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Effect of ethanolic extract of *Petroselinum crispum* (Mill.) Fuss (Apiaceae) strand on acetaminophen-induced hepatotoxicity in wistar rat

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Abstract
Petroselinum sativum (Apiaceae) plant is used in traditional medicine practice for the management of many pathologies including renal and liver diseases. Therefore, the current study aims to investigate the hepatoprotective effect of *Petroselinum sativum* (Apiaceae) against acetaminophen hepatotoxicity in rats. To achieve this aim, thirty adult male albino rats were divided into equal five groups as following, Group I, negative control received 0.9% NaCl orally (Control + NaCl); Groups II, Positive control, received acetaminophen solution at 200 mg/kg bw (Acetam. 200), Groups III, IV, and V received acetaminophen solution at 200 mg/kg bw and vitamin E (250 mg/kg bw), *Petroselinum sativum* strand ethanolic extract at 200 and 400 mg/kg bw respectively. At the end of experiment (after 7 days), blood samples were collected for biochemical and hematologic analysis.
Renal toxicity and oxidative stress were observed in untreated paracetamol-intoxicated rats asResult shown the body-weight gain (p<0.0001) was observed at the 200 mg/kg bw dose of EEBPs. Water consumption (p<0.001) and food consumption (p<0.0001) were improved at 200 and 400 mg/kg bw. Extract of *Petroselinum sativum* strand resulted in a significant improvement in blood ionograms and renal biomarkers compared with group II, including a significant (p<0.05; p<0.001; p<0.0001)) in creatinine, urea, and total protein. In the liver, there was a significant reduction in hepatic biomarkers and an improvement in hematological parameters.

Keywords: *Petroselinum sativum* (*Apiaceae*), acetaminophen, hepatotoxicity, wistar rat

1. Introduction
The kidney and liver are essential organs for the proper functioning of the body. Their importance is even greater in maintaining performance and regulating homeostasis. Involved in biochemical pathways, disease control, reproduction, energy and nutrient supply [1] the liver, like the kidney, is involved in the excretion of toxins that enter the bloodstream. This exposure to pollutants has effects on the organism [2]. These effects are caused by prolonged accumulation during drug intoxication. Drug poisoning is a common cause of emergency department visits. It is the most common cause of hospital admission in people under 30 years of age [3]. In France, the annual incidence is estimated to be about 4 per 1000 population, while in the United Kingdom the mortality rate has increased from 9 to 7 million [4]. A study conducted in Algeria showed that drug intoxication affects all age groups from 10 months to 87 years [5]. These include acetaminophen, which is used in recommanded doses for its antipyretic and analgesic effects. However, regular use of acetaminophen makes it a drug to be feared because of the risk of intoxication, which is often fatal [6]. Acetaminophen doses above 10 mg/kg bw are extremely dangerous [7]. These intoxications are characterized by nausea, vomiting, anorexia, and abdominal pain [8]. Acetaminophen poisoning is a leading cause of liver failure in countries such as the United States and the United Kingdom [9]. The associated damage can be prevented by the use of an antidote.
Petroselinum sativum commonly known as parsley, is a bright green with a height of between 25 and 80 cm. This plant is grown in Ivory coast. In its fresh state, parsley is used as a condiment for seasoning dishes. These plant is used as raw materials for the pharmaceutical industries, perfumery and cosmetics [10]. His differents parts have been traditionally used since antiquity for the treatment of numerous pathologies [11].
The aim of our study is to participate in the ethnopharmacological evaluation of *Petroselinum sativum* strands after oral acetaminophen intoxication in male Wistar rats.

2. Materials and Methods

2.1 Plant collection and extraction method

The *Petroselinum sativum* (Apiaceae) Strand was purchassed in Adjamé town to Côte d'Ivoire. This plant is authenticated the July 10 1980, by an expert in Botany (Professor Ake-Assi Laurent) of the Centre National de Floristique (UFR-Biosciences, Félix Houphouët-Boigny University, Abidjan, Côte d'Ivoire).

