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Article

Acute and chronic effects of methanolic extract of *Teucrium polium* on blood parameters and histo-pathology of liver and kidney in Female Rats

Krache Imane [1], *TrabsaHayet* [1, 2], *Boussoualim Naouel* [1*], *Ouhida Sorya* [3], *Arrar Lekhmici* [1]

[1] *Laboratory of Applied Biochemistry, Department of Biochemistry, Faculty of Nature and Life Sciences, University Ferhat Abbas of Setif 1, Setif 19000, Algeria;*
[2] *Faculties of Exact Sciencesand Nature and Life Sciences, University of Biskra, Biskra 07000,*
[3] *Laboratory of Anaphatology, Hospitalo-University Center (CHU) of Setif, Setif 19000, Algeria*
* *Corresponding author: Email: naouel_24@yahoo.fr*

ABSTRACT

Teucrium polium L. is commonly used as a medicinal plant in Algeria to fight various human diseases. In this study, extracting aerial parts of *T. polium* with methanol gave a dry matter yield of 8.24 %. The effects of methanolic extract of *T. polium* "TPME" were examined *per os* on female rats *Albino Wistar* for six weeks. Biochemical and hematological serum parameters and morphology and histopathology of organs of treated rats were studied. Acute toxicity showed low toxicity with a lethal dose of 50% LD_{50} > 2400 mg / Kg of body weight. These data can be used to classify these plants as slightly toxic. However, sub-acute treatment for six weeks of rats with 75, 150, and 300 mg of methanolic extract / Kg of body weight significantly increased the most studied hematological parameters. Biochemical analysis revealed a significant increase of renal parameters (urea, creatinine, uric acid, Na, and K), accompanied by an increase in the relative weight of kidney, lipidic (cholesterol), and hepatic glutamate oxaloacetate transaminase (GOT) values in all treated rats. Histopathological examination confirmed the biochemical tests by the observation of perilobular necrosis areas, bile duct and inflammatory infiltration of the liver, and the presence of marked intracytoplasmic vacuoles in the kidney with the dose 300 mg of TPME Kg of animal body weight. Use of *Teucrium polium* L. may cause hepatotoxicity and nephrotoxicity after prolonged herb administration.

Keywords: *Teucrium polium L*, TPME, $LD_{50,}$ biochemical parameters, toxicity.

INTRODUCTION

In Algeria, the genus *Teucrium* (Lamiaceae) includes 20 species among them we focus our study on *Teucrium polium*. This sub-species is an Algerian endemic plant known as "Jaadaa". It grows spontaneously in the south of the Sahara, mainly in stony beds of wadis and rocks [1]. Mountain germander, *Teucrium polium* L. originating from the southwest of Asia, Europe, and North Africa [2]. In the literature, the crude extracts of *T.*

polium have been investigated by several researchers and these studies have focused on common biological activities of the extract's antioxidant [3], fever-reducing, sudorific, antispasmodic, anodyne of *T. polium* were reported [4,5]. Pharmacological properties of *T. polium* L. include antibacterial, antifungal, antiviral[6] anti-inflammatory [7]analgesic, antispasmodic and hypolipidemic anti-ulcer, antidiabetic and diuretic [8, 9]effects. Phytochemical investigations have shown that *T. Polium* contains various compounds such as flavonoids, polyphenols, iridoids, tannins, essential oils, and alkaloids diterpenoids, principally furano neo clerodanes [10]. One of these major components is teucrine A[7].

However, many herbal medicinal plants, including *T. polium* were found to induce fatal hepatic effects and severe acute liver failure with marked hematological and biochemical alterations after prolonged administration [11]. Several cases of germander hepatitis were reported. Several reports linked the consumption of *T. polium* with hepatitis in man [12]. *polium* is consumed by many people in Mediterranean countries, such as Jordanians and Algerians for the treatment of several diseases, and there is no detailed information on the liver status after the consumption of the plant tea. Cytotoxic effects of *Teucrium polium* on some cell lines have been reported [13]. All studies have focused on aqueous or infusion ethanolic and ethyl acetate extracts, and no toxicological study has reported the effects of methanolic extract, which is rich in flavonoids and polyphenols [14]. It is well known that every drug has been associated with hepatotoxicity, almost certainly due to the pivotal role of the liver in drug metabolism. Hepatic metabolism is a mechanism that converts drugs and other compounds into products that are more easily excreted and that usually have a lower pharmacologic activity than the portent compound. A metabolite may have higher activity and/or greater toxicity than the original drug. Metabolites of the drugs that are excreted from kidneys may also cause cellular damage leading to kidney dysfunction [15].

