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Original Article:

Hepatoprotective Effects of Taraxacum officinale Root Extract on Permethrin-induced Liver Toxicity in Adult Mice

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ABSTRACT

Background: Globally, permethrin is used as an insecticide for pest control in indoor environments and in agriculture to enhance food production by eradicating undesirable insects and controlling disease vectors.

Objective: The present study investigated the protective effects of Taraxacum officinale (dandelion) on permethrin-induced liver injury in mice.

Methods: Adult mice were divided into four groups. The first group was the negative control group, whereas the second group was the positive control group that received dandelion through the diet at 2% (corresponding to a dose of 5 g/kg bw). The third group received permethrin (96 mg/kg bw) by gavage, whereas the fourth group received permethrin and a diet enriched with dandelion (cotreatment). All mice were sacrificed after 14 days of treatment.

Results: Biomarkers of liver toxicity (AST, ALT, ALP, and LDH activities and bilirubin level) increased following permethrin treatment. Permethrin induced oxidative stress, which was indicated by an increase in MDA and GSH levels as well as GPx activity and a decrease in SOD activity. Permethrin treatment caused histological alterations in the liver, whereas co-treatment with dandelion reduced liver injury. Our results revealed that alterations of biochemical parameters and liver histological profile in mice following permethrin exposure were reversed towards normalization by the treatment with dandelion roots extract.

Conclusion: The protective effect of this plant might be due to its antioxidant capacity.

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1. Introduction

Permethrin is one of the most common synthetic pyrethroids, and it is considered a universal pesticide class. Organochlorine, organophosphate, and carbamate insecticides are substituted by pyrethroids due to their high toxicity [1, 2]. Permethrin, a broad-spectrum product, is widely and globally used in agriculture and for indoor pest control in the public health sector and housing [3, 4]. Humans may be exposed to this pollutant via multiple routes such as skin contact, respiration, or the ingestion of food and water contaminated with its residues [5]. Numerous studies have suggested that permethrin can cause toxicity in animals and humans, affecting the central nervous system [6-8], the immune system [9, 10], the heart [11, 12], and the liver [13]. It also causes genotoxicity [14-16] and damages the digestive and reproductive systems [17, 18]. Permethrin-induced toxicity is correlated with oxidative stress resulting from excessive production of reactive oxygen species and reactive nitrogen species, causing damage to lipids, DNA, and proteins in vertebrates and invertebrates [19].

Oxidative damage, induced by permethrin, can be prevented in animals after the supplementation of antioxidants in their diet. Among antioxidants, medicinal plants, including dandelion (*Taraxacum officinale* L.) (Figure 1) are an important source. This plant presents high amounts of minerals, proteins, fibers, and vitamins. It has been used extensively in traditional medicine for the treatment of many diseases such as cystitis, splenomegaly, hepatic disorders, gout, and diarrhea [20-23]. Nowadays, dandelion is used as an available dietary supplement as well as in pharmaceutical preparations due to its choleretic, diuretic, growth-promoting, antirheumatic, anticancer, antimicrobial, and anti-inflammatory properties [24-26]. According to European Pharmacopoeia (2005) and the Committee on Herbal Medicinal Products of the European Medicines Agency, the different parts of this plant, including the roots, can be exploited for therapeutic purposes [27]. Also, Park et al. [24, 28] reported that dandelion roots contained high levels of inulin (2%–40%) along with other polysaccharides, considered as the powerful antioxidants, and could inhibit oxidative stress and inflammatory response.

The present study aimed to investigate the effects of dandelion roots, administered via the diet, against liver injury induced by permethrin in mice.

2. Materials and Methods

Chemicals

Microspheres of *Taraxacum officinale* roots were purchased from Tunisia Parachimic Laboratory (ref. TADL 150939 SD). Permethrin (ref. 45614) and all chemicals used in the present study with analytical grade were purchased from Sigma Aldrich (France).

In vitro study

Antioxidant activities of the ethanolic dandelion roots extract and the standard (Gallic acid GA or vitamin C) were performed in triplicate. Results were expressed as IC50, corresponding to the test material concentration required to cause a 50% decrease in free radicals' concentration.