2.2 Preparation of the ethanolic extract

The fresh Strand of *Petroselinum sativum* (Apiaceae) are dried in ambient air, away from the sun. They are then milled in a micro mill (IKA LABORTECHNIK TYPE A 10). One hundred grams (100 g) of powder are added to one liter ethanol and boilled during 15 minutes. The solution obtained is carefully filtered on hydrophilic cotton and "Wattman" filter paper. The filtrate collected in a flask is then evaporated under vacum at 60 °C., using a rotary evaporator of "Büchi" type and oven-dried at 50±5 °C. A perfectly water-soluble fine powder it represents an ethanolic extract of *Petroselinum sativum*. The residual moisture is expressed at 0.17±0.045%. The yield of the extract obtained is estimated at 42.26%.

2.3 Animals

The healthy adult wistar albino rats (150- 250 g) were used in these experiment. Animals are kept in plastic cages at an ambiant temperature and exposed to a 12-hour light/dark cycle. They are fed ad libithum with pellets, dry bread, corn and dried herring fish and watered with tap water a twill. They were trated with human care in accordance with the guidelines of the Animal Research and Ethics Committee.

3. Experimental design

3.1 Acute Toxicity Study

Acute toxicity study of ethanolic extract of *Petroselinum sativum* strand, is carried out according to Organisation for Economic Co-operative and development 423 [12] guidelines. Animals was fasted 3 – 4 hures before experiment starting. They are treated by a single dose at different dose level. Three groups of albino wistar rat (n=3) is used in this study. The control group was treated with the normal saline; the group two received starting of EEBPs (1000 mg/kg bw) and the three group received EEBPs 2000 mg/kg bw). Animals are observed every 30 minutes for 24 hours and then for 14 days following administration of the extract. Particular attention should be paid to clinical signs as changes in body weight, skin and hair changes, somatomotor activity and behavior. Following by various other manifestation such as teeming, convulsions, diarrhea, salivation, sleep and death.

3.2 Evaluation of ethanolic extract of *Petroselinum sativum* (Mill.) Fuss (Apiaceae) Strand on acetaminophen-induced hepatotoxicity in Wistar rat

Thirty (30) Wistar rats weighing between 150- 200 g were divided into equal five groups as following

- Group I, negative control received 0.9% NaCl orally (Control + NaCl);
- Groups II, Positive control, received acetaminophen solution at 200 mg/kg bw (Acetam. 200);
- Groups III, IV, and V received acetaminophen solution at 200 mg/kg bw and vitamin E (250 mg/kg bw), *Petroselinum sativum* strand ethanolic extract at 200 and 400 mg/kg bw respectively.

The rats of groups III, IV and V; received Vitamin E (250 mg/kg bw) and doses 200 and 400 mg/kg bw of EEBPs respectively. On the eighth day, rats blood was collected from the orbital sinus for biochemical and hematologic analysis. Rats are then anesthetized by inhaling diethyl ether in a glass bell jar and sacrificed by cervical dislocation.

3.3 Determination of serum biochemical parameters and hematological parameters

The collected blood is centrifuged to separate the serum. The serum obtained was used to determine the biochemical parameters of liver like Alanine Aminotransferase (ALAT) Aspartate Aminotransferase (ASAT), Direct and Total Bilirubin and renal biomarkers like Sodium (Na^+), Potassium (K^+) and Chloride (Cl^-). The hematologic parameters studied were white blood cells; red blood cells; hemoglobin; hematocrit; mean corpuscular volume; mean corpuscular hemoglobin concentration; platelets; and lymphocyte.

4. Statistical analysis

The values are expressed as mean±standard of mean. GraphPad 8 software is used for statistical analysis of data and graphical representations. The significance differences between treatments is determine using to the variance analysis (ANOVA) of the Turkey- Kramer multiple comparison Test. Difference is considered as statistically significant when $p<0.05$.

