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Research Article

BIOCHEMICAL, ANTINOCICEPTIVE AND HEPATOTOXIC EFFECTS OF THE CHRONIC ADMINISTRATION OF *TEUCRIUM POLIUM* ESSENTIAL OIL IN RATS

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ABSTRACT

The aim of the present study is to explore some of the pharmacological and toxicological effects of the essential oil of *Teucrium Polium* after identifying the components. The main component of the essential oil α-Pinene (27.5%). Biochemical parameters including plasma glucose, cholesterol, triglycerides, and liver functions were determined, antinociceptive effect was investigated, following intraperitoneal administration of essential oils (50, 100, 200 mg/kg) of *T. Polium* for 21 days in naive rats. The essential oil increased and decreased the levels of plasma glucose and cholesterol respectively in dose dependent manner. The essential oil, on the other hand, produced an anti-nociceptive effects, and hepatotoxicity. Further studies are needed to determine possible mechanisms of action of the *T. polium* essential oil.

Keywords: Teucrium Polium, Essential oil, Biochemical parameters, Anti-nociceptive, Liver function

INTRODUCTION

The *Teucrium polium* L. is a wild-growing flowering plant that belongs to the family *Labiatae,* and is found mainly in south western Asia, Europe and North Africa.

Teucriurn polium has been used in the Mediterranean region as a traditional medicine for the treatment of diabetes, inflammation, and infections (Yaniv et al, 1987; Ali-Shtayeh et al, 2000; Alachkar et al, 2011; Alzweiri et al, 2011).

The biological effects of T. polium have been widely investigated, and the plant has been reported to possess antioxidant (Couladis et al., 2003; Ljubuncic et al, 2006; Al-Mustafa et al, 2008; Esmaeili et al, 2009), anti-inflammatory (Capasso et al, 1983; Autore et al, 1984; Tariq et al., 1989; Mehrabani et al, 2009; Amini et al, 2009), anti-nociceptive (Abdollahi et al., 2003; Baluchnejadmojarad et al, 2005), anti-bacterial (Autore et al, 1984; Darwish & Aburjai, 2010; Motamedi et al, 2010), anti-hypertensive (Suleiman et al, 1988), hypolipidemic (Rasekh et al., 2001), hypoglycaemic (Gharaibeh et al., 1988; Afifi et al, 2005; Esmaeili & Yazdanparast, 2004; Esmaeili et al, 2009; Kasabri et al, 2010; Mirghazanfari, 2010; Mohseni & Pournourmohammadi, 2010; Nosrati et al, 2010), and anti-tumor (Ljubuncic et al, 2005; Rajabalian et al, 2008; BaniHani et al, 2009; Kanduz et al, 2010) effects. In these studies, the routes of administrations varied widely, and included feeding the animals with the plants (Amini et al, 2009; Amini et al, 2010), oral administration of the plant extracts (Esmaeili et al, 2004; Mehrabani et al, 2009; Kasabri et al, 2010), intraperitoneal (Abdollahi et al, 2003; Shahraki et al, 2007), intravenous (Gharaibeh et al, 1988), and intranasal administration (Afifi et al, 2005). On the other hand, the extracts used in the previous works broadly differed and ranged from crude extracts, to aqueous extracts, ethanolic, and essential oils (Gharaibeh et al., 1988; BaniHani et al, 2009; Abdollahi et al, 2003).

Despite the noticeable interest in pharmacological effects of the *T. polium* crude extract, very few studies have evaluated the biological activities of essential oil of *T. Polium.* Therefore, the aim of the present study was to explore some of the pharmacological and toxicological effects of the essential oil of *T. Polium*. Biochemical parameters were determined, antinociceptive effect was investigated, and liver functions were examined following intraperitoneal administration of essential oils of *T. Polium* for 21 days in normal rats.

