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Evaluation of acute and chronic toxic effects of Algerian germander in Swiss albino mice

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ABSTRACT

Germander (*Teucrium polium*) is commonly used as medicinal plant in Algeria against a variety of human diseases. This study aims to evaluate toxic effects of *T. polium* methanol extract (TPME) in *Swiss albino* mice. Biochemical parameters, organs morophology and histopathology were investigated. TPME gave a LD_{50} of 442.81 and 686.77 mg/kg of body weight (b.w.) in male and female mice, respectively. The acute treatment for seven days at a dose of 100 mg/kg of b.w. didn't show any difference in body weight, relative mass and blood biochemical parameters. Histopathological examination revealed a moderate congestion in kidneys and an inflammatory infiltrate in liver. The chronic effect for 30 days at doses of 50 and 75 mg of TPME/kg of b.w. resulted in a significant increase of renal (urea), hepatic (aspartate aminotransferase and alanine aminotransferase) parameters, accompanied by a significant decrease of cholesterol level. Histopathological examination confirmed the biochemical tests by the observation of necrosis areas, ballooning degeneration and peliosis in liver sections and the presence of marked vascular congestion in kidneys in both sexes. In conclusion, the use of *Teucrium polium* L. may cause hepatotoxicity and nephrotoxicity after prolonged herb administration.

INTRODUCTION

Traditional medicine has maintained greater popularity all over the world and the use is rapidly on the increase. The use of herbs in treatment of disease has declined in the west, but it continues to exist throughout the developing countries (Mugisha *et al*., 2014). Mountain germander, *Teucrium polium* L (Ja'adeh in Arabic) is a shrub plant which grows wild in Mediterranean countries (El-Mokasabi, 2014). In folk medicine, *Teucrium* species have been used for their diuretic, diaphoretic, tonic, antipyretic, antispasmodic, anti ulcer and antidiabetic properties (Ljubuncic *et al*., 2006; Twaij and Al-Dujaili, 2014). Tea preparation of the aerial parts of the plant of *T. polium* is used for to treat abdominal colic, headache, diabetes and as an astringent (Dehghani *et al*., 2005). In experimental animal models the aqueous extract of the plant exhibited antispasmodic, anorexic, hypolipidemic effects (Gharaibeh *et al.*, 1988; Rasekh *et al.*, 2001) . Most of these effects have been related to the volatile oil, flavonoids, phenylpropanoid glycosides, iridoid glycosides, terpenoids as diterpenes, monoterpenes and sesquiterpenes components (Guetat and Al-Ghamdi, 2014; Elmasri *et al*., 2014), principally furano-neoclerodanes (Fiorentino *et al*., 2011). One of these major compounds is teucrine A (Abdualmdjid and Sergi, 2013). *Teucrium polium* is consumed as tea by many people in Mediterranean countries such as Jordanians, Iranians and Algerians for the treatment of several diseases, and there is no detailed informations on the liver status. However, many herbal medicinal plants including *T. polium* were found to induce fatal hepatic effects and severe acute liver failure with marked haematological and biochemical alterations after prolonged administration (Khleifat *et al.*, 2002). Several cases of germander hepatitis were reported linked the herb consumption with hepatitis in man (Mazokopakis, 2004; Savvidou *et al*., 2007).

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All studies has been focused on aqueous or infusion (Zal *et al*., 2001; Rasekh *et al*., 2005), ethanolic (Al Ashban *et al.*, 2006; Nematollahi-Mahani *et al*., 2007) and no toxicological studies has reported the *in vivo* toxic effects of methanolic extract, which is rich in flavonoids and terpenoids. The major flavonoids from *T. polium* methanolic extract are rutin and apigenin (Lewandowska *et al*., 2014).

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, first and foremost, a mechanism that converts drugs and other compounds into products that are easily excreted and that usually have a lower pharmacologic activity than the portent compound (Sergi, 2013). 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 (Atici *et al*., 2005).