The present study aims to investigate *in vivo* acute and chronic toxicity tests. The primary concern was to determine how toxic of methanolic extract of *T. Polium* TPME may be after acute administration to rats. Second, what would be the target organ for that toxicity, and whether there would be any correlation between the toxic effects and phytochemicals contained in the plant materials after chronic oral administration in rats?

MATERIAL AND METHODS

Plant material

The medicinal plant used in the present study was *Teucrium polium* called 'Jaadaa', which belongs to the Lamiaceae family. The aerial parts of *Teucrium polium* were collected during June 2008 from the Bougaa region in the north of Setif province in the northeast of Algeria, identified by Prof Laouar and a voucher specimen was deposited at the Applied Biochemistry Laboratory, University Ferhat Abbas, Setif, Algeria. The plant materials were dried at room temperature and powdered. The dry plant samples were extracted with absolute methanol. The dry extract was obtained after removing the solvent by evaporation under reduced pressure at 45° C. The extract was stored at – 20° C until use [2].

Animal

Experiments were performed on adult female Wistar albino rats, weighing 201.61 ± 7.04 g. The animals obtained from 'Institut Pasteur d'Algérie' were housed in groups of eight to ten in plastic cages at controlled

room temperature. Water and food were freely available and housed for seven days before the experiments in plastic cages under standard laboratory conditions (relative humidity 50-70%, 20-22°C temperature, 12:12 h light: dark cycles, with free access to food and water).

Oral acute toxicity

To study any possible toxic effect or changes in normal behavior, 5 groups of 7 rats were used in this experiment. The animals were fasted 24 hours before the treatment [16]. The acute toxicity of the plant was studied by preparing four different concentrations of the extract (0.3, 0,6, 1.2, and 2.4 g/kg), and administered orally to four groups of animals. The fifth group was taken as a control and given 1.0 ml NaCl 9‰. The behavioral changes, posture, and mortality were checked for 24 hours [17]. The method of Karber [2] was employed for the determination of an acute oral lethal dose of 50 % (LD_{50}).

Chronic toxicity

Animals were divided into four dose groups of 8 animals /dose. The first group was given 1ml of normal saline and taken as a control. The second, third, and fourth groups were given single doses of 75, 150, and 300 mg/ Kg of TPME extract by gavage daily. Body weight food consumption and clinical observations were monitored daily. Animals were fasted for 3h before dosing to facilitate the administration of the complete dose. All animals were treated for 42 days then, they were fasted for about three hours and sacrificed by euthanasia [1, 2] . Immediately after decapitation blood samples were obtained directly from the neck for hematological and serum analysis. By thoracic abdominal longitudinal incision, the animal abdomen was opened, the liver and kidney were removed, and the wet weights were recorded [16].

Hematological and biochemical analysis

Under ether anesthesia, all the rats were euthanized, and blood samples (2.0-4.0 ml) were withdrawn by sinus retro-orbital puncture in tubes containing EDTA and immediately processed for hematological tests using a Beckman colter-automatic hematology analyzer (USA). The hematological parameters measured were mean cell volume (MCV), red blood cells (RBC), white blood cells (WBC), hematocrit (HCT), platelets (PLT), mean platelet volume (MPV), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC). For biochemical analyses, 2 to 3 ml of blood were collected in a heparinized tube and centrifuged at 4000 g/ 5min. at4°C. The plasma obtained was stored at –20° C until use. The biochemical parameters including glucose (Glu), urea (Urea), creatinin (Creat), uric acid (UA), Na, K, cholesterol (Chol), triglycerides (TG), glutamate oxaloacetate transaminases (GOT), glutamate pyruvate transaminases (GPT), alkaline phosphatase (ALP) were measured at the Central Laboratory of the University Hospital (CHU) of Setif.