5. Results and Discussion

Acetaminophen is a drug recommanded for its antipyretic an analgesic properties. However, its regular use carries risk associated with the production of toxic metabolites such as glucuronide and sulfate. In the liver, where they are metabolized, thes metabolites cause lesions leading to loss of functional integrity [13, 14], followed by nephrotoxicity in the kidney, where they are excreted. Acetaminophen intoxication resulted in changes in anthropometric parameters, liver and kidney parameters. Ethanolic extract of *Petroselinum sativum* strand is used for its hepatoprotective properties. This study was conducted to elucidate the hepatoprotective effects of ethanolic extract of *Petroselinum sativum* in intoxicated Wistar rats. Intoxication was induced in Wistar rats by daily administration of acetaminophen at a dose of 200 mg/kg bw for 7 days.

A single orale dose of EEBPs (2000 and 5000 mg/kg bw) did not cause any behavioral abnormalities or mortalitiy in wistar rat after 14 days of observation (Table I).

Table I: Acute toxicity

Parameters	30 to 60 min			24 hours			14 days		
Doses (mg/kg bw	**Control**	**2000**	**5000**	**Control**	**2000**	**5000**	**Control**	**2000**	**5000**
Respiratory rhythm	No	No	No	No	No	No	No	No	No
Contorsion	No	No	No	No	No	No	No	No	No
Isolation	No	No	No	No	No	No	No	No	No
Stretching	No	No	No	No	No	No	No	No	No
Diarrhea	No	No	No	No	No	No	No	No	No
Bleeding	No	No	No	No	No	No	No	No	No
Variation in food/ water	No	No	No	No	No	No	No	No	No
Body weight	No	No	No	No	No	No	No	No	Yes
Mortality	No	No	No	No	No	No	No	No	No

n=3, Control: rats treated with the normal saline (NaCl); 2000 &5000 : rats treated with EEBPs at 1000 or 5000 mg/kg bw respectively; EEBPs: Ethanolic Extract of *Petroselinum sativum*.

The non- lethality of EEBPs at the maximum dose of 5000 mg/kg bw indicates a higher LD_{50} [15]. According to the globally harmonized OECD classification, EEBPs are classified as category 5 and are considered to be non- toxic by the oral route. On the basis of these observations, the doses of 200 and 400 mg/kg bw were selected for further pharmacological studies.

Figure 1 respectively show the body weight and the change in weight of the experimental rats during the treatment period. A reduction in body weight loss is observed in the intoxicated rats.

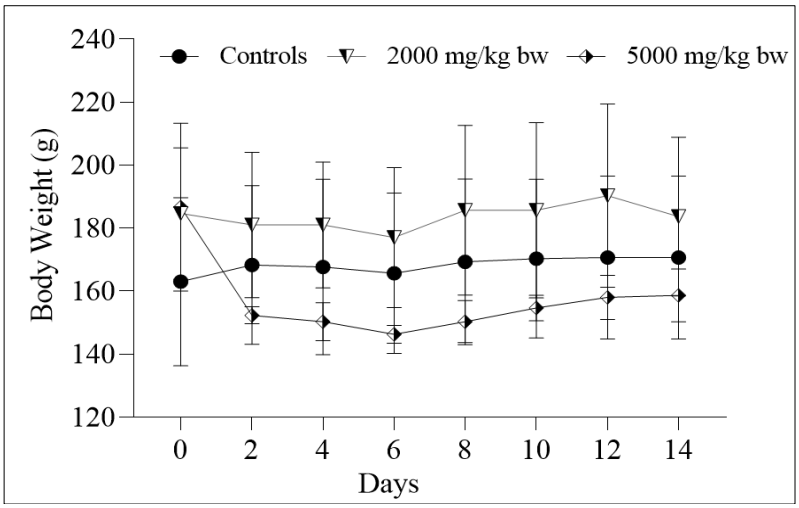

Fig 1: Effect of ethanolic extract of *Petroselinum sativum* strand (EEBPs) on Wistar rat weight; n=3, Control: rats treated with the normal saline (NaCl); 2000 & 5000: rats treated with EEBPs at 1000 or 5000 mg/kg bw respectively; EEBPs: Ethanolic Extract of *Petroselinum sativum*

