*,#
Relative liver weight[c]	2.22 ± 0.41	1.95 ± 0.06	4.10 ± 0.98**	2.52 ± 0.26*,#

Note: Values are mean ± standard deviation, $n = 6$ determinants. PER and PER + FOP treated group versus control group: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$; PER + F group versus PER group: $^{\#}p < 0.05$ and $^{\#\#\#}p < 0.001$.

[a]g/day/rat.

[b]g.

[c]%.

TABLE 3 Effects of permethrin (PER), *Fumaria officinalis* extract (F), and their combination (PER + F) on biochemical parameters in liver and plasma (ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ϒ-GT, Gamma-glutamyl transpeptidase) and on plasma lactate, pyruvate, and lactate to pyruvate ratio in rats of different groups after 7 days of treatment

Parameters	C	F	PER	PER + F
Liver				
ALT[a]	31,867.02 ± 1320.32	31,309.00 ± 3401.96	20,434.01 ± 3156.66***	24,833.33 ± 866.67**,#
AST[a]	4201.96 ± 200.00	4532.50 ± 790.86	2823.33 ± 411.66***	3877.46 ± 177.46*,###
ϒ-GT[a]	11.65 ± 2.03	8.00 ± 6.00	26.00 ± 7.00***	20.00 ± 5.132**,##
CRP[b]	4.76 ± 0.09	4.06 ± 0.93	2.40 ± 0.60***	2.93 ± 0.73**,#
Plasma				
ALT[a]	63.33 ± 9.20	82.33 ± 6.33	104.16 ± 0.92***	95.03 ± 8.03**,##
AST[a]	192.40 ± 15.00	143.53 ± 0.23	268.86 ± 5.56***	219.45 ± 27.23*,##
CRP[b]	0.90 ± 0.02	0.92 ± 0.06	2.36 ± 0.06***	1.83 ± 1.18**,#
Lactate[c]	1.62 ± 0.00	1.89 ± 0.00	2.11 ± 0.03***	1.97 ± 0.17*,##
Pyruvate[c]	0.18 ± 0.03	0.17 ± 0.00	0.16 ± 0.01***	0.17 ± 0.00**,#
Lactate to pyruvate ratio	9.35 ± 2.07	10.98 ± 0.06	12.51 ± 1.15***	11.31 ± 1.19*,##

Note: Values are means ± standard deviation, $n = 6$. PER and PER + F treated group versus control group: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; PER + F group versus PER group: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$.

[a]U/L.

[b]g/L.

[c]mmol/L.

3.6 | Effect of permethrin on oxidative stress biomarkers in liver and mitochondria

After exposure to PER, hepatic and mitochondrial TBARS, PCO, AOPP, and nitrite formation levels were significantly increased in comparison to the normal values (Table 4). When NPSH and ascorbic acid (vit C) concentrations were significantly reduced as compared with control group (Table 5).

Hepatic and mitochondrial CAT and GPx activities and GSH levels were significantly increased in PER-treated rats as compared to control rats (Table 5). Hepatic SOD activity was also increased, while mitochondrial SOD activity was reduced after PER treatment when compared to control group. However, coadministration of *F. officinalis* to PER group restored significantly the oxidative biomarkers when compared to PER group.

3.7 | Effects of permethrin on mitochondrial enzyme activities

Changes in mitochondrial enzyme activities of all treated groups were indicated in Figure 3. In fact, PER induced a significant reduction in NADH-ubiquinone reductase (Complex I), Ubiquinol-cytochrome C reductase (Complex III), and Cytochrome C oxidase (Complex IV) activities (−157.14%, −69.61%, and −133.33%, respectively) compared to normal group. coadministration of *F. officinalis* to PER group restored these mitochondrial enzyme activities.

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TABLE 4 Thiobarbituric acid reactive substances (TBARS), protein carbonyl (PCO), protein oxidation products (AOPP), and nitrite oxide (NO) levels in liver and mitochondria in rats of different groups after 7 days of treatment

	Test groups			
	C	F	PER	PER + F
Liver				
TBARS[a]	0.06 ± 0.01	0.09 ± 0.01	1.21 ± 0.05***	0.32 ± 0.01*,###
PCO[b]	0.24 ± 0.06	0.28 ± 0.02	1.04 ± 0.02***	0.79 ± 0.01**,#
AOPP[c]	1.52 ± 0.38	1.14 ± 0.28	2.22 ± 0.55***	1.21 ± 0.30##
NO[d]	1.72 ± 0.07	1.67 ± 0.05	2.17 ± 0.03***	1.84 ± 0.04*,##
Mitochondria				
TBARS[a]	0.45 ± 0.08	0.48 ± 0.03	1.33 ± 0.07***	0.61 ± 0.04**,##
PCO[b]	0.61 ± 0.02	0.62 ± 0.03	0.81 ± 0.02***	0.71 ± 0.01#
AOPP[c]	0.22 ± 0.05	0.34 ± 0.08	1.21 ± 0.30***	0.69 ± 0.17*,###
NO[d]	1.23 ± 0.08	1.12 ± 0.25	1.77 ± 0.02***	1.47 ± 0.03*,##

Note: Values are means ± standard deviation, $n = 6$. PER and PER + F treated group versus control group: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; PER + F group versus PER group: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$.

[a]nmol/mg protein.

[b]μmol/mg protein.

[c]μmol/mg protein.