Evaluation of organs

The animals were weighed and euthanized by ether inhalation, all the organs/tissues were carefully examined macroscopically, and the brain, lungs, heart, spleen, liver, kidneys, and ovaries were weighed. The specimens were fixed in 10% formalin for 24 h, and standard dehydration and paraffin-wax embedding procedures were used. Sections (5 µm) were cut in a microtome and adhered to glass slides. Hematoxylin and eosin-stained slides were prepared by using standard methods and evaluated by light microscopy[2].

Statistical analysis

Statistical analysis was performed using Student's *t*-test for significance and analysis of variance (ANOVA), followed by Dunnett's test, which was done for multiple comparisons of the effect of different extract doses. Values of $p < 0.05$ were considered statistically significant. The comparison of the averages and the variances was done using Graph pad V8.

RESULTS

Oral acute toxicity

The methanolic extraction yielded 8.24 % of the aerial parts of *T. polium*. Rats were individually observed during the first 30 min and regularly during the first 24 hours after TPME administration. Clinical signs observed were summarized in Table 1. Mortality due to different doses administered to female rats was 10 %and 20 % for 1200 and 2400 mg/Kg, respectively. LD_{50} is higher than 2400 mg/kg body weight.

Dose (mg/kg)	Signs and symptoms	Time
0	Normal	-
300	Piloerection, stressed rats	15min.
600	Piloerection, Laboured breathing, and immobilization of the rats.	15min.
1200	Irritability, Tremblement, Labored breathing, immobilization of the rats	6 days
2400	Paralysis, Tremor, Labored breathing, Death	30 min.

Table 1. Signs and symptoms of TPME toxicity on female rat score based on the order of severity.

Effects of TPME *on* body weight

Percentage changes in body weights during the administration period are shown in Figure 1. Values for the group treated with 75 mg of TPME/kg of body weight slowly decreased compared to those of the control group, but the differences were not significant. Meanwhile, 150 and 300 mg/kg administration resulted in a significant decrease except in the fifth week with 300 mg/ Kg. It seems that, at the concentration of 300 mg/kg, there is a certain adaptation of the animals, which is not seen in the other concentrations.

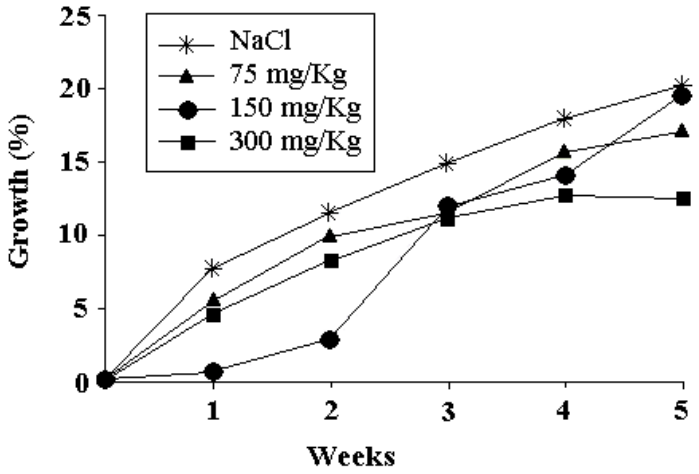

Figure 1. Changes of body weight growth (%) of treated rats and control.

The macroscopic analysis of the target organs of the treated animals (liver, lung, heart, brain, and spleen) did not show significant changes in color and texture when compared with the control group. Nevertheless, a significant increase in the values of the relative mass of kidneys with 150 and 300 mg/kg is observed. The results of organ weight are summarized in Figure 2.