Total antioxidant activity

The total antioxidant activity of the plant ethanolic extract was based on the reduction of ammonium molybdate (IV) to the state (V) and the subsequent formation of green phosphate/ Mo (V) compounds with maximum absorption at 695 nm [29]. The scavenging activity was calculated as follows: PI%=[(A0 – A1)/A0]×100, where A0 and A1 were the optical densities of the control reaction and in the presence of either dandelion roots extract or the standard (Gallic Acid [GA]).

Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

DPPH radical scavenging activity was assayed using the experimental protocol of Hou et al. [30]. The radical scavenging capacity of the tested samples was measured as a decrease in the absorbance of the DPPH radical and it was calculated using the following equation: % inhibition=100×[(AC-AE)/AC], where AC was the absorbance of the control reaction and AE the absorbance in the presence of either dandelion roots extract or the standard (vitamin C).

Hydrogen peroxide (H_2O_2) scavenging activity

The activity of H_2O_2 was determined using the method described by Ruch et al. [31]. The optical densities were measured at 240 nm at the beginning of the reaction and after one hour. The percentage of H_2O_2 scavenging activity in the extract was calculated using the following formula: % inhibition=100 x [1-(A1/A0)], where A0 and A1 were the optical densities of the control reaction and in the presence of either dandelion roots extract or the standard (Vitamin C).

Ferric Reducing Power (FRP) assay

The Ferric Reducing Power (FRP) assay was carried out according to the method of Oyaizu [32]. The optical density was measured at 700 nm. The scavenging activity was calculated with PI%=[(D0–D1)/D0]×100, where D0 and D1 were the optical densities of the control reaction and in the presence of either dandelion roots extract or the standard (vitamin C).

Table 1. Standard diet nutritional composition

Compounds		Concentrations
Moisture	%	14
Fibers		3.4
Ash		6.7
Proteins		22
Lipids		3.5
Carbohydrate		50.4
Amino acids		-
Methionine		0.6
Cysteine		0.38
Threonine		0.80
Tryptophane		0.30
Minerals (mg/kg)		-
Manganese		80
Iron		48
Copper		18.75
Zinc		65
Selenium		0.3
Cobalt		0.20
Iodine		1.2
Vitamins (IU/kg)		-
Vit A		13000
Vit D3		4375
Vit H		62.5
Antioxidants (mg/kg)		-
BHA-BHT		125
Caloric value (Kcal/kg)		2850

BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; Vit: vitamin.

Figure 1. *Taraxacum officinale* (dandelion) PBR

Mineral composition of *Taraxacum officinale*

The contents of magnesium (Mg2+), calcium (Ca2+), zinc (Zn2+), iron (Fe2+), and copper (Cu2+) in dandelion roots were determined by the atomic absorption spectrometry (Zeeman Z-61000, HITACHI) at 228.5 nm of absorbance. They were expressed as mg/100g of dandelion roots.

In vivo study

Animals and experimental design

Adult male mice of Swiss strain weighing between 25 and 28 g (SIPHAT, Tunisia) were housed in cages and maintained in an acclimated room, where the temperature was 22±3°C, relative humidity was 40% and with a photoperiod of 12 h light/dark cycle. They had free access to standard pellet diet (SNA, Sfax, Tunisia) (Table 1) and water.

Experiments were conducted according to the International Guidelines for Animal Care (ETS No.123) and approved by the Ethics Committee of Sfax Sciences Faculty with the approval number 1204. Seven days after acclimatization, mice were divided into four groups (n=8) as follows:

Group I: Represented negative controls. Mice received 0.1 mL of distilled water by gavage daily.

Group II: Represented the positive controls. Mice received dandelion daily via the diet at 2% (corresponding to a dose of 5 g/kg body weight [bw]) according to Gargouri et al. [21] and 0.1 mL of distilled water by gavage.

Group III: Mice received 96 mg of permethrin/kg bw dissolved in distilled water by gavage. According to Roma et al. [33], the chosen dose represents 30% of LD50 of permethrin administered by an oral route.

Group IV: Animals received the same diet as group II and permethrin by gavage at the same dose as group III.

Mice of groups I and III received a standard diet. All mice received tap water during the experiment. After 14 days of treatment, mice were sacrificed by cervical decapitation to avoid stress. Blood samples were drawn from the trunk into heparin-coated tubes. Plasma samples were collected after centrifugation at 2200×g (4°C) for 10 min and were kept at -80°C until the analysis of biochemical parameters. Their livers were excised and weighed. Some portions were homogenized by Ultra Turrax T25 (Germany) in an ice-cold Tris-buffered saline solution (TBS) at pH 7.4) and centrifuged at 4500×g (4°C) for 10 min. Supernatants were stored at -80°C for biochemical analysis. Other portions of liver tissues were fixed in Bouin solution and embedded in paraffin for histological studies.