[d]nmol/mg protein.

TABLE 5 Catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) activities and glutathione (GSH) level in liver and mitochondria after 7 days of treatment

	Test groups			
	C	F	PER	PER + F
Liver				
SOD[a]	137.05 ± 12.44	154.51 ± 14.59	926.13 ± 20.87***	176.04 ± 15.79*,###
CAT[b]	460.76 ± 97.02	314.57 ± 21.16	2135.71 ± 187.72***	1097.32 ± 46.87**,##
GPx[c]	0.06 ± 0.01	0.05 ± 0.01	0.25 ± 0.04***	0.06 ± 0.01###
GSH[d]	288.03 ± 48.55	306.78 ± 54.62	388.93 ± 3.53***	328.820 ± 10.27*,###
NPSH[e]	0.11 ± 0.03	0.10 ± 0.02	0.09 ± 0.01***	0.09 ± 0.01*,#
Vit C[f]	0.22 ± 0.01	0.13 ± 0.01	0.06 ± 0.01***	0.12 ± 0.03**,##
Mitochondria				
SOD[a]	49.81 ± 2.18	31.46 ± 2.52	20.21 ± 15.51***	30.35 ± 5.78*,##
CAT[b]	281.67 ± 17.59	287.08 ± 44.39	494.54 ± 437.51***	290.01 ± 83.99###
GPx[c]	0.04 ± 0.01	0.03 ± 0.01	0.14 ± 0.05***	0.07 ± 0.01*,##
GSH[d]	91.86 ± 4.41	80.63 ± 0.26	141.28 ± 4.55***	91.45 ± 9.59###
NPSH[e]	0.13 ± 0.02	0.12 ± 0.03	0.12 ± 0.07***	0.12 ± 0.03*,#
Vit C[f]	0.87 ± 0.01	1.27 ± 0.04	0.57 ± 0.17***	0.93 ± 0.02*,##

[a]U/mg protein.

[b]μmol of H_2O_2/mg protein.

[c]nmol of GSH oxidized/mg protein.

[d]μmol/mg protein.

[e]μmol/mg protein.

[f]ng/ml.

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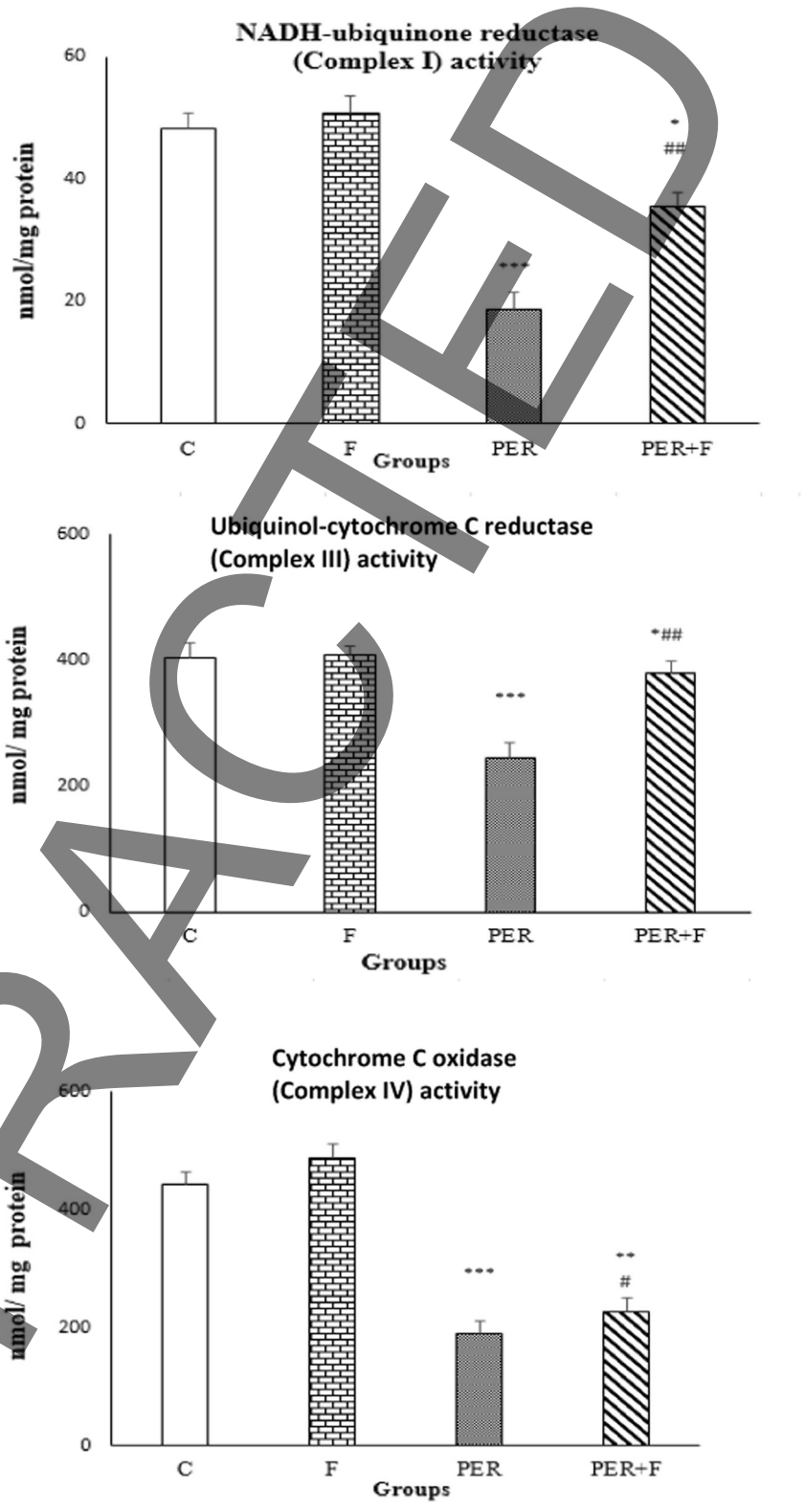