In the present study, the focus was on the acute and chronic toxicity assays of *Teucrium polium* methanolic extract. The first concern was to determine how toxic effect of TPME may be after acute administration to the two sexes of mice as a model. The second is to investigate the target organ for the toxicity after chronic administration.

MATERIALS AND METHODS

Plant material

The green aerial parts of *Teucrium polium* were collected during June 2011 from Ouled Sidi Amor, Bordj Bouarreridj province in the northeast of Algeria, identified by Prof H. Laouer and a voucher specimen was deposited at the Department of vegetal biology and Ecology, University Ferhat Abbas, Setif 1, Algeria. The plant material was dried at room temperature and powdered. The obtained powder was extracted with absolute methanol for seven days. The methanolic extract was obtained after removing the solvent by rotary evaporation under reduced pressure at 45° C, then air dried and stored at -20° C until use (Arrar *et al*., 2013).

Animals

Experiments were performed on adult male and female *Swiss albino* mice weighting 25 to 30 g. The animals obtained from 'Institut Pasteur d'Algérie', Algiers, were kept for one week for acclimatization before the commencement of experiment. Mice were kept in polycarbonate cages under standard conditions (temperature 24 ± 3°C) with 12 h light/dark cycle. They were provided with standard pellet diet and water *ad libitum.* All procedures were performed in compliance with laws and institutional guidelines.

Acute toxicity assay

In order to study the toxic effect or changes in normal behavior, eight (8) groups of male and female mice (n = 10) were used. The animals were fasted 24 hours before the treatment. The TPME was freshly dissolved in normal saline solution 0.9% (vehicle) at the corresponding concentration immediately before administration (Rasekh *et al*., 2005). The acute toxicity of the plant was studied by preparing four different concentrations of the TPME: 100, 150, 200, 250, 300, 350 and 400 mg/kg and administered intraperitoneally to seven groups of animals .The eighth group was taken as a control and was given 100 µl of normal saline. The behavioral changes, posture and mortality were checked for 24 hours. Alive mice were kept under observation for 14 days (Umamaheswari *et al*., 2007). Mortality was recorded daily and the LD_{50} value was estimated by computerized techniques (Abu Sitta *et al*., 2009).

However, for the acute treatment, male and female mice were organized into two groups of 8 animals per dose (Khleifat *et al*., 2002). The first one was given 100 µl normal saline and taken as a control and the second one was given a single intraperitoneal dose of 100 mg of TPME / Kg b.w. (100 µl) for 7 days (Bouzidi *et al*.,2011 with slight modifications).

Chronic toxicity treatment

Animals were divided into three groups (n = 8). The first group was given normal saline and taken as a control. The second and third ones were given a single intraperitoneal dose of 50 or 75 mg of TPME / Kg b.w. (volume 100 µl) once daily for a month. Body weight, food consumption and clinical observations were recorded daily. 24 h after the last treatment, all treated animals were fasted for about 3 hours and sacrificed by decapitation under anesthesia. Blood samples were collected in heparinized tubes and plasma were obtained by centrifugation at 4000 g for 5 min. at 4°C then stored at -20° C until use. Organs including testes, ovaries, liver, kidneys, heart, lungs and brain were obtained, weighed and placed in formalin for histopathological examination (Abu Sitta *et al*., 2009). Paraffin sections of liver and kidney were made and stained with hematoxylin/eosin then microscopic evaluation was carried out in the laboratory of Anatomo-pathology, CHU of Setif.

Biochemical analysis

The collected plasma samples obtained from acute and chronic toxicity experiments were assayed for biochemical parameters, including glucose (Glu), urea, creatinin (Creat), Na, K, cholesterol (Chol), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alcaline phosphatase (ALP), measured with Beckman Coulter Synchro CX-9 Clinical System ALX, at the Central Laboratory of the CHU of Setif, Algeria.

Statistical analysis

Statistical analysis were performed using Student's *t*-test for significance and analysis of variance univariate (ANOVA) followed by Dunnett's test for the multiple comparison 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 « Graphpad Prism» version 5.0. LD_{50} is determined using stat PLUS 5.8.0.0 (2009).