MATERIALS AND METHODS

Plant material and isolation of the essential oils

T. polium aerial parts were collected during the flowering period from Ephrine in Aleppo Governorate. Samples of the plant were identified by a botanist from the Division of Pharmacognosy, University of Aleppo. The plant material was air dried and powdered, and essential oils was prepared from powdered plant using Clevenger apparatus and hydro-distillation method. The percentage yields based on the dried plant was 0.24% (v/w).

GC–MS analyses

Samples were injected into a GC-MS system consisting of a Shimadzu GC 2010 Series gas chromatograph coupled with a Shimadzu QP 2010 mass spectrometer, with the mass range at m/z 10–500. A capillary column DB-23 (60 m x 0.25 mm id), of 0.25 µm film thickness of coated material) was used. The injector and detector were set at 250°C. GC was performed in the splitless mode with split ratio of 40. The temperature programme was as follows: 60°C for 40 min, gradually increased to 250°C at 4°C/min and held for 5min. Identification of compounds was achieved by comparing the retention times with those of authentic compounds and the spectral data obtained from the NIST library.

Animal Treatment

Male Wistar rats (University of Aleppo, Animal unit) weighing 200–250 g (7–9 weeks old) were housed under controlled conditions: temperature (19-21°C), humidity 55% and lights 12/12 hours dark, light cycle. Food and water were available *ad libitum*. Procedures involving animals and their care were conducted in conformity with the institutional guidelines of University of Aleppo.

Animals were randomly divided into 4 groups (n = 6 in each), and injected intraperitoneally for 21 days with vehicle or volatile oil *Teucrium polium* (50, 100, 200mg/kg). Volatile oil was dissolved in saline containing Crosscarmellose, Tween 80. Control rats received the vehicle (200µl /kg, i.p.).

Measurement of body weight, plasma Glucose, Triglyceride, Cholesterol

Body weights were recorded from before the extract administration to the end of the experiment.

The plasma levels of glucose, were measured using enzymatic kit that, in which glucose is determined after enzymatic oxidation in the presence of glucose oxidase. The hydrogen peroxide formed reacts with phenol and 4-aminophenazone to form red-violet quinoneimine (Randox, UK). Tests were carried out according to the manufacturer's instructions. Total cholesterol levels in the plasma were determined using enzymatic endpoint method, in which cholesterol is quantified after enzymatic hydrolysis and oxidation (Randox, UK). Tests were carried out according to the manufacturer's instructions.

Triglycerides were determined using enzymatic hydrolysis with lipases (RANDOX, GPO-PAP method). Tests were carried out according to the manufacturer's instructions.

Assessment of Pain

To examine the antinociceptive effects of *T. polium*, the present experiment was designed to investigate the effects of *Teucrium'*s essential oil on the tail flick latency in rats. Briefly, each animal was acclimatized to the observation box before any testing began. A high-intensity light was focused on the rat's tail, and the time for the rat to spontaneously move its tail out of the light beam, which is referred to as tail-flick latency, was automatically recorded (Tail Flick Analgesia System (TSE System Technical & scientific Equipment CmbH (USA)) (Millan & Colpaert, 1991; Millan et al., 1991).

Liver Functions

The liver functions were determined by measuring the levels of liver enzymes SGOT and SGPT in the plasma. These tests were carried out using kinetic UV optimized method (Gesan production, Italy). The procedures were performed according to the manufacturer's instructions.

Statistical analysis

All values were given as mean± S.E.M. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Statistical *P*-value less than 0.05 was considered significant.

RESULTS

Composition of the essential oils

Seventeen compounds were identified n the essential oils (Table. 1), with α-Pinene showing the highest levels (27.5%). The essential oil also contains considerable amounts of β-Pinene (12.38%), Myrtenal (8.48%), Terpinol (8.473%), α-Humulene (3.601%), Citronellol (2.786%), Bornyl acetate (2.417%), Phytol (1.679%), Amounts less than 1% were detected of each of the following compounds: 1.8-Cineole, Camphor, Terpinene-4-ol, Nirol, Linalyl acetate, Linalool, Pentacosane, and Trans-pinocarveol.