FIGURE 3 Hepatic mitochondrial enzyme activities in rats after 7 days of treatment. Values were means ± standard deviation ($n = 6$). PER and PER + F treated group versus control group: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; PER + F group versus PER group: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$.

3.8 | Effects of permethrin on Ca^{2+} and Mg^{2+}-ATPase activities

After exposure to PER, Ca^{2+} and Mg^{2+}-ATPase activities were significantly reduced in liver (−48.58% and −128.43%, respectively) and mitochondria (−60.62% and −56.53%, respectively) as compared to normal values. Coadministration of *F. officinalis* to PER group significantly increased these activities (Figure 4).

3.9 | Liver histopathology

Figure 5 illustrated the histological changes in the liver tissue of control and experimental groups of animals. Group (C) had normal cellular architecture that included complete hepatic structure (Figure 5, C). PER-induced rats exhibited an abnormal cellular morphology accompanied by various vacuolation and fragmentation of chromatin (Figure 5, PER). H&E staining of group (F) demonstrated

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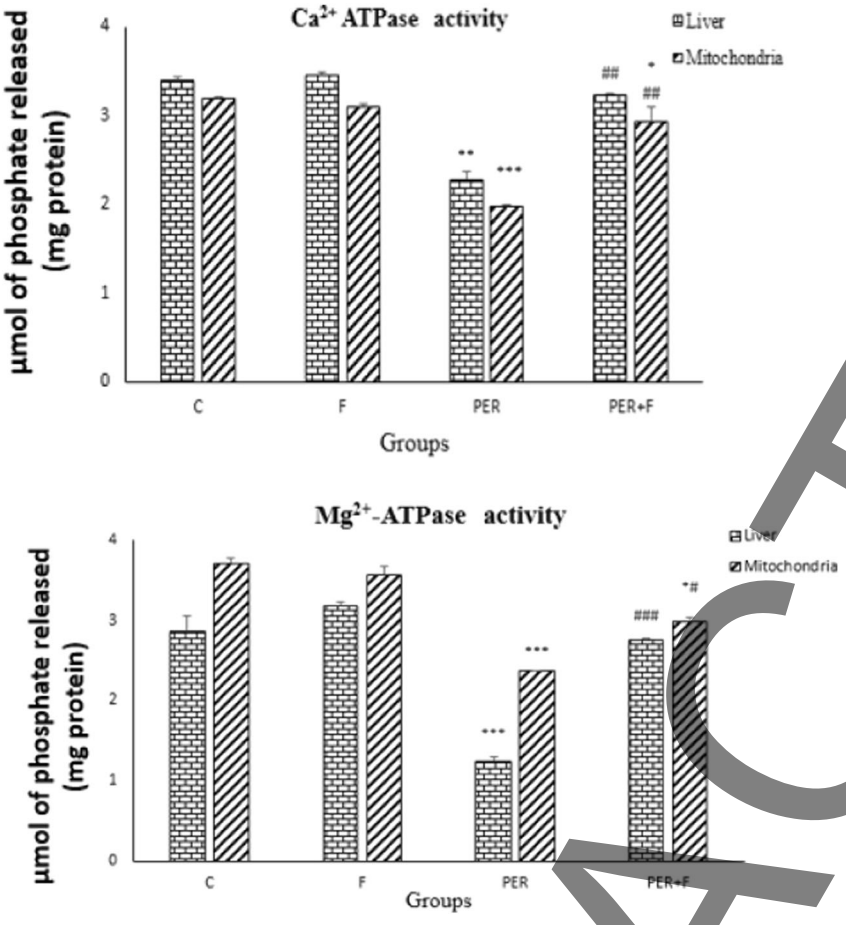


FIGURE 4 Hepatic and mitochondrial ATPases activities of control (C) and treated rats after 7 days of treatment. Values were means ± standard deviation ($n = 6$). PER and PER + F treated group versus control group: $^{*}p < 0.05$, $^{***}p < 0.001$; PER + F group versus PER group: $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$.