RESULTS

Lethal toxicity of TPME

Males and females mice were individually observed during the first 30 min and regularly during the first 24 h after TPME administration. The estimation of LD_{50} value of TPME, using computerized technique was about 442.81 and 686.77 mg/kg of body weight in male and female mice, respectively (Table 1). Survived mice were apparently healthy.

Table 1: Toxic Effect of TPME in mice. TPME was administered as single intraperitoneal dose to groups of mice (n=10). All treated mice were carefully examined for any signs of toxicity during a period of 14 days.

Dose (mg/kg)	Signs and symptoms	% of Death	
		Male	Female
0	Normal	0	0
100	stressed mice	0	0
150	piloerection	0	0
200	piloerection	10	0
250	piloerection, stressed mice	10	0
300	Piloerection, immobilization of the mice	10	0
350	Irritability, immobilization of the mice	20	0
400	Paralysis, Tremor , Labored breathing, Death	50	20

Effects of *T. polium on* body and organ weights

In general, no significant differences were observed in body weight of both sexes between treated and control. Nevertheless, body weight of male mice was significantly decreased at the first week compared to those of the controls group in chronic conditions but after, they restore their body weight normally during the period of experimentation. Percentages of changes in body weights during the chronic administration period are shown in Figure 1. The macroscopic analysis of the target organs in acute and chronic treatment of both animals (liver, kidneys, lung, heart, brain and spleen) did not show significant changes in color, texture and values compared with the control group.

Effects of TPME on biochemical parameters

In acute treatment, no significant changes were observed in both sexes. The effect of chronic treatment with 100 mg of TPME /kg b.w., for 30 days on biochemical parameters is shown in table 2. Urea, AST and ALT in female and AST in male were significantly increased after chronic treatment, and a significant decrease in cholesterol level in both sexes compared to controls (Table 2).

Histopathological examination

The observation of the histological slices of kidneys of treated mice compared to controls are presented in Figures 2, 3. The examination of kidneys revealed presence of a vascular congestion around vessels in acute and chronic intraperitoneal administration of TPME in both sexes. Histological examination of the liver of treated animals in acute toxicity conditions showed portal congestion and inflammatory infiltrates. It also showed important inflammatory infiltrates of mono and polynuclear neutrophils around vessels and in sinusoids, a vascular congestion, necrosis, peliosis and ballooning degeneration was also observed in both animals treated in chrnonic toxicity especially with 75 mg/kg (Fig. 4, 5).

Table 2: Serum biochemical parameters for male and female mice intraperitoneally treated by TPME for 30 days.

Biochemical parameters	Male			Female		
	Control	50 mg/kg	75 mg/kg	Control	50 mg/kg	75 mg/kg
Urea (gr/ L)	ND	ND	ND	0.56 ± 0.02	0.69 ± 0.04	0.77 ± 0.07*
Chol (gr/ L)	1.47 ± 0.09	1.13 ± 0.06**	1.08 ± 0.04**	1.24 ± 0.01	0.97 ± 0.04*	0.98 ± 0.04*
TG (gr/ L)	1.60 ± 0.07	1.53 ± 0.06	1.62 ± 0.14	1.10 ± 0.05	0.87 ± 0.05	1.24 ± 0.15
ALP (UI/L)	114.5 ± 18.08	89.83 ± 14.10	71.20 ± 10.87	251.0 ± 10.16	230.1 ± 8.20	252.3 ± 17.05
AST (UI/L)	193.7 ± 15.93	257.2±14.11*	196.2 ± 14.88	191.0 ± 8.90	243.2±8.003**	188.6 ± 10.96
ALT (UI/L)	33.33 ± 1.54	38.20 ± 3.26	32.80 ± 7.08	46.43 ± 2.60	59.13 ± 1.06**	50.67 ± 4.38
Creat (mg/ L)	10.46 ± 1.15	7.95 ± 0.68	10.06 ± 2.29	9.83 ± 0.67	11.92 ± 0.56	12.37 ± 1.94
Glu (gr/ L)	0.99 ± 0.05	0.76 ± 0.07	0.94 ± 0.09	1.11 ± 0.17	1.31± 0.17	1.34± 0.25
Na (meq/l)	171.70 ± 2.03	166.90 ± 2.48	164.10 ± 4.07	172.6 ± 3.37	172.9 ± 0.79	169.3 ± 5.84
K (meq/l)	5.47 ± 0.22	5.743 ± 0.27	6.23 ± 0.25	5.06 ± 0.23	5.50 ± 0.25	6.23 ± 0.96