Biochemical assays

Liver parameters determination

Protein content in the liver was assayed using the experimental protocol described by Lowry et al. [34]. Lipid peroxidation was determined as malondialdehyde (MDA) formation according to the method of Yagi [35] and expressed as nmol MDA/mg protein. Superoxide dismutase (SOD) activity was estimated according to Asada et al. [36] method and expressed as units/mg protein.

Table 2. Contents of some minerals in dandelion roots

Minerals	Concentrations (mg/100 g of Dandelion Roots)
Zn++	8.58
Fe++	6.22
Cu++	0.34
Mg++	7.20

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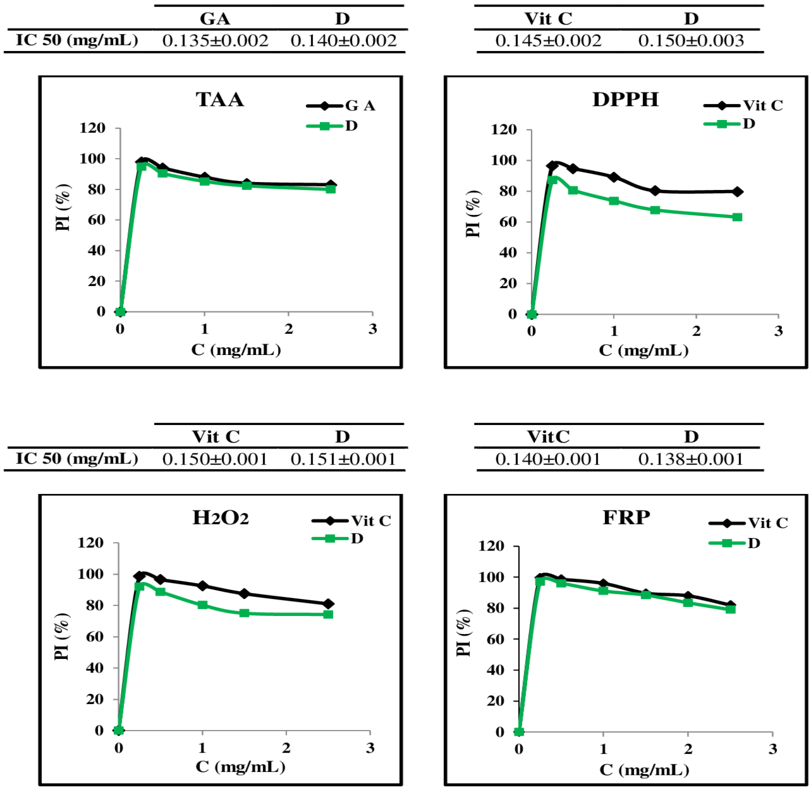

	GA	D
IC 50 (mg/mL)	0.135±0.002	0.140±0.002

Vit C	D
0.145±0.002	0.150±0.003

	Vit C	D
IC 50 (mg/mL)	0.150±0.001	0.151±0.001

VitC	D
0.140±0.001	0.138±0.001

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Figure 2. Total antioxidant (TAA), diphenyl picrylhydrazyl radical scavenging (DPPH), hydrogen peroxide scavenging (H_2O_2) activities, and ferric-reducing power (FRP) of ethanolic extracted from dandelion roots (D)

GA: gallic acid; Vit C: vitamin C.

Glutathione peroxidase activity (GPx) was assayed using the experimental protocol described by Flohe and Gunzler [37] and expressed as nmol GSH oxidized/min/mg protein. Glutathione level (GSH) was determined using the method described by Ellman [38] and was expressed as nmol/mg protein.

Plasma parameters determination

Aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) activities and total bilirubin level were assayed spectrophotometrically using commercial diagnostic kits (Abbott Park, IL, USA) Architect/Aeroset, refs. 7D81-21, 7D56, 2P56-21, 7D55 and 6L45.