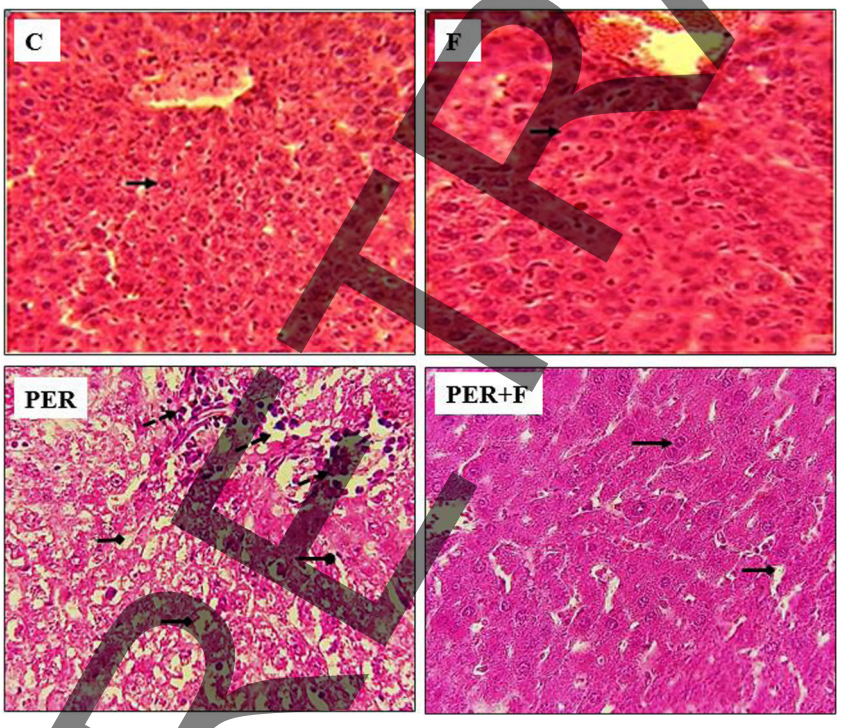


FIGURE 5 Histological examination of hepatic cells in control (C), permethrin (PER), *Fumaria officinalis* extract (F) and PER associated with *F. officinalis* extract (PER + F). Magnification at 400×, stained in hematoxylin-eosin solution (H&E), arrows indicated, pyknotic nuclei ⟶: Necrosis ⇢: cytoplasmic vacuolation ⟶, nuclear fragmentation ⟶•.

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normal cell architecture as control group (Figure 5, F). *F. officinalis* cotreated with PER alleviated the cell injury and returned in normal hepatic architecture as compared to (PER) group (Figure 5, PER + F).

3.10 | Genotoxicity analysis

DNA gel electrophoresis results in Figure 6 showed the qualitative changes in the integrity of the liver genomic DNA. The latter of the control group is intact. PER-treated rats caused a marked degradation of DNA. However, coadministration of *F. officinalis* to PER-treated rats exhibited a significant restoration of DNA as compared to permethrin group. No specific DNA fragments were observed in the *F. officinalis*-treated rats.

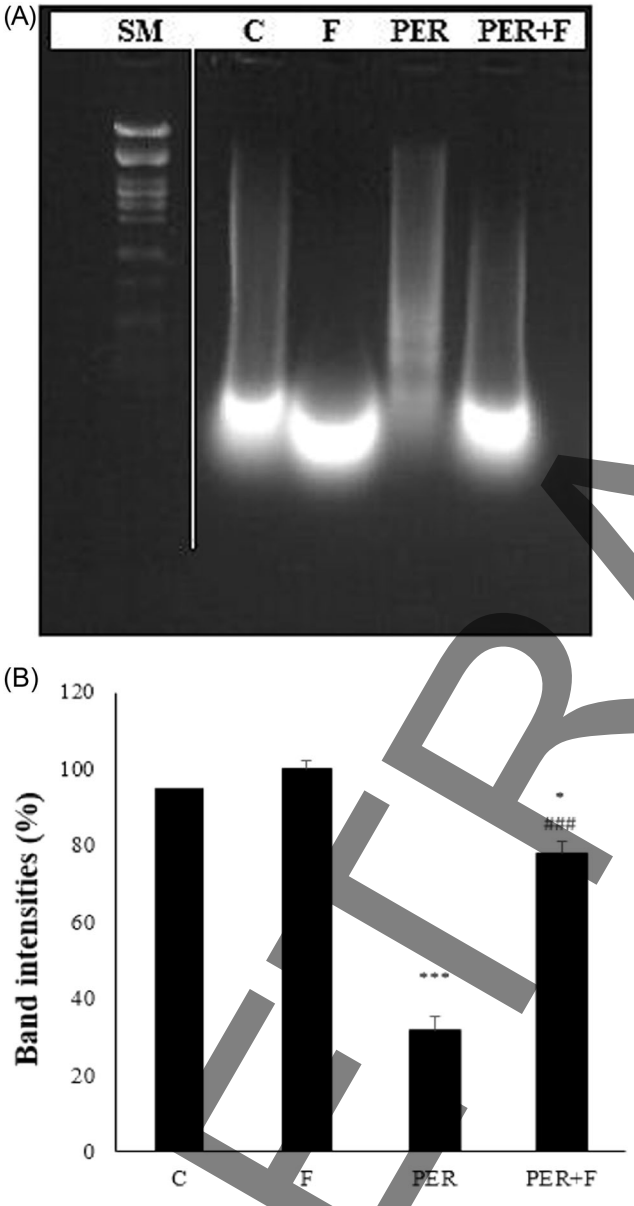


FIGURE 6 (A) Agarose gel electrophoresis of the liver DNA fragmentation. Lane 1, control group (C); lane 2, *Fumaria officinalis* group (F); lane 3, PER-treated rats (PER); lane 4, cotreated with F to the permethrin-treated rats (PER+ F). (B) Graph showed the densitometric analysis of the DNA bands obtained from gel electrophoresis. Each value is expressed as mean ± standard deviation ($n = 3$). PER and PER + F treated group versus control group: $^{*}p < 0.05$, $^{***}p < 0.001$; PER + F group versus PER group: $^{###}p < 0.001$.