When rats are intoxicated with acetaminophen administration, a reduction in food and water consumption is observed (Fig.2). The reduction in water and food consumption is the result of acetaminophen action on the hypothalamic structures responsible for digestion.

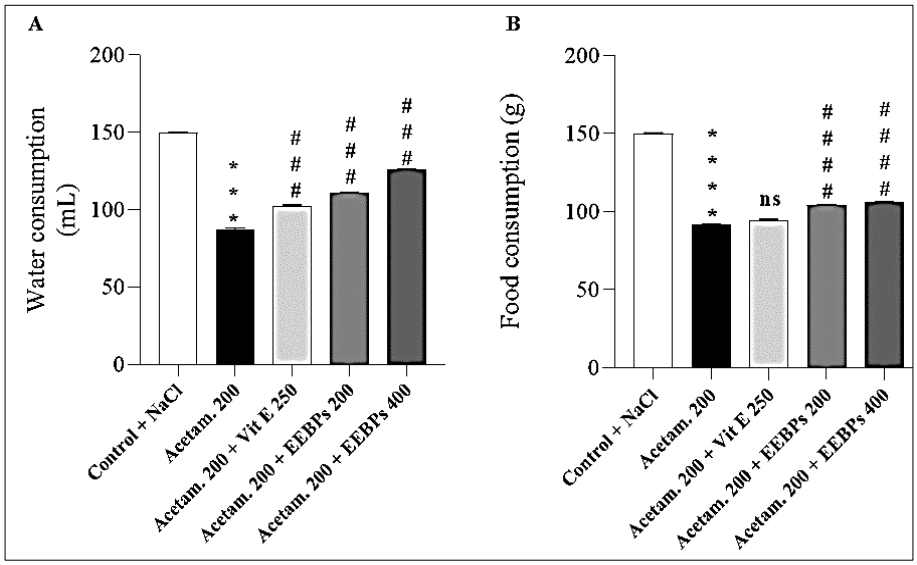

Fig 2: Effect of EEBPs on water (A) and food (B) consumption after acetaminophen treatment in rats.

Each value represents the mean±Standard deviation or Error Standard on the Mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One-way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test. Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (200 mg/ kg bw); Acetam. 200 + EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (400 mg/ kg bw).

The resulting weight loss is attributed to reduced water and food consumption, but also by the onset of anorexia nervosa (Figure 3).

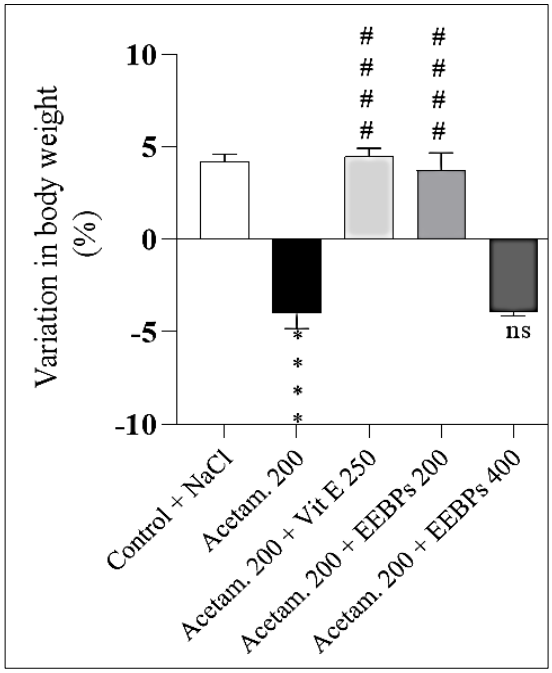

Fig 3: Histogram of the variation in body weight after administration of EEBPs to intoxicated rat with acetaminophen

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (200 mg/ kg bw); Acetam. 200 +EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (400 mg/ kg bw).