Values are expressed as mean (n = 8) ± SEM ,* $p \leq 0.05$, ** $p \leq 0.01$. ND: not determinated.

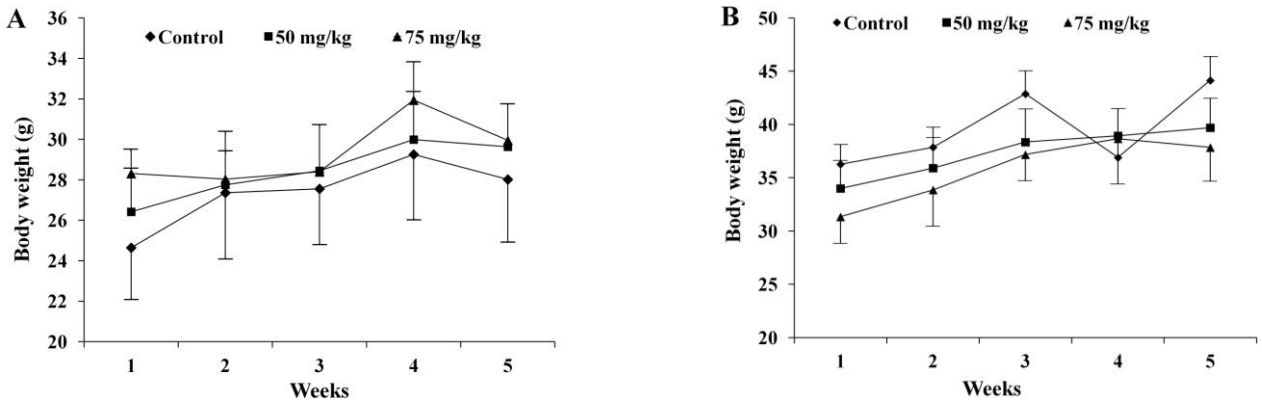

Fig. 1: Changes of body weight of male (A) and female (B) mice treated with *Teucrium polium* methanolic extract.

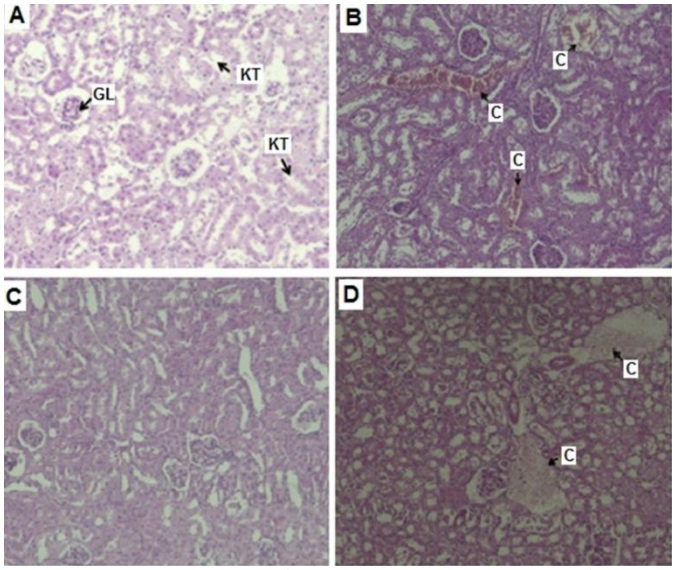

Fig. 2 : Renal histological cuts of male (A: control, B: treated) and female (C: control, D: teated) mice. Histological slides were carried out after treatment of animals with 100 mg/kg of TPME (Hematoxylin/eosin stain; X 10).GL: glomeruli, KT: kidney tubes, C: congestion.