4 | DISCUSSION

Recently, the intensive use of insecticides would become the main part in our environment. The biological effects of their exposure at low concentration can be attributed to severe pathologies in animal and human health.[43] Our results showed that permethrin exposure caused a significant reduction of body weight[44] with an increase of absolute and relative liver weights. The reduction in the body weight could presumably be ascribed either to the decrease of food intake and/or malabsorption of nutrients in rats and also to the action of PER on the gastrointestinal tract and/or inhibition of protein synthesis. Our results were an accordance with previous studies which have reported a decrease of body weight under the same conditions.[45,46] Administration of *F. officinalis* to permethrin-treated rats significantly improved body weight and markedly increased the possibility to receive food rewards. This effect could be explained by the richness of *F. officinalis* in quercetin, which stimulates appetite[47] and reduced the weight loss.[48] The liver is considered as a target organ which transforms, accumulates metabolite, neutralizes, and eliminates countless toxic substances in blood.[49] Moreover, previous investigations have revealed that exposure to permethrin is able to induce histopathological, biochemical, and physiological perturbations in liver tissue. Thus could explained by an excessive production of ROS.[1,50,51] In fact, free radicals cause a disturbance in the transport, the function, and membrane permeability of hepatocytes.[52,53] Hepatic dysfunction has been highlighted by an increase of serum aminotransferases activities.[54,55] Similarly, our results showed an increase of AST and ALT activities in plasma and a decrease in the liver tissue of PER-treated rats when compared to those of control group. Coadministration of *F. officinalis* to the PER-treated rats improved significantly these activities. This beneficial action could be explained by the richness of *F. officinalis* in caffeic acid which stabilizes membrane of hepatocytes.[56–58]

The perturbations of hepatic cells function could alter also ATPase activities which have an effect on ionic gradients between the intracellular and extracellular compartments and provide metabolic energy in the living system.[59] A significant reduction was observed in hepatic and mitochondrial Ca^{2+} and Mg^{2+}-ATPases activities in PER-treated rats when compared to those of control group. This effect was attributed to the lipophilic nature of permethrin reducing the osmo ion regulations.[60] PER could also alter these ATPases by disrupting energy-producing metabolic pathways.[61] Coadministration of *F. officinalis* to the PER-treated rats improved ATPase activities. This effect could be attributed to Kaempferol, which influences the bio-membrane permeability and intermingle with ATPases pumps, as confirmed by Langeswaran

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et al.[58,60] According to Abdallah et al. and Yang et al.,[61,62] a decrease of ATPase activities is the main perturbation of the membrane potential causing an increase of TBARS levels.

Indeed, PER induced an increase of hepatic and mitochondrial TBARS, PCO, and AOPP levels compared to the normal values. In addition, a rise of CRP in plasma was correlated with a reduction in hepatic tissue of PER-treated rats. These alterations confirmed the significant mitochondrial dysfunction and the deficient antioxidant defense system. Coadministration of *F. officinalis* to the PER-treated rats significantly improved these parameters reaching normal values. The protective action can be attributed to quercetin which protects hepatic cell damage by inducing heme oxygenase-1 via the MAPK/Nrf2 pathways. Among MAPK signaling pathways, p38 and ERK-mediated quercetin-derived Nrf2 translocation into nuclei cells and following induction of heme oxygenase-1 action, which gives a beneficial effect as reported by Yao et al.[63] and Joshi et al.[64]

Glutathione (GSH) and other thiol-containing proteins play the main role in a cellular defense against xenobiotics toxicity. In the present study, a remarkable rise of GSH levels and a decrease of NPSH and vitamin C levels in the liver and mitochondria were observed in PER group compared to those of the control group. The increase of GSH content may be explained by the protective response of liver against PER via the overexpression of ϒ-glutamylcysteine synthetase.[65] Coadministration of *F. officinalis* into PER-treated rats attenuated the hepatic and mitochondrial cells damage. Our data were in accordance with previous reports highlighting that naringenin, a main compound of this plant, improved these parameters.[62,66,67] In fact, naringenin can scavenge free radicals and/or modulate the expression of ϒ-glutamylcysteine synthetase limiting the synthesis pathways of GSH.[60,61]

Moreover, superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and gamma-glutamyl transpeptidase (ϒ-GT) are the main enzymatic antioxidant defense system protecting cells against free radicals' toxicity. SOD transforms the O_2^- to H_2O_2 and CAT cleaves this H_2O_2 into O_2 and H_2O, while GPx is a seleno-enzyme that scavenges the hydrogen peroxidase and catalyzes the oxidation of GSH to GSSG. Hence, our results demonstrated that PER induced an increase in the CAT, GPx, and ϒ-GT activities confirming the ROS overproduction. Our results were in agreement with previous reports indicating that PER causes perturbations in CAT and SOD activities in the liver and mitochondria.[50,68] The antioxidant status was significantly restored after cotreatment of PER-treated rats with *F. officinalis*. Upon the literature review, it is found that *F. officinalis* extract contains mainly protopine, fumarine, benzazeein, alkaloids, phenols, and flavonoids which might possess antioxidant capacity involving its protective action in rat hepatic cell.[50,68]