After 7 days of acetaminophen administration, a reduction in liver and kidney weights are observed (figure 4). The reduction in relative liver and kidney weights is thought to be due to the concentration of acetaminophen in the liver parenchyma and renal cortex.

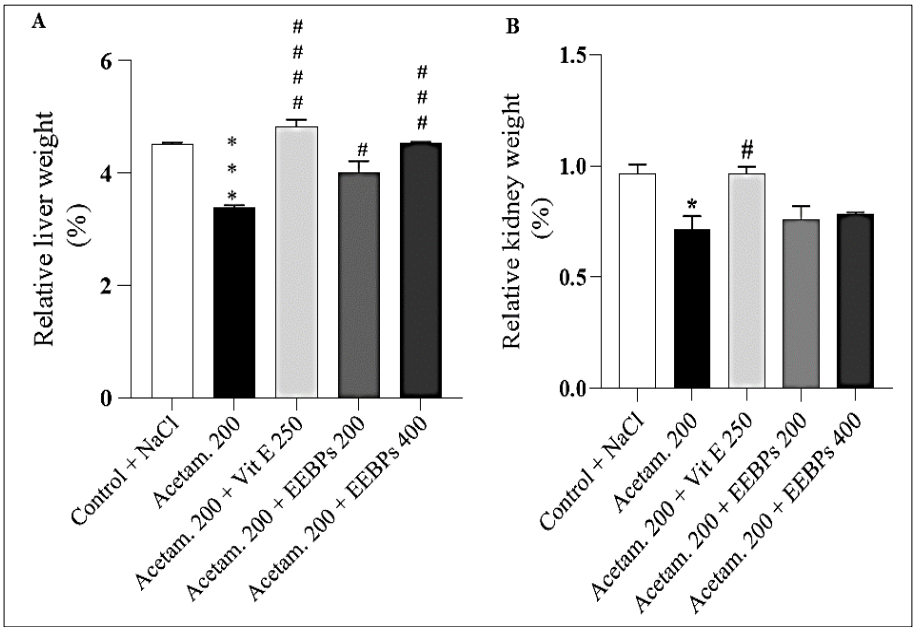

Fig 4: Variation in relative liver (A) and kidney (B) weights after administration of EEBPs to intoxicated with acetaminophen on rats

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (200 mg/ kg bw); Acetam. 200 +EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (400 mg/ kg bw).

Tables II, III, and V show the reductions in blood ionogram concentrations and kidney and liver parameters, respectively. Table V show a redduction in blood proteins. Daily oral administration of EEBPs at doses 200 and 400 mg/kg bw to rats made it possible to normalize water and food consumption, increase body weight and the relative weights of the liver and kidneys. EEBPs protect the liver and kidneys of rats from intoxication caused by daily intake of paracetamol. The hepatoprotective effect of EEBPs is presented by a decrease in ALAT, AST, Direct and Total Bilirubin levels. However, an increase in total proteins synthesis is observed. A fall in the plasma concentration of Total proteins [16] followed by a reduction in the plasma concentration of urea and creatinin levels in rats poisoned with acetaminophen [17]. EEBPs could both inhibit the formation of radicals free by restoration of antioxidant defense systems. Polyphenolics compounds prevent nephrotoxicity induced by oxidative stress [18]. Likewise, Terpenoid and phenolic compounds are known for their effect on liver cells. Triterpenes act as direct antioxidants by scavengering free radicals whilephenolic compound s mediate the expression of antioxidant enzymes, which play a rolein liver protection [19].