Table 1: Composition of the essential oils of *Teucrium polium*

Component Name	(% in Oil)
α-Pinene	27.499
β-Pinene	12.380
Myrtenal	8.479
Terpinol	8.473
α-Humulene	3.601
Citronellol	2.786
Bornyl acetate	2.417
Phytol	1.679
1.8-Cineole	0.679
Camphor	0.609
Terpinene-4-ol	0.586
Nirol	0.550
Linalyl acetate	0.534
Linalool	0.521
Pentacosane	0.507
Mertenol	0.453
Trans-pinocarveol	0.986
unknown	27.255
Total	100.00

Body weight and Biochemical Effects

Regarding body weights, there was no significant difference between the groups before the experiment. The essential oil of *T. polium* caused a decrease in body weight (Fig 1).

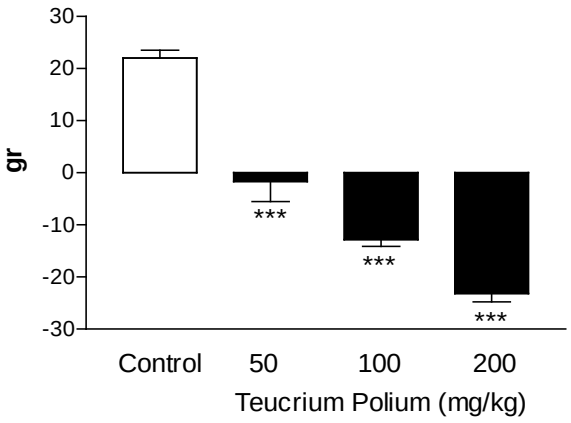

Fig. 1: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on body weight.

Data are presented as mean±S.E.M of changes of body weight between day1 and day 21. ****P* < 0.01 (as compared to control group).

The dose 100mg/kg of the essential oil of *T. polium*, unexpectedly, caused a significant increase in the plasma glucose concentration to 164±13mg/dl compared with 113±12 mg/dl in the control group *P*<0.01 one way ANOVA, followed by Tukey-post test (Fig 2). No effect on the glucose levels was observed with the lower (5omg/dl, and higher (200mg/dl) doses of the essential oil (*P*>0.05).

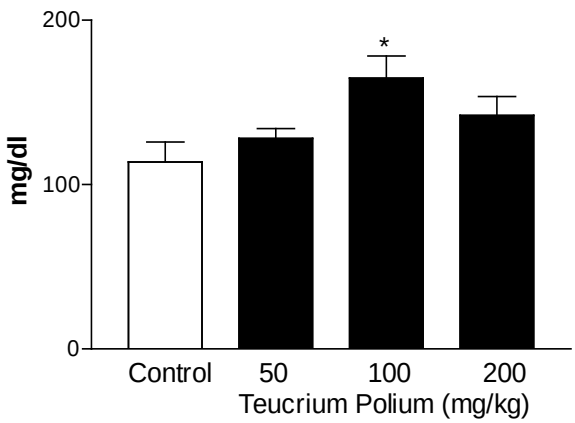

Fig. 2: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on plasma glucose level.

Data are presented as mean±S.E.M. **P* < 0.05 (as compared to control group).

The doses 50, and 100mg/kg of the essential oil of *T. polium* caused a decrease in the plasma cholesterol levels to 73±6 and 56±5mg/dl respectively, compared with 137±10 in the control group, *P*<0.001 (for both doses) one way ANOVA followed by Tukey-post test (Fig 3). The highest dose (200mg/kg) had no effect on the cholesterol levels *P*>0.05 one way ANOVA followed by Tukey-post test.