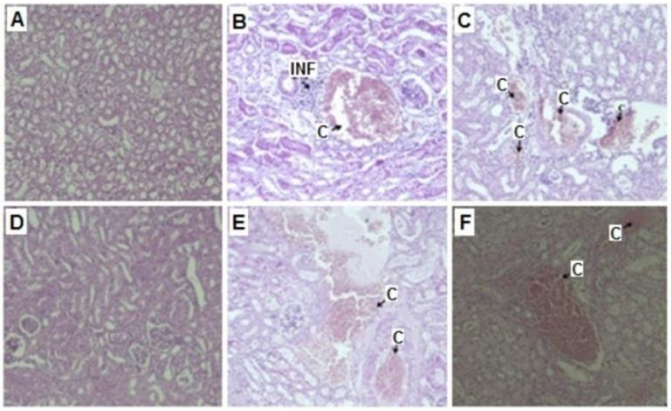

Fig. 3 : Renal Histological cuts of male and female control group (A and D) and treated mice with dose of 50 (B and E) and 75 (C and F) mg/kg of TPME (Hematoxylin/eosin stain, X 100).C: congestion, INF: inflammatory infiltrate.

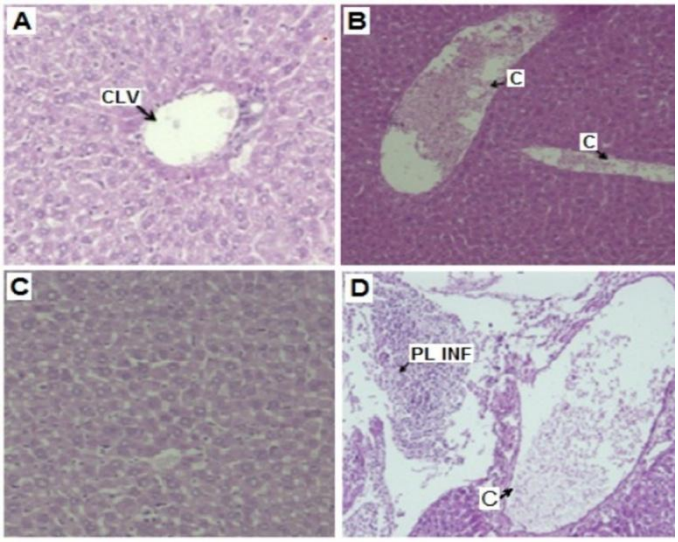

Fig. 4 : Hepatic histological sections of a male and female control group (A and C) and treated mice (B and D) with 100 mg/kg of TPME (Hematoxylin/eosin stain; X 100). CLV: centolobular vein, C: congestion, PL INF: polynuclear inflammatory infiltrate.

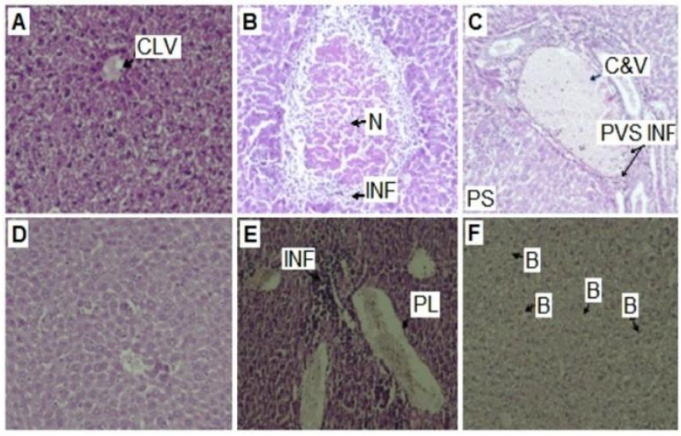

Fig. 5 : Hepatic Histological sections of a male and female control group and treated mice with dose of 50 and 75 mg/kg of TPME (Hematoxylin/eosin stain; X 100)**.** N: necrosis, INF: inflammatory infiltrate, PS: portal space, V&C: vasodilatation and congestion, PVS INF: perivascular inflammatory infiltrate**,** PL: peliosis, B: ballooning.