Histological studies

Liver samples, fixed in Bouin solution for 48 h, were processed using graded ethanol series, embedded in paraffin, cut (5 µm), and then stained with hematoxylin-eosin. Six slides were prepared from liver tissue collected from each mouse belonging to each group. All sections were evaluated for liver injury degree and assigned for the severity of changes using scores on a scale of none (-), slight (+), moderate (++), and acute (+++) damages.

Statistical analysis

The data were analyzed using the statistical package program StatView 5 for Windows (SAS Institute, Berkley, CA). Statistical analysis was performed using a 1-way analysis of variance followed by Fisher's protected least significant difference test as a post hoc test for comparison between groups. The Student unpaired t test was also used when a comparison the between two groups was required. All values are expressed as Means±SD. Differences were considered significant at P<0.05.

3. Results

In vitro study

Total antioxidant activity

Dandelion root extract had a powerful antioxidant capacity. Based on the phosphomolybdate test, our results showed that the IC50 of the plant extract (0.140±0.002

Table 3. Initial and final body weights, absolute and relative liver weights, daily food and water consumption by mice of controls (I, II) and treated mice for 14 days with permethrin (III) or with permethrin associated with dandelion (IV)

Parameters	Means±SD			
	I	II	III	IV
Initial body weight (g)	25.89±1.72	25.01±1.40	25.83±1.7	25.68±1.01
Final body weight (g/100g)	29.71±1.78	28.68±1.40	28.03±1.60	29.22±2.16
Absolute liver weight (g)	1.56±0.13	1.66±0.08	2.01±0.10***	1.66±0.10+++
Relative liver weight (g/100g)	5.23±0.35	5.68±0.27	6.67±0.15***	5.86±0.31+++
Food intake (g/d)	6.97±0.18	6.62±0.19	7.23±0.31	6.74±0.47
Water intake (mL/d)	5.02±0.18	5.21±0.16	5.99±0.31**	4.94±0.38+

Group III vs control groups I and II: **P<0.01; ***P<0.001. Group IV vs Group III: +P<0.05; +++P<0.001.

mg/mL) was not different from that of gallic acid (0.135±0.002 mg/mL) (Figure 2).

DPPH radical scavenging activity

Dandelion root extract showed an important antiradical activity. Its IC50 value (0.150±0.003 mg/mL) was similar to that of vitamin C (0.145±0.002 mg/ml) (Figure 2).

H_2O_2 scavenging activity

Dandelion root extract exhibited a potent H_2O_2 scavenging capacity with an IC50 value (0.151±0.001 mg/mL) reaching that of vitamin C (0.150±0.001 mg/mL) (Figure 2).

Ferric reducing power

The ferric reducing power of dandelion root extract was comparable to that of vitamin C, with respective IC50 values of 0.138±0.001 mg/mL and 0.140±0.001 mg/mL (Figure 2).

Mineral composition of dandelion

Dandelion roots extract contained important amounts of zinc (8.58 mg/100 g), iron (6.22 mg/100 g), and magnesium (7.20 mg/100 g) and a small content of copper (0.34 mg/100 g) (Table 2).

In vivo study

Body, absolute, and relative liver weights, food, and water intakes

During the experimental period, there was no mortality in all groups. Moreover, the body and the daily food intake of treated mice were similar to those of the controls. Meanwhile, a significant increase (+19.32%) in the daily water consumption was shown in permethrin-treated mice (group III), as compared to that of the controls. Absolute and relative liver weights increased in permethrin-treated mice by 28.85% and 27.53%, respectively, and reversed by co-treatment for 14 days with dandelion (Group IV) (Table 3).

Biomarkers of liver toxicity in plasma

Plasma transaminases (ALT, AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) activities significantly increased by 87.3%, 26.9%, 17.5%, and 126.4%, respectively in the permethrin-treated group for 14 days compared to the corresponding control values. Bilirubin plasma level also increased in this group by 96.67%. The parameters cited above significantly decreased by 45.7%, 26.4%, 13.32%, 41.66%, and 37%, respectively in permethrin-treated mice co-administered with dandelion (Group IV) when compared to those of mice treated only with permethrin (Group III) (Figure 3).

Liver redox status

Lipid peroxidation level in the liver

Our results revealed an increase in lipid peroxidation in the liver of permethrin-treated mice as evidenced by the enhanced MDA level (+108.86%) when compared to the control group (Group I). Co-treatment with dandelion (group IV) decreased liver MDA level reaching the control values (Table 4).