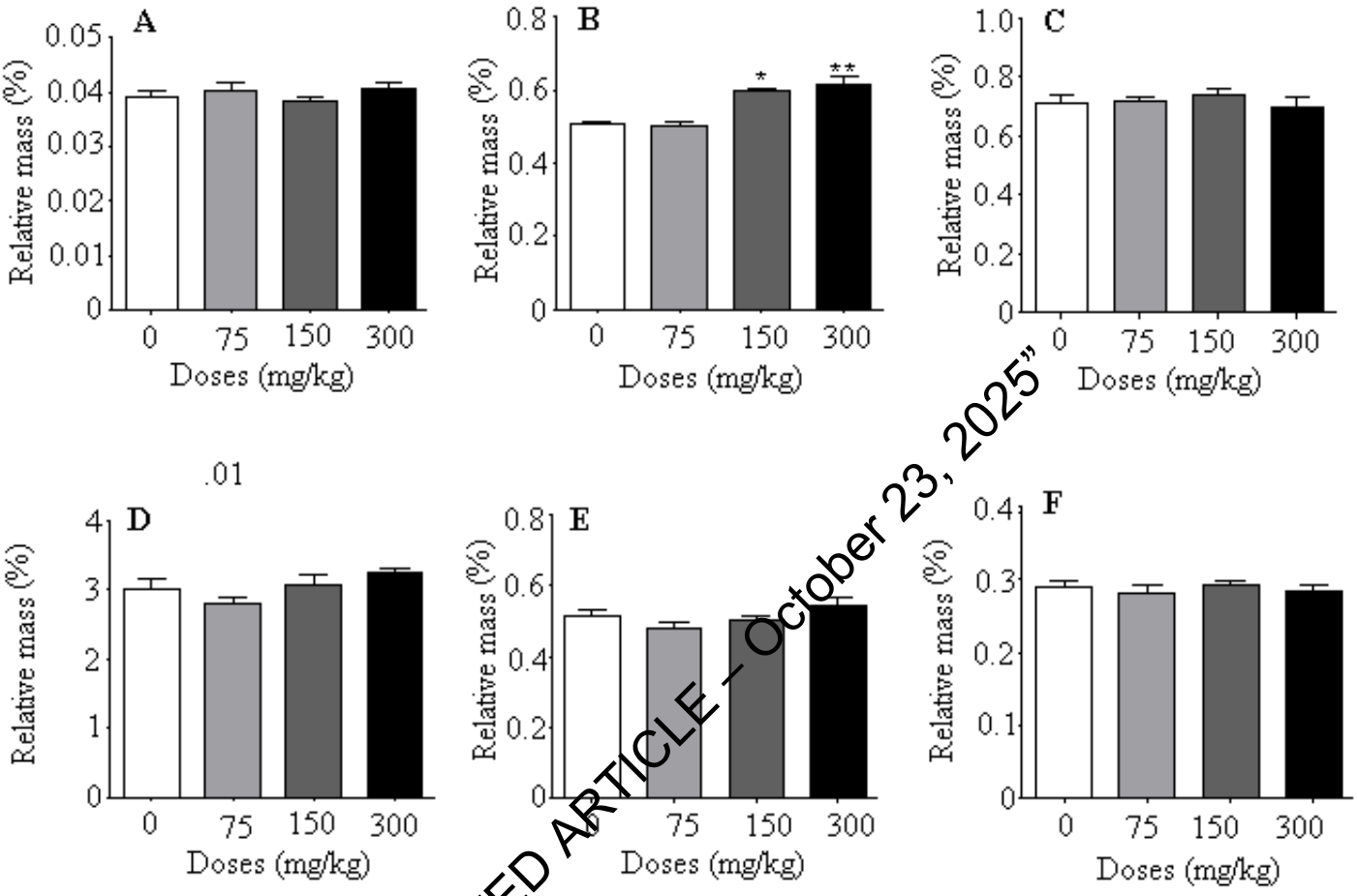

Figure 2:Effects of TPMEon organ relative weights of female rats in chronic toxicity. A; ovaries, B; kidneys, C; brain, D; liver, E; lungs, F; heart. The values are mean ± SEM (n = 7-8). * p <0.05, ** p <0.01.

Effects of TPME on hematological and biochemical parameters

Hematological parameters of the blood in the four groups of rats are represented in Table 2. A significant increase was observed in the following parameters: RBC, MPV, HCT, PLT, and HGB compared to the non-treated rats.