DISCUSSION

In the literature reviewed, no data referring to the acute and chronic activity of *Teucrium polium* from Algeria *in vivo*. The present study investigated the effects of TPME treatment with sub-lethal doses of the herb on the biochemical composition of the blood and histological appearance of the liver and kidney in mice.

The LD_{50} for TPME was 442.81 and 686.77 mg/kg of body weight in male and female mice respectively. In view of the results of the LD_{50} ($50<DL_{50}<500$ mg/kg), according to Hodge and Sterner (1949), TPME can be classified in the category of moderately toxic products. All mice treated with different concentrations of TPME were alive during the 14 days of observation and did not produce any other changes in behavior, food and water intake (Twaij and Al-Dujaili, 2014)

Biochemical parameters showed a significant difference in female urea level at 75 mg/kg. Urea increases could be explained by an increase in degradation of protein compounds, but also by an injure of renal function (Benouadah *et al.*, 2012). These results agree with Khleifat *et al.* (2002), Rasekh *et al.* (2005) and Iriadam *et al*. (2006). Really, kidneys were clearly damaged and their histological aspects indicated a congestion and discret inflammatory infiltates in the two sexes. These damages were previously observed by researchers (Khleifat *et al*., 2002; Mohammed, 2010), who demonstrated the accentual phytotoxic effects on kidneys of male rat and mice treated with *Teucrium polium* ethanolic and aqueous extracts respectively.

The Cholesterol level was appreciably decreased after chronic treatment in both sexes using the two doses tested of TPME, it concords with works of Abu Sitta *et al*., (2009). Shahraki *et al.* (2007) showed that suspension and tea preparation of *T. polium* led to an increase in TG and cholesterol. These controversies may be due to the difference in method of *T. polium* extraction and routes of its administration (Vahidi *et al*., 2010).

Liver enzymes especially AST (in the two sexes) and ALT (in female) were very significantly increased at 50 mg/kg of TPME. It is attributed a hepatotoxic effect of this plant and suggested that it is not suitable to use in humans (Vahidi *et al.*, 2010). Histopathological result of liver sections confirmed these effects indicating important inflammatory infiltrates of polynuclears around vessels and in sinusoids, a vascular congestion, necrosis and peliosis. These results supported the study of Al-Ashban *et al.* (2006) and Rasekh et *al.* (2005). Mazokopakis *et al.* (2005) reported that a dysfunction of the liver appears after one month of treatment by an infusion of *T. polium*. In parallel, Savvidoua *et al*. (2007) report two cases of lethal hepatitis due to the treatment containing germander.

The clinical pictures of most human cases presented with hepatitis reported in the literature exhibited elevation in plasma levels of liver enzymes such as AST and ALT. The liver lesions of these cases (Zal *et al*, 2001) were similar to mice model. In fact, Mattei *et al*. (1995) reported a massive hepatocyte necrosis predominantly in the centrilobular areas of the liver in a patient with acute liver failure after consumption of *T. polium*. Although, the mechanism of hepatotoxicity of *T. polium* is not well elucidated, teucrine A isolated from *Teucrium chamaedrys* (Chen *et al*., 2011) and several diterpenoids neoclerodans, present in aeral parts, were suspected as hepatotoxic precursors of this plant (Fiorentino *et al*., 2011). In conclusion, TPME perturb biochemical serum parameters related to renal and hepatic function after prolonged administration. The liver histology can indicate images of an acute or chronic hepatitis. People should consider about the use *T. polium*, particularly if they are not officially informed of their possible unfavorable reactions.

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