Enzymatic antioxidant status

Table 4. Lipid peroxidation (MDA) and glutathione (GSH) levels. Antioxidant activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the liver tissue of controls (I, II) and treated mice for 14 days with permethrin (III) or with permethrin associated with dandelion (IV)

Parameters	Means±SD			
	I	II	III	IV
MDA (nmol/mg protein)	0.79±0.10	0.68±0.04	1.65±0.08***	0.71±0.11+++
GSH (nmol/mg of protein)	1.27±0.14	1.17±0.08	3.02±0.02***	1.23±0.06+++
SOD (U SOD/mg protein)	9.87±0.90	8.77±0.46	3.70±0.59***	8.46±0.57+++
GPx (nmol GSH/mg of protein)	1.15±0.12	1.13±0.06	1.60±0.01***	1.24±0.05+++

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Group III vs. control groups I and II: ***P<0.001. Group IV vs. Group III: ++ P<0.01; +++ P<0.001.

SOD and GPx activities were measured as an index of enzymatic antioxidant status in tissues. The liver activity of SOD decreased by 62.51% while that of GPx increased by 39.13% in permethrin-treated mice (Group III) when compared to the control group (Group I) (Table 4). Diet supplementation with dandelion normalized these parameters in permethrin-treated mice (Group IV) when compared to the corresponding control values.

Non-enzymatic antioxidant status

Results showed that permethrin treatment increased significantly the levels of GSH (+137.8%) as compared with the controls (Table 4). These modifications were alleviated following dandelion administration to permethrin-treated mice (Group IV).

Histological examination of liver tissue

Liver sections of the control (Group I) and dandelion treated mice (Group II) showed a normal histo-architecture with hepatic lobules consisting of a central vein surrounded by radiating hepatocytes (Figure 4A & B). Permethrin treatment produced hepatic histopathological changes including vacuolization, congestion, and condensed nuclei (Figure 4C, Table 5). These changes were reduced significantly in the liver of mice treated with permethrin along with dandelion (Figure 4D) as shown in the histological sections (Figure 4, Table 5).

4. Discussion

Although pyrethroids are believed to be only mildly toxic to mammals, they have some adverse effects. The present work examined the potential hepatotoxicity induced by permethrin in mice and its alleviation by dandelion.

In the present study, after 14 days of permethrin treatment, body weight and food intake were not affected in adult mice, suggesting that this pesticide did not affect their appetite. Similarly, Wang et al. [39] did not observe a significant variation in mice body weights for 6 weeks after the oral administration of permethrin. Nevertheless, a significant rise in water consumption was recorded in the present study for permethrin-treated mice to eliminate the toxic metabolites via the urinary tract.

Moreover, absolute and relative liver weights were significantly increased following permethrin exposure. Thus, hepatomegaly could be explained by the vacuolization and binucleation observed in hepatocytes of permethrin-treated mice. According to Kostka et al. [40], oral administration of permethrin to rats for 14 days causes hepatomegaly, which could be explained by the

Table 5. Grading of the histopathological changes in the liver sections of control (I, II) and treated mice for 14 days with permethrin (III) or with permethrin associated with dandelion (IV)

Liver Histopathological Changes	I	II	III	IV
Vacuolization	-	-	+++	+
Nuclei condensation	-	-	+++	+
Congestion	-	-	++	-

Scoring was done as follows: none (-), slight (+), moderate (++) and acute (+++) damages.