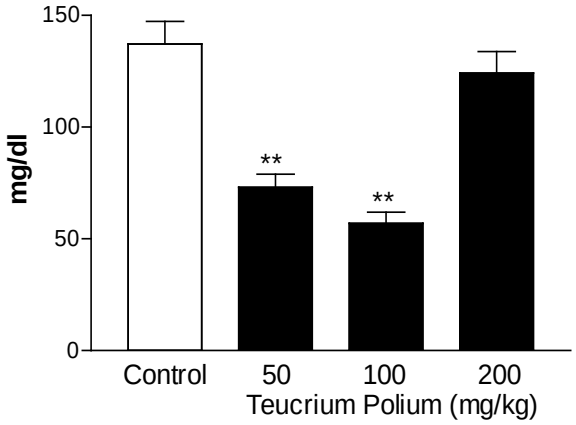

Fig. 3: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on plasma cholesterol level.

Data are presented as mean±S.E.M. **P* < 0.05 and ***P* < 0.01 (as compared to control group).

The essential oil of *T. polium* caused no significant effect on the levels of plasma triglycerides *P*>0.05 one way ANOVA followed by Tukey-post test (Fig 4).

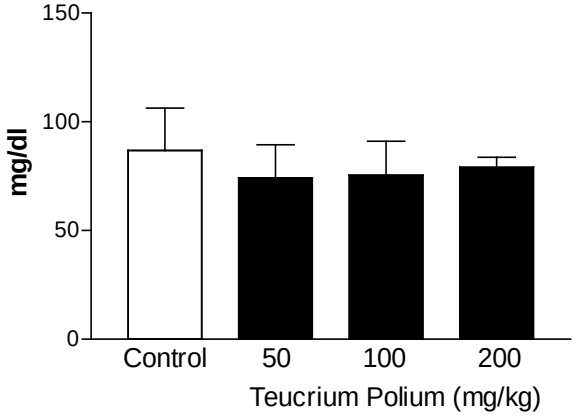

Fig. 4: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on plasma triglyceride level.

Data are presented as mean±S.E.M.

Antinociceptive Effect

Essential oil of *T. polium* increased the tail-flick latency in the tail flick test in a dose dependent manner. In the day 11, the time thresholds obtained following the injection of the extract were 4.4±0.1 min, 5.5±0.2min, 5.2±0.3min compared to 3.6±0.2min in the control group *P*<0.05, 0.001, 0.001 respectively, one way ANOVA (data not shown). In day 21 the tail-flick latencies obtained following the injection of the extract were 4.1±0.1, 6±0.8, 5.5±0.9min compared with 2.8±0.2 in the control group *P*<0.05, 0.001, 0.001, one way ANOVA followed by Tukey-post test (Fig 5).

Effect on hepatic Enzymes

To examine the effect of the essential oil of *T. polium* on the liver functions, we measured the levels of hepatic enzymes (SGOT, and SGPT) in the plasma. *T. polium* caused an augmentation in the levels of SGOT and SGPT. The levels of SGOT obtained following the injection for 21days of essential oil of *T. polium* (50, 100, 200mg/kg) were 69.9±6.1, 125.8±13, 147±28.2, compared with 60.6±5.3 in the control group *P*>0.05, *P*<0.05, *P*<0.01 respectively, one way ANOVA, followed by Tukey-post test (Fig 6).

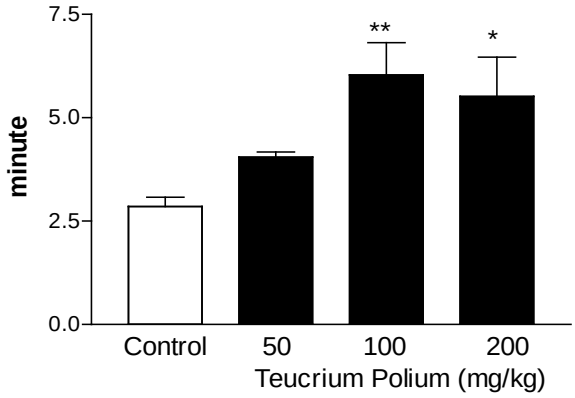

Fig. 5: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on nociceptive scores in the tail flick test.