Haematologic tests	Non-treated	75 mg/kg	150 mg/kg	300 mg/kg
RBC (10^6/mm^3)	5.41 ± 0.29	7.65 ± 1.03**	6.36 ± 0.16*	**7.41 ± 0.32****
HCT (%)	29 ± 1.83	39.06 ± 0.32**	38.96 ± 0.71**	**36.52 ± 2.17***
PLT (10^3/mm)	303 ± 27.76	548 ± 19.78**	532.29 ± 20.93**	**638.60± 34.42****
MPV (^{3}µm)	6.46 ± 0.07	7.04 ± 0.05**	6.71 ± 0.09*	**7.12 ± 0.11****
HGB (gr/dl)	9.90 ± 0.59	14.23 ± 0.08**	13.93 ± 0.25**	**13.62 ± 0.61****

WBC (10^3/mm^3)	7.46 ± 0.82	5.80 ± 0.53	6.76 ± 0.55	**6.48 ± 0.43**
MCV (^{3}µm)	50.84 ± 0.67	50.40 ± 0.50	49.29 ± 0.47	**49.08 ± 1.11**
MCH (pg)	17.81 ± 0.23	18.35 ± 0.13	17.42 ± 0.26	**17.63 ± 0.37**
MCHC (g/dl)	**35.35 ± 0.41**	**36.32 ± 0.19**	**35.53 ± 0.23**	**35.93 ± 0.41**

Table 2. Hematological data for female rats orally treated by TPME for 6 weeks * P<0.05, **P<0.01.

Similarly, biochemical parameters in the four groups of rats, Glu, Creat, K, Urea, Na, UA, and GOT, were significantly increased after chronic treatment with 75, 150, and 300 mg/kg and a significant increase in GPT levels with the dose of 75 mg/kg and in Chol level with the dose of 300 mg/kg compared to controls (Table 3).

Biochemical data	Non-treated	75 mg/kg	150 mg/kg	300 mg/kg
Na (mEq/L)	134.57 ± 2.10	169.07± 4.74**	170.13 ± 1.32**	**165.55 ± 1.81****
UA (mg/ L)	8 ± 1.21	27.14 ± 1.97**	17.13 ± 1.29*	**16.53 ± 2.90***
Urea (gr/ L)	0.51 ± 0.03	0.64 ± 0.05	0.65 ± 0.03	**0.61 ± 0.06**
Chol (gr/ L)	0.34 ± 0.08	0.33 ± 0.026	0.35 ± 0.03	**0.57 ± 0.041****
TG (gr/ L)	0.47 ± 0.084	0.39 ± 0.02	0.49 ± 0.03	**0.39 ± 0.04**
ALP (UI/L)	93.80 ± 7.07	74.33 ± 2.67	97.83 ± 3.31	**86.30 ± 41.98**
GOT (UI/L)	43.86 ± 3.77	96.67± 7.84**	85.17 ± 4.39**	**85.00 ± 16.16****
GPT (UI/L)	96.67 ± 8.66	35.57 ± 3.09**	59.43 ± 5.22**	**56.00 ± 16.76****
Creat (mg/ L)	6.58 ± 0.37	6.15 ± 0.27	6.79 ± 0.36	**6.0 ± 0.45**
Glu (gr/ L)	**1.47 ± 0.11**	**1.27 ± 0.11**	**1.30 ± 0.06**	**1.24 ± 0.05**

Table 3. Serum biochemical data for female rats orally treated by TPME for 6 weeks. Values are expressed as mean (n=8) ± SED, * p ≤0.05, ** p ≤0.01.

Histopathological examination

The observation of the histological slices of the liver and kidneys of treated rats compared to controls is presented in Figures 3 and 4, respectively. Kidney examination revealed the presence of intracytoplasmic vacuoles; precisely on the cortical area, a dose of 300 mg/kg was used. Histological examination of the liver showed moderate portal inflammatory infiltrates and vascular congestion around vessels. Mild lobular necrosis, vascular congestion, and steatosis were also seen in the cuts of the rats treated with a group of 75 mg/kg. A perilobular necrosis and an inflammatory infiltrate around the portal vein of the cuts of the rats treated with the second group. Moderate inflammatory infiltrates in portal tracts were seen, and proliferation of bile ducts and portal fibrosis were noted on 300 mg/kg of TPME.