PBR

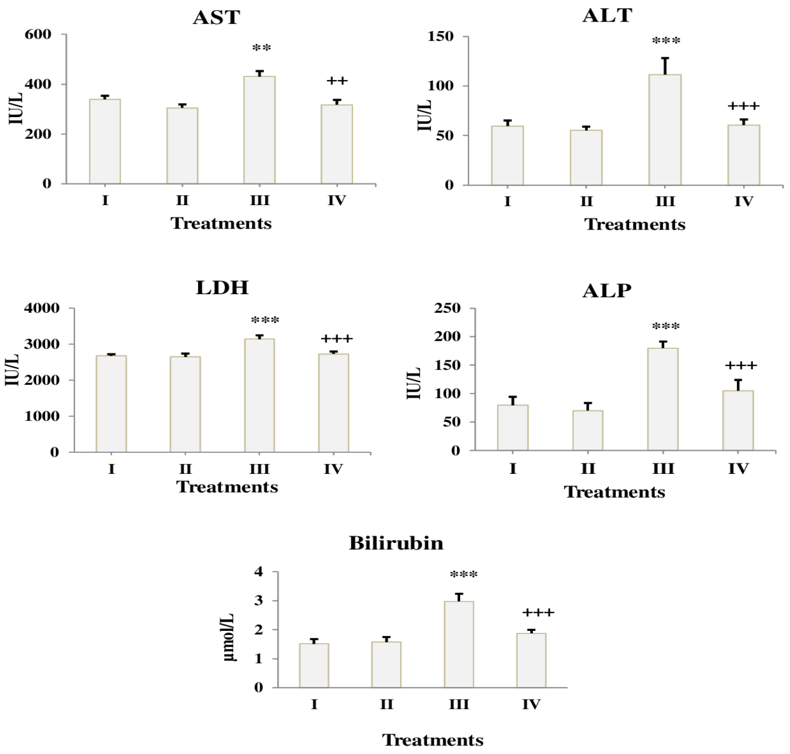

Figure 3. Plasma activities

Plasma activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and levels of total bilirubin, in control (I) and treated mice for 14 days with dandelion (II), with permethrin (III) or with permethrin associated with dandelion (IV).

Values are presented as means±SD for eight mice in each group.

induction of CYP 2B apoenzyme associated with hypertrophy of smooth endoplasmic reticulum and an increase in binucleation of hepatocytes.

In addition to the morphological liver changes in permethrin-treated mice, alteration of hepatic function was observed. Indeed, Gabbianelli et al. [13] have reported that sub-chronic exposure to permethrin provokes physical alterations of cell membranes objectified by a decreased membrane fluidity which disturbs, according to Zimmerman [41], the liver function. Thus, enzymes normally in the cytoplasm leak into the blood circulation. According to Rajesh and Latha [42], elevated activities of serum transaminases reflect a cellular leakage resulting from the loss of functional integrity of hepatocytes membrane. As observed in our work, activities of AST and ALT in the plasma of treated mice were high. Treatment with dandelion caused a decrease in the activities of these enzymes, which might be a consequence of cell membrane stabilization in the hepatic tissue.

Moreover, the activity of plasma alkaline phosphatase (ALP), the liver enzyme excreted normally via the bile, was also elevated in permethrin-treated mice. Permethrin treatment also increased plasma bilirubin levels in mice. Depletion of elevated bilirubin level as well as ALP activity in the plasma of permethrin-exposed mice co-treated with dandelion suggested protection of liver function against injury induced by this pesticide. According to Wirngo et al. [43], dandelion roots are endowed with choleric effects because of their bioactive compounds such as sesquiterpene lactones which stimulate bile secretion by the liver and its transport to the duodenum. Besides, an increased LDH activity in the plasma of permethrin-treated mice confirmed the occurrence of severe damages in liver cells. Co-treatment with dandelion decreased LDH activity, indicating an improvement of the liver functional status.

According to De La Haba et al. [44], the alteration of membrane fluidity is linked to the induction of oxidative stress and the impairment of enzymatic antioxidant mechanisms. In other words, the antioxidant enzyme system (SOD, CAT, GPx) represents the primary defense line in the body against oxidative stress generated due to the environmental stimuli. Oxidative stress induced by