Table 2: Effects of EEBPs on blood ionograms in wistar intoxicated rats treated with acetaminophen for seven days

Parameters	Control + NaCl	Treatments and Doses (mg/Kg B. W)			
		Acetam. 200 + NaCl	Acetam. 200 + Vit. E 250	Acetam. 200 + EEBPs 200	Acetam. 200 + EEBPs 400
Na^+ (mmol/l)	158.7±0.33	$144±0.7^{***}$	$149.7±0,88^{\#\#}$	$159±0.8^{\#\#\#\#}$	$156.5±0.88^{\#\#\#\#}$
K^+ (mmol/l)	12.09±0,75	$20.37±0.04^{****}$	$12.94±0.99^{\#\#\#\#}$	$10.29±0.95^{\#\#\#\#}$	$11.3±0.13^{\#\#\#\#}$
Cl^- (mmol/l)	106.6±0.75	$112.1±0.55^{***}$	$93.15±0.86^{\#\#\#}$	$111.9±0.69^{\#}$	$109.1±0.32^{\#}$

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. On-way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200: Acetaminophen (200 mg/kg bw) + Ethanolic extract of Petroselinum sativum strand (200 mg/ kg bw); Acetam. 200 +EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of Petroselinum sativum strand (400 mg/ kg bw)

Table 3: Effect of EEBPs on rénal balance in acetaminophen intoxicated wistar rat

Parameters	Control + NaCl	Treatments and Doses (mg/kg b. w.)			
		Acetam. 250 + NaCl	Acetam. 250 +Vit. E 250	Acetam. 250 + EEBPs 200	Acetam. 250 + EEBPs 400
reate. (mg/L)	7.57±0.13	$10.15±0.14^{**}$	$7.55±0.03^{\#\#}$	$8.65±0.61^{\#}$	$7.8±0.29^{\#\#}$
Urea (g/L)	4.18±0.03	$6.31±0.19^{***}$	$5.16±0.02^{\#}$	$3.99±0.35^{\#\#\#\#}$	$3.58±0.19^{\#\#\#\#}$
T. Protein (g/L)	87.17±0.45	$70.9±0.4^{****}$	$84.4±0.06^{\#\#\#\#}$	$78.9±0.98^{\#\#\#\#}$	71.45±0.72
CRP (mg/L)	0.2±0.06	$0.32±0.01^{***}$	$0.27±0.08^{ns}$	$0.29±0.12^{ns}$	$0.26±0.03^{\#}$

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One-way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test. 388reate. : Creatinine; T. Protein : Total protein; CRP: C-reative Protein; Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200 : Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (200 mg/ kg bw); Acetam. 200 +EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (400 mg/ kg bw)

Table 4: Effect of EEBPs on liver parameters in acetaminophen-intoxicated Wistar rats

Parameters	Control + NaCl	Treatments and Doses (mg/kg b. w.)			
		Acetam. 200 + NaCl	Acetam. 200 + Vit. E 250	Acetam. 200 + EEBPs 200	Acetam. 200 + EEBPs 400
ALAT (UI/L)	55.3±0,1	$101.9±0,46^{****}$	$82.67±0.5^{\#\#\#\#}$	$36.95±0.37^{\#\#\#\#}$	$41.5±0.17^{\#\#\#\#}$
ASAT (UI/L)	372.1±0.36	$441.9±0.37^{****}$	$176.6±0.03^{\#\#\#\#}$	$299.9±0.09^{\#\#\#\#}$	$293.9±0.87^{\#\#\#\#}$
Bilirubin D (mg/dL)	0.23±0.01	$1.09±0.02^{****}$	$0.41±0.02^{\#\#\#}$	$0.46±0.01^{\#\#\#}$	$0.51±0.01^{\#\#\#}$
Bilirubin T(mg/dL)	1.21±0.01	$2.53±0.02^{***}$	$1.49±0.01^{\#\#}$	$1.55±0.03^{\#\#}$	$1.04±0.03^{\#\#\#}$