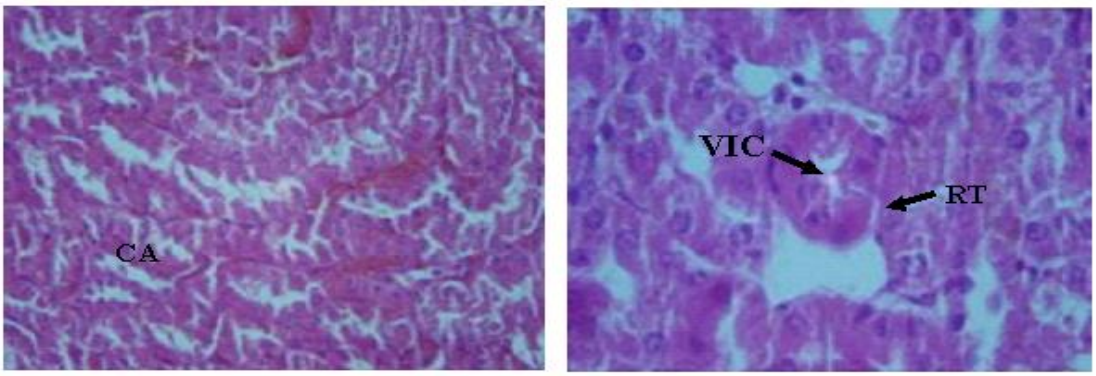

Figure 3. Renal Histological cuts of the control group and treated rats with 300 mg/kg TPME.(hematoxyline, eosin; Ã—600). **CA: cortical area, RT: renal tube, VIC: intracytoplasmic vacuoles.**