Under oxidative reactions, the tricarboxylic acid (TCA) cycle is slowed down in biological cellular regulation to decrease free radicals generation.[69] The downregulated rates of lactate and pyruvate in PER group implied the inhibition of natural energy production. Energy metabolism disorders were significantly improved in PER + F group. The preventive action of *F. officinalis* could be due to its antioxidant and free scavenging properties, which accelerates the clearance of lactate and boosts ATP production.[70]

Energy generation by oxidative phosphorylation is readily catalyzed by membrane-bound protein complexes such as NADH ubiquinone reductase (Complex I), succinate dehydrogenase (Complex II), Ubiquinol-cytochrome C reductase (Complex III), and Cytochrome C oxidase (Complex IV). Our results demonstrated that PER-treated rats reduced the respiratory chain system mainly for Complex I, to a lesser for Complex III and IV when compared to normal values. In accordance with the findings of Falcioni et al.[71] and Gassner et al.[72] who have reported that xenobiotics-like PER causes a reduction in O_2^- release from a respiratory chain by inhibition of mitochondrial Complex I. Coadministration of *F. officinalis* in PER-treated rats restored enzyme activities in mitochondria. This improvement may reflect the ability of *F. officinalis* to boost the scavenging and inactivates H_2O_2 and OH.[73]

Following oxidative stress, cell death can result in apoptotic or necrotic mechanisms. The histopathological examination of permethrin-treated rats demonstrated that PER caused nuclear, morphological, and ultrastructural changes including elevation of chromatin condensation, cell membrane rupture, and vacuoles formation considered as the common apoptotic characteristics. Mitochondrial damage could play a pivotal role in cell death. Similar results found by Falcioni et al.[71] indicate that ROS generation starts the release of mitochondrial cytochrome C into the cytosol, which is considered as a critical process occurring during apoptosis.[74,75] Our results showed that the addition of *F. officinalis* restored the histological changes induced by PER. This effect refers basically to the presence of ferulic acid, which effectively reduces pathological and histological carbon tetrachloride rat's liver alterations.[76]

Histological and genotoxic disturbances come mainly from oxidative stress installation and ROS attacks on cell biomolecules such as lipids, proteins, and DNA leading to mutagenic alterations.[77] Our results showed that PER-treated rats induced a significant DNA reduction as well DNA fragmentation confirming PER-caused necrosis and apoptosis as revealed by histological analysis. However, coadministration of *F. officinalis* to the PER-treated rats alleviated the histoarchitecture alterations. The ability of this extract to prevent DNA against free radicals as mentioned to be the main factors of the anti-mutagenic action.[78] According to Marimuthu et al.,[79] this improvement could be explained by its richness in quercetin, which protects liver cells against mercury-induced DNA injury and redox status alterations.

5 | CONCLUSION

It may be concluded that permethrin caused hepatic injury and mitochondrial dysfunction as well as DNA damage. This study also identified the beneficial effect of *F. officinalis* administration by increasing the cellular antioxidant defense machineries. The mechanism underlying its effectiveness involves free radicals scavenging and their antioxidant ability due to the highest content of quercetin, ferulic acid, and naringenin.

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AUTHOR CONTRIBUTIONS

Nissaf Aoiadni: investigation, methodology, analysis, writing—review and editing. **Nour Chiab**: methodology. **Hajer Jdidi**: methodology. **Radhia Gargouri Bouzid**: resources. **Abdelfattah El Feki**: resources. **Hamadi Fetoui**: resources. **Fatma Ghorbel Koubaa**: project administration, resources, conceptualization, supervision, writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available in the article.