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One-way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test. Acetam. 200 + NaCl : Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250 : Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200 + EEBPs 200 : Acetaminophen (200 mg/kg bw) + Ethanolic extract of Petroselinum sativum strand (200 mg/ kg bw); Acetam. 200 + EEBPs 400 : Acetaminophen (200 mg/kg bw) + Ethanolic extract of Petroselinum sativum strand (400 mg/ kg bw)

Table 5: Hematological parameters of males rats after treatment with *Petroselinum sativum* strand ethanolic extract

Parameters	Control + NaCl	Treatments and Doses (mg/Kg B. W)			
		Acetam. 250 + NaCl	Acetam. 250 + Vit. E 250	Acetam. 250 + EEBPs 200	Acetam. 250 + EEBPs 400
RBC ($10^{6/\mu l}$)	6.47±0.13	3.00±0.25****	5.54±0.11$^{\#\#\#}$	4.61±0.38$^{\#\#}$	5.23±0.23$^{\#\#}$
WBC ($10^{6/\mu l}$)	10.27±0.48	7.93±0.61****	8.80±0.17$^{\#\#}$	10.97±0.58	13.3±0.35$^{\#\#}$
Hemoglobin (g/L)	10.40±0.10	12.67±0.14****	11.73±0.18$^{\#\#\#}$	12.10±0.17$^{\#\#}$	10.27±0.14$^{\#\#}$
Hematocrit (%)	39.15±0.55	20.10±0.90****	34.90±0,10$^{\#\#\#\#}$	22.37±0.47	26.83±0.34$^{\#\#\#\#}$
VGM (fl)	60.67±0.24	75.20±0.40****	60.70±0.34$^{\#\#\#\#}$	64.30±0.87$^{\#\#\#\#}$	65.47±0.92$^{\#\#\#\#}$
CCMH (g/L)	39.00±0.98	27.67±1.30***	60.95±0.35$^{\#\#\#\#}$	46.07±0.78$^{\#\#\#\#}$	42.63±0.72$^{\#\#\#\#}$
Platelets ($10^{9/\mu L}$)	1556.50±1.20	316.30±1.30****	709.00±2.5$^{\#\#\#\#}$	530.00±4.50$^{\#\#\#\#}$	1021±1.76$^{\#\#\#\#}$
Lymphocytes (%)	73.37±0.77	58.10±0.91****	80.80±0.80$^{\#\#\#\#}$	89.65±0.85$^{\#\#\#\#}$	74.37±0.73$^{\#\#\#\#}$

Each value represents the mean±Standard deviation or Error Standar on the mean (ESM); (n = 6); values are statistically different from control at $^{\#\#}p<0.05$ and $^{\#\#\#}p<0.01$. $^{\#\#\#\#}p<0.001$ and ** $p<0.01$. One way analysis of variance (ANOVA) and Tukey-Kramer multiple comparisons test.; Acetam. 200 + NaCl: Acetaminophen (200 mg/kg bw) + Salin solution; Acetam. 200 + Vit. E 250: Acetaminophen (200 mg/kg bw) + Vitamin E; Acetam. 200+EEBPs 200: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (200 mg/ kg bw); Acetam. 200 +EEBPs 400: Acetaminophen (200 mg/kg bw) + Ethanolic extract of *Petroselinum sativum* strand (400 mg/ kg bw)

6. Conclusion

Administration of acetaminophen 200 mg/kg bw per day for seven days cause disturbances in hepatic and renal parameters. These disturbances lead to hepatic and renal impairment. The results obtained demonstrated the preventive effect of *Petroselinum sativum* and its ability to modulate the toxic effects caused by acetaminophen. The results show that EEBPs normalize hepatic and renal parameters thanks to the presence of these phenolic compounds. In another study, we will prepare histological sections of liver and kidney to visualize the hepatoprotective effect of EEBPs.

7. References

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