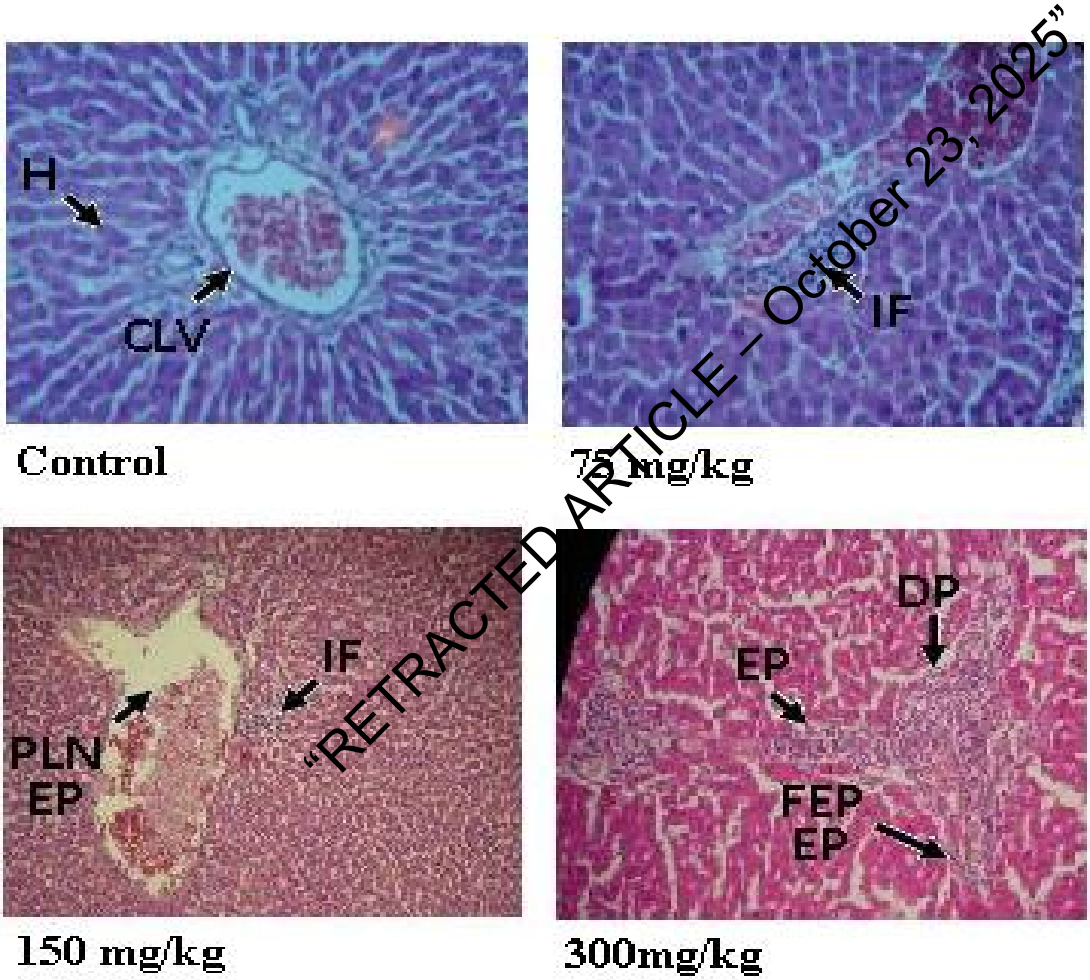

Figure 4. Hepatic histological cuts of the control group and rats treated with 75 mg/kg, 150 mg/kg, and 300 mg/kg *T. polium* extract. (hematoxyline/eosin).H: hepatic cell, CLV: centrolobular vein, IF: Inflammatory infiltrate, PLN: perilobular necrosis, EP: space porte, DP: duct proliferation, FEP: Fibrosis in bridge.

DISCUSSION

Acute toxicity

No sign of acute toxicity for female rats treated by TPME was seen; this suggests that LD_{50} is higher than 2400 mg/Kg of body weight. The results are in agreement with studies of [14, 18] dismount that the nature of the sex influences the administration of this plant. This data is correlated with the adopted administration route, which targets the liver directly [16].

Body weight

A moderately significant reduction of (3%) in body weights during the sixth week of treated rats was reported with a dose of 75 mg/kg of TPME. Indeed, the loss of a rat's weight is correlated with the animal's physiological state and can be explained by a reduction in food consumption. This result agrees with those published by [14]where female rats show a significant decrease of body weight ($p<0.05$) with a dose of 100 mg/kg of aqueous extract of *T. polium*. The other groups show a normal evolution of their body weight as shows compared to the control during the experimentation duration.

Effects of TPME on hematological and biochemical parameters

According to the bibliography [11, 14], no disturbance of hematologic values was reported in rats treated with the aqueous and ethanolic extract of *T. polium*. Conversely, the methanolic extract increased the red globule cells observed with the three groups treated (75, 150, 300 mg/kg), implying a potentiality of erythropoiesis. However, these data are associated with hematocrit and hemoglobin increases with 75 mg/kg doses and 300 mg/kg. The significant increase in hemoglobin is associated with a significant increase in MCV and MCH, indicating a tendency to macrocytose and hypochromy. Platelet level increase on 75 and 300 mg/kg doses can be commented on by secondary hyperplaquettosis associated with an attack of spleen [19].

TPME shows a significant reduction in glucose with the dose of 75 mg/kg, this agrees with works [20, 21,] and [22]. Several flavonoids such as quercetin and different terpenoids discovered in *T. Polium* decrease the serum glucose level only in diabetic rats. It is, therefore, possible that these effects of the areal parts of *T. polium can* be due to the flavonoids and/or terpenoids accorded the hypoglycemic effects of aqueous *T. polium* extract to their composition in ions: potassium, Zinc, Cadmium, and Chromium. This suggests that the hypoglycemic property of this plant depends on the type of ground and the geographical area of harvest. The richness of *T. polium* in flavonoids and polyphenolic compounds such as cirsimaritin, apigenin-7-glucoside, vicenin, and luteolin-7-glucoside gifted of antioxidant activities in particular with the dose of 50 and 100 mg/kg [23, 24], thus explain the use of *T. polium* in folk medicine in the treatment of diabetes [8]. Cholesterol level was appreciably increased after chronic treatment with the dose of 300 mg/kg TPME. This agrees with the observations of the human ones 11 and [12].