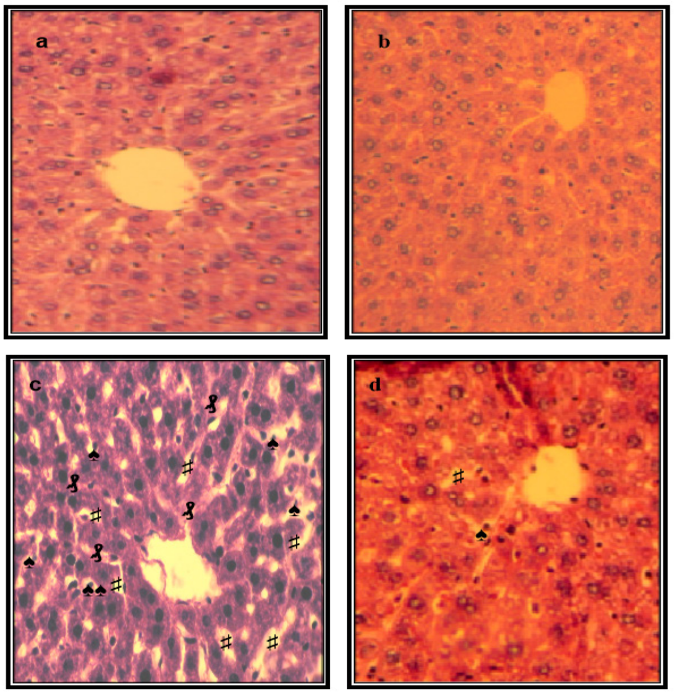

Figure 4. Histological liver sections of control (a, b), and treated mice for 14 days, with permethrin (c) or with permethrin and dandelion (d)

Optic microscopy: H&E (400 X). The control group (a) and dandelion treated group (b) showed normal hepatic histo-architecture. Permethrin treated group (c) showed swollen hepatocytes with vacuoles (♯) and condensed nuclei (♠) as well as congestion in sinusoid (§). Group (d) showed hepatocytes with few vacuoles and nuclei condensation.

pesticides enhances ROS production due to the alteration of mitochondrial respiration or through their redox cycles. The first response to free radicals' generation is the increment of antioxidant enzyme levels to scavenge ROS, but when stressor agents persist, the levels of these enzymes decrease [45]. Our data confirmed the disruption of the enzymatic antioxidant system after permethrin treatment observed in the previous reports [13, 19].

Our results showed that the activity of SOD decreased while that of GPx increased after permethrin treatment. Co-administration of dandelion modulated the levels of these antioxidant enzymes. Such effect could be attributed to the antioxidant capacity of the plant extract, as demonstrated by our obtained from the results *in vitro* study, and/or to its richness in mineral compounds (Zn2+, Fe2+, Cu2+, and Mg2+) which are considered as precursors of antioxidant enzymes. According to Xue et al. [46], leaf, flower, root, and stem extracts of this plant are rich in chicoric acid and possess high total phenolic and flavonoid contents. Moreover, Park et al. [47] have demonstrated that the extracts of dandelion could inhibit oxidative stress and NF- κB transcription factor as well as the expression of inducible NO synthase, increasing consequently the activity of antioxidant defense enzymes.

Interestingly, according to Park et al. [28], two polysaccharides extracted from dandelion roots exert relevant anti-inflammatory and Nrf2-mediated antioxidant effects in RAW 264.7 cells through the inhibition of NF-κB and the modulation of PI3K/Akt pathways, respectively. Therefore, the dandelion extract could provide alternative anti-oxidative and anti-inflammatory therapeutics for several diseases [23, 24, 28, 48, 49]. Rehman et al. [50] have indicated that dandelion root extract would enhance the phosphorylation level of adenosine monophosphate-activated protein kinase (AMPK) of HepG2 cells, which is considered as crucial in metabolic diseases by influencing TNF-α and IL-1α secretion [51].

On the other hand, GSH considered as an important endogenous antioxidant can prevent ROS-induced damages to cellular components. It can increase the solubility of toxic compounds, causing oxidative stress, and remove them from the body [52]. Our study indicated that permethrin increased GSH level in the liver of treated mice reflects the occurrence of hepatic oxidative damage. GSH levels decreased in the liver of mice treated

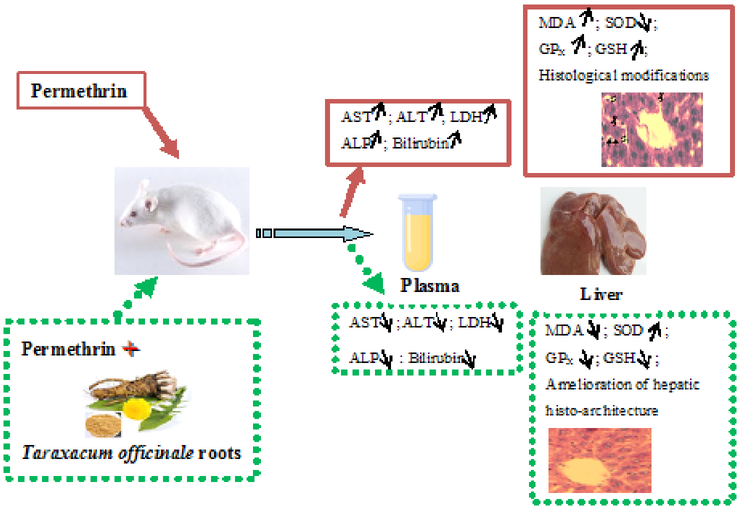

Figure 5. Graphical abstract

with permethrin along with dandelion, thus showing the antioxidant capacity of this plant because of its richness in inulin. Previously, Kalantari et al. [53] have demonstrated that dandelion exerts in mice protective effects against the hepatotoxicity induced by methotrexate.