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REFERENCES

[1] C. G. Roma, P. R. Oliveira, G. H. Bechara, M. I. C. Mathias, *Microsc. Res. Tech.* **2012**, *75*, 229.
[2] D. M. Roberts, A. Karunarathna, N. A. Buckley, G. Manuweera, M. H. R. Sheriff, M. Eddleston, *Bull. World Health Organ.* **2003**, *81*, 789.
[3] D. E. Ray, J. R. Fry, *Pharmacol. Ther.* **2006**, *111*, 174.
[4] S. M. Bradberry, S. M. Cage, A. T. Proudfoot, J. A. Vale, *Toxicol. Rev.* **2005**, *24*, 93.
[5] R. Gabbianelli, M. L. Falcioni, C. Nasuti, F. Cantalamessa, I. Imada, M. Inoue, *Chem.-Biol. Interact.* **2009**, *182*, 245.
[6] C. Nasuti, F. Cantalamessa, G. Falcioni, R. Gabbianelli, *Toxicology* **2003**, *191*, 233.
[7] M. Carloni, C. Nasuti, D. Fedeli, M. Montani, A. Amici, M. S. Vadhana, R. Gabbianelli, *Exp. Gerontol.* **2012**, *47*, 60.
[8] H. Turkez, E. Aydin, *Arh. Hig. Rada Toksikol.* **2012**, *63*, 27.
[9] B. Erkmen, *Bull. Environ. Contam. Toxicol.* **2015**, *94*, 419.
[10] L. Imamura, H. Hasegawa, K. Kurashina, A. Hamanishi, A. Tabuchi, M. Tsuda, *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1175.
[11] J. S. Jeeva, J. Sunitha, R. Ananthalakshmi, S. Rajkumari, M. Ramesh, R. Krishman, *J. Pharm. Bioallied Sci.* **2015**, *7*, S331.
[12] M. Alves-Benzerra, D. E. Cohen, *Compr. Physiol.* **2017**, *8*, 1.
[13] R. Gabbianelli, C. Nasuti, G. Falcioni, *Toxicology* **2004**, *203*, 17.
[14] A. Zablocka, M. Janusz, *Postepy Hig. Med. Dosw.* **2008**, *62*, 18.
[15] H. Ouassou, M. Bouhrim, N. E. Daoudi, H. Mekhfi, A. Ziyyat, H. Mekhfi, A. Ziyyat, A. Legssyerr, M. Aziz, *Bnouham. Adv. Pharm. Pharma. Sci.* **2021**, *2021*, 1.
[16] L. Bhoopat, S. Srichairatanakool, D. Kanjanapothi, T. Taesotikul, H. Thananchai, J. Bhoopat, *Ethnopharmacol.* **2009**, *136*, 55.
[17] F. C. Stintzing, K. M. Herbach, M. R. Mosshammer, R. Carle, W. Yi, S. Sellappan, C. C. Akoh, R. Bunch, P. Felker, *J. Agric. Food Chem.* **2005**, *53*, 442.
[18] J. Zhishen, T. Mengcheng, W. Jianming, *Food Chem.* **1999**, *64*, 555.
[19] B. Sun, L. M. Ricardo-da-Silva, I. Spranger, *J. Agric. Food Chem.* **1998**, *46*, 4267.
[20] W. C. Hou, F. L. Hsu, M. H. Lee, *Planta Med.* **2002**, *68*, 1072.
[21] M. Oyaizu, *JPN J. Nut. Diet.* **1986**, *44*, 307.
[22] P. Prieto, M. Pineda, M. Aguilar, *Anal. Biochem.* **1999**, *269*, 337.
[23] R. J. Ruch, S. Cheng, A. Jun, J. E. Klaunig, *Carcinogenesis* **1989**, *10*, 1003.
[24] R. Sharma, D. Goli, *Pharmacologia* **2012**, *3*, 9.
[25] F. Cantalamessa, *Arch. Toxicol.* **1993**, *67*, 510.
[26] C. Hoppel, J. P. DiMarco, B. Tandler, *J. Biol. Chem.* **1979**, *254*, 4164.
[27] O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. J. Randall, *J. Biol. Chem.* **1951**, *193*, 265.
[28] H. Esterbauer, K. H. Cheeseman, *Methods Enzymol.* **1990**, *186*, 407.
[29] A. Z. Resnik, L. Packer, *Methods Enzymol.* **1951**, *233*, 357.
[30] V. Witko, A. T. Nguyen, *J. Clin. Lab. Anal.* **1962**, *6*, 47.
[31] L. C. Green, D. A. Wagner, J. Glogowski, P. L. Skipper, J. S. Wishnok, S. R. Tannenbaun, *Anal. Biochem.* **1982**, *126*, 131.
[32] K. Asada, M. A. Takahashi, M. Nagate, *Agric. Biol. Chem.* **1974**, *38*, 471.
[33] H. Aebi, *Methods Enzymol.* **1984**, *105*, 121.
[34] L. Flohé, W. A. Günzler, *Methods Enzymol.* **1984**, *105*, 114.
[35] G. L. Ellman, *Arch. Biochem. Bioph.* **1959**, *82*, 70.
[36] D. J. Jollow, J. R. Mitchell, N. Zampaglione, J. R. Gillete, *Pharmacology* **1974**, *11*, 151.
[37] J. Sedlak, R.H. Lindsay, *Anal. Biochem.* **1986**, *25*, 192.
[38] S. K. Jagota, H. M. Dani, *Anal. Biochem.* **1982**, *127*, 178.
[39] M. Malgat, G. Durrieu, J. P. Mazat, *Mitochondrial Diseases*, 357, Springer Verlag, Paris **1999**.
[40] S. Hjerten, H. Pan, *Biochim. Biophys. Acta.* **1983**, *728*, 28.
[41] T. Ohinishi, T. Suzuki, K. Y. Suzuki, K. Ozawa, *Biochim. Biophys. Acta* **1982**, *684*, 67.
[42] S. Kanno, A. Shouji, R. Hirata, K. Asou, M. Ishikawa, *Life Sci.* **2004**, *75*, 353.
[43] V. P. Kalyabina, E. N. Esimbekova, K. V. Kopylova, V. A. Kratasyuk, *Toxic. Rep.* **2021**, *8*, 1179.
[44] Q. Zhu, Y. Yang, Z. Lao, Y. Zhong, K. Zhang, S. Zhao, *Pest Mang. Sci.* **2020**, *76*, 636.
[45] R. Rachid, *Algeria* **2010**, pp. 1–538.
[46] Y. Zhu, X. Li, C. Chen, F. Wang, J. Li, C. Hu, Y. Li, L. Miao, *Food Chem. Toxicol.* **2012**, *50*, 2911.
[47] S. Gasmi, R. Rouabhi, M. Kebieche, S. Boussekine, A. Salmi, N. Toualbia, C. Taib, Z. Bouterra, H. Chenikher, S. Henine, B. Djabri, *Environ. Sci. Pollut. Res.* **2017**, *24*, 16440.
[48] F. E. R. Hashish, M. M. Abdel-Wahed, M. H. El-Odemi, S. S. El-Naidamy, M.M Elbatsh, *Men. Med. J.* **2021**, *34*, 333.
[49] T. Braunbeck, *Fish Ecotoxicology*. **1989**, 61.
[50] R. Gabbianelli, M. Palan, D. J. Flis, D. Fedeli, C. Nasuti, L. Skarydova, W. Ziolkowski, *Xenobiotica* **2013**, *43*, 1103.
[51] A. Feriani, M. Tir, R. Hachani, M. S. Allagui, N. Tlili, S. Nahdi, S. Alwasel, A. H. Harrath, *Eco. Rev. Safety.* **2021**, *207*, 111269.
[52] M. L. C. Zentella, R. H. Munoz, *Oxid. Med. Cell. Longev.* **2016**, *2016*, 1.
[53] J. Ozer, M. Ratner, M. Shaw, W. Bailey, S. Schomoker, *Toxicology* **2008**, *245*, 194.
[54] N. Amir, E. Suprayitno, H. Nursyam, *Int. J. Pharmtech Res.* **2015**, *2*, 235.
[55] L. Pari, A. Prasath, *Chem.-Biol. Interact.* **2008**, *173*, 77.
[56] A. Balakrishman, R. Kokilavani, *South As. J. Biol. Sci.* **2011**, *1*, 58.
[57] M. S. Prashanth, M. David, *Bull. Environ. Contam. Toxicol.* **2010**, *84*, 80.
[58] M. Manju, G. Jagadeesan, *Asian J. Pharma. Clin. Res.* **2019**, *12*, 119.
[59] C. Guven, Y. Sevgiler, E. Taskin, *Mitochondrial Diseases, Turky* **2018**. https://doi.org/10.5772/intechopen.80283
[60] K. Langeswaran, R. Revathy, S. G. Kumar, S. Vijayaprakash, M. P. Balasubramanian, *Trop. Biomed.* **2012**, *2*, 1653.
[61] F. H. Abdallah, R. Schmatz, M. C. Andréia, B. C. Fabiano, B. Jucimara, S. D. O. Juliane, M. R. Michelle, A. G. N. Matheus,