Renal parameters showed a very significant level of urea, creat Na, and K. Urea increases could be explained by an increase in degradation of protein compounds, but also by an injury of renal function [19]. Kidneys were damaged and its histological aspect indicated a remarkable cytoplasmic vacuolization of tubular cells of the cortical area which explains the increase in the relative weight of the kidney (mainly with the doses of 150

and 300 mg/kg), while the other values of the various studied organs are normal. These results agree with the works of [25, 26,] which showed a significant increase in urea and creatinine levels in diabetic rabbits after treatment by aqueous extract of T. polium, confirmed by apoptosis in some renal sections.

The values of the hepatic analysis presented a significantly higher TGO in the three groups and a reduction in TGP in the first group. The hepatorenal toxicity of TP has always been a topic of scientific debate, but its beneficial health effects have gradually reappeared with new insight. This is due to our increasing knowledge of different TP chemotypes and toxicity new chemical tools and techniques, the dose-dependent nature of TP properties, the route of TP administration, acute and chronic courses of treatment, diverse plant species, and the disparity between animal and human [27].

Histopathological examination

Histological examinations of the liver are the same ones observed in this study, particularly in treated rats with 150 and 300 mg/kg doses. These results are also supported by the preceding work of [14,] which is an acute and serious failure of the liver in a man after prolonged administration of *T. polium, T. chamaedrys*, and *T. Capitatum* [28].

Although the mechanism of hepatotoxicity of *T. polium* is not well elucidated, tacrine A and several diterpenoids neoclerodans, present in areal parts, were suspected as hepatotoxic precursors of this plant [19, 28]. Experiments in mice showed a formation of toxic metabolites starting from these diterpenoids, which interact with cytochrome P450 3A and the inactivation of glutathione. The detoxified diterpenoids are effective inductors of hepatocyte apoptosis[13, 29]. That suggests a dual mechanism, direct toxicity, and a series of secondary immune reactions 28 attenuate liver necrosis. Direct cytotoxicity is known for being the fundamental cause of damage to the liver in certain cases, while in others, the immunological mechanisms or even a mixture of cytotoxicity and immunogenicity can be implied [30]. A covalent bond of the epoxy hydrolase will take place on the external surface of human hepatocytes and, in the presence of Teucrine A, could start immune reactions and induce a formation of autoantibody, leading the cells to apoptosis[31].

CONCLUSIONS

Teucrium polium's (TPME) methanolic extract demonstrates low acute toxicity in female Wistar albino rats, with an LD_{50} exceeding 2400 mg/kg body weight. However, sub-acute administration of TPME for six weeks at doses of 75, 150, and 300 mg/kg resulted in significant alterations in hematological and biochemical parameters, indicating dose-dependent toxicity.

Specifically, TPME induced changes in red blood cell parameters, suggesting a potential impact on erythropoiesis. Moreover, it significantly increased renal parameters (urea, creatinine, uric acid, Na, and K) and liver enzymes (GOT), suggesting potential nephrotoxicity and hepatotoxicity. These findings were further supported by histopathological examinations revealing intracytoplasmic vacuoles in kidney cells and various degrees of liver damage, including perilobular necrosis, inflammatory infiltrates, bile duct proliferation, and portal fibrosis.

In conclusion, while TPME may be relatively safe for acute use, prolonged administration can lead to hepatotoxicity and nephrotoxicity in rats. These findings raise concerns regarding the safety of long-term use of *Teucrium polium* in traditional medicine and highlight the need for further investigation into its potential adverse effects in humans.

Author Contributions: methodology, KI.; software, BN; validation, OS., TH, and BN; formal analysis, KI.; investigation, KI.; resources, OS.; data curation, KI; writing—original draft preparation, BN.; writing—review and editing, TH.; visualization, AL.; supervision, AL.; project administration, KI.; funding acquisition, AL. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethics statement

The animal experiments were according to the guidelines and procedural details in the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 86-23, 1985). Permission for experimental use was obtained from the Laboratory of Applied Biochemistry, Ferhat Abbas University of Setif 1. All procedures were performed in compliance with laws and institutional guidelines.

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Conflicts of Interest: The authors declare no conflict of interest.

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Correspondence should be addressed to *naouel_24@yahoo.fr*

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