In recent years, studies have shown that oxidative stress is one of the main molecular mechanisms of organophosphate compounds' toxicity. The liver is principally sensitive to oxidative damage because of high oxidative metabolism and a very high cytochrome P450 activity related to the xenobiotics biotransformation process and hypoxia simultaneously [54]. Another well-known hepatotoxic chemical is CCL4 that also induces harmful free radicals and oxidative stress conditions in the liver. Several studies have shown that CCL4 could increase liver toxicity enzymes in serum, inflammation, and necrosis in the liver of mice [55, 56]. Most of the hepatotoxic chemicals, including pesticides, provoke liver damage mainly by inducing lipid peroxidation [19]. In other words, permethrin, used in the present work, increased the hepatic MDA level. Nevertheless, the significant decrease in this parameter observed in the liver of mice treated with permethrin associated with dandelion confirmed that co-treatment with dandelion roots extract could effectively protect the liver against lipid peroxidation induced by permethrin.

On the whole, the ameliorative effect exerted by dandelion extract on the liver redox status of permethrin-exposed mice confirmed its *in vitro* antioxidant activity. According to Hu and Kitts [57], the inhibitory effect of dandelion on oxidative stress has been attributed to luteolin and luteolin-7-O-glucoside. These flavones significantly suppress the inducible nitric oxide synthase and cyclooxygenase-2 protein expressions in lipopolysaccharide activated RAW 264.7 cells [57].

The biochemical changes confirmed the histological study. Indeed, the liver histology of permethrin-intoxicated mice showed vacuolization, congestion, and condensed nuclei. The enlarged cell volume of damaged hepatocytes with chromatin condensation might suggest necrotic cell death induced by permethrin. Similarly, Roma et al. [33] have reported that hepatocytes of mice treated with graded doses of permethrin show clear disorganization with the presence of vacuoles in the cytoplasm which would be considered as a defense mechanism to inactivate or even eliminate the toxic compounds from the system. These vacuoles could permit the dislocation of the nucleus to the periphery of the cell, followed by nuclear atrophy and or its degradation. According to Kostka [40], administration of permethrin to rats for 14 days causes liver pathological changes inducing cell death by apoptosis. Permethrin appears to block phase G2 in the cell cycle which prevents the hepatocytes to enter in mitosis. Our microscopic observation of the hepatic tissue of mice co-treated with dandelion revealed an improvement of their liver histo-architecture without reaching the aspect observed in control mice. The effects of dandelion roots can be attributed to its richness in inulin [24]. Recently, this dietary fiber has been demonstrated, by Kalantari et al. [53], to protect against liver toxicity induced in mice by methotrexate, a folic acid antagonist. According to these authors, the hepatoprotective effects of inulin are mediated through its antioxidant activity, causing the reduction of miR-122 expression (a liver-specific miRNA involved in the regulation of liver function) and the inhibition of apoptosis via a decrease in B-cell lymphoma 2 activity and an increase in caspase-3 activity.

5. Conclusions

Our results revealed that alterations of biochemical parameters and liver histological profile in mice following permethrin exposure were reversed towards normalization by the treatment with dandelion roots extract (Figure 5). The protective effect of this plant might be due to its antioxidant capacity.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Committee for Ethics of Sfax Sciences Faculty (ethics approval number: 1204), and all efforts were made to minimize animal suffering and to reduce the number of animals used.

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Authors' contributions

Conceptualization, Supervision: Fatma Koubaa-Ghorbel, Mariem Chaâbane; Methodology: Bochra Choura, Mouna Turki, Fatma Ayadi ; Writing – review & editing: Fatma Koubaa-Ghorbel, Mariem Chaâbane; Writing – original draft: Fatma Koubaa-Ghorbel; Funding acquisition, Resources: Abdelfattah Feki.

Conflict of interest

The authors declared no conflict of interest.

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