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A. R. Maribel, B. M. D. C. Ivana, B. Fernanda, L. D. Valderi, B. P. Luciane, R. C. S. Maria, M. M. Vera, F. G. Jamile, M. M. Cinthia, *Physiol. Behav.* **2014**, *135*, 152.
[62] C. Yang, W. Yang, Z. He, J. Guo, X. Yang, R. Wang, H. Li, *Front. Pharmacol.* **2021**, *12*, 624402.
[63] P. Yao, A. Nussler, I. Liu, L. Hao, F. Song, A. Schirmeier, N. Nussler, *J. Hepatol.* **2007**, *47*, 253.
[64] M. S. Joshi, J. L. Ponthier, J. R. Lancaster, *Free Radic. Biol. Med.* **1999**, *27*, 1357.
[65] L. S. Chang, C. C. Chang, *Bichem. Mol. Biol. Int.* **1994**, *32*, 697.
[66] A. Hermenean, A. Ardelean, M. Stan, N. Hadaruga, C. V. Mihali, M. Costache, A. Dinischiotu, *J. Med. Food* **2014**, *17*, 670.
[67] N. Sahu, G. Mishra, H. K. Chandra, S. K. Nirala, M. Bhadauria, *J. Tradit. Complement. Med.* **2020**, *10*, 26.
[68] P. Chetia, A. Bala, B. Khandelwal, P. K. Haldar, *Pharmacologia* **2012**, *3*, 724.
[69] J. O. Moskaug, H. Carlsen, M. C Myhrstad, R. Blomhoff, *Am. J. Clin. Nutr.* **2005**, *81*, 277.
[70] A. F. Wali, S. Rashid, S. M. Rshid, M. Ansari, M. R. Khan, N. Haq, D. Y. Alhareth, A. Ahmed, M. U. Rehman, *Plants* **2020**, *9*, 550.
[71] M. L. Falcioni, C. Nasuti, C. Bergamini, R. Fato, G. Lenaz, R. Gabbianelli, *Neuroscience* **2010**, *168*, 2.
[72] P. Wang, M. Y. Xu, Y. J. Liang, H. P. Wang, Y. J. Sun, D. X. Long, Y. J. Wu, *Chem.-Biol. Interact.* **2017**, *272*, 21.
[73] X. Huang, L. Shao, Y. Gong, Y. Mao, C. Liu, H. Qu, Y. Cheng, *J. Chromatogr.* **2008**, *870*, 178.
[74] E. S. H. AbdAllah, A. M. Mohmoud, *Pathophysiology* **2018**, *25*, 353.
[75] B. Gassner, A. Wuthrich, G. Scholtysik, M. Solioz, *J. Pharmacol. Exp. Ther.* **1997**, *281*, 855.
[76] Y. R. Chen, C. L. Chen, L. Zhang, K. B. J. Church, J. L. Zweier, *J. Biol. Chem.* **2005**, *280*, 37339.
[77] J. E. Lee, J. S. Kang, Y. W. Ki, *Toxicol. Lett.* **2011**, *202*, 133.
[78] J. H. Li, X. R. Liu, Y. Zhang, *Toxicol. Res.* **2012**, *51*, 1137.
[79] S. Marimuthu, R. S. Adluri, R. Rajagopalan, V. P. Menon, *J. Basic Clin. Physiol. Pharmacol.* **2013**, *24*, 59.

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