Data are presented as mean±S.E.M. **P* < 0.05 and ***P* < 0.01 (as compared to control group).

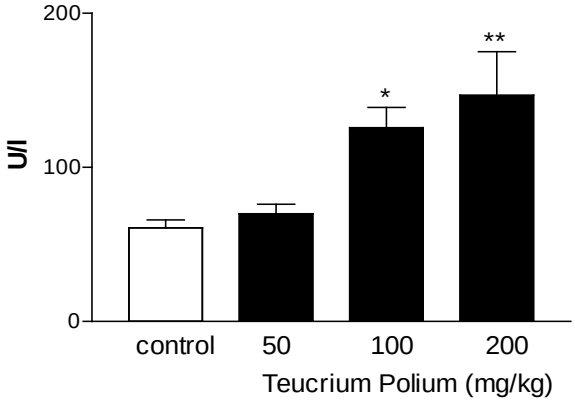

Fig. 6: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on SGOT.

Data are presented as mean±S.E.M. **P* < 0.05 and ***P* < 0.01 (as compared to control group).

SGPT levels were, after 21 days of treatment with *T. polium* essential oil (50, 100, 200mg/kg), 60.5±0.4, 67.6±0.2, 99±1 respectively, compared with 59±0.3 in the control group *P*>0.05, *P*<0.01, *P*<0.01 respectively, one way ANOVA, followed by Tukey-post test (Fig 7).

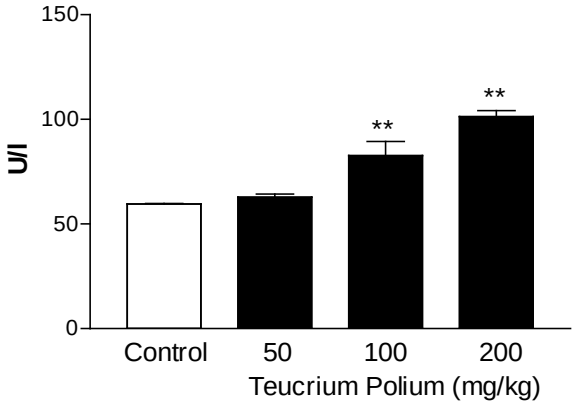

Fig. 7: The effect of *Teucrium polium* essential oil (50, 100 and 200 mg/kg, i.p.) on SGPT.

Data are presented as mean±S.E.M. ***P* < 0.01 (as compared to control group).

DISCUSSION

A number of pharmacological effects of *T. polium* essential oil have been evaluated in normal rats. It is evident from our work that essential oil of *T. polium* exerts several pharmacological activities, but also causes hepatotoxicity. Our data show that *T. polium* essential oil has weight lowering and antinociceptive effects. In addition, this oil reduced levels of plasma cholesterol but not of plasma triglycerides. This essential oil, on the other hand, produced hyperglycaemic and hepatotoxic effects.

The oil from *T. polium*, collected in Syria showed different compositions from that collected in Greece (Menichini et al, 2009). However, Sesquiterpenes constituted, in both, the most abundant fraction of the oil. Our results are consistent with previous reports on the analysis of the essential oils of Teucrium spp. that showed that the sesquiterpenes compounds are usually dominant, although the main component may vary (El-Shazly & Hussein, 2004; Proestos et al, 2006).

Regarding the effect of Teucrium polium extracts on body weight, our data are consistent with reports referring to the use of *T. Polium* for its body weight lowering effect (Chitturi & Farrell, 2008). However, this is the first study that attributes the body weight lowering effect, in part, to the essential oil of Teucrium polium.

Teucrium polium is known for its antinociceptive effect. This effect was demonstrated in two pain models, writhing test or the so called the visceral pain model in mice (Abdollahi et al, 2003), and in formalin test in rats (Baluchnejadmojarad et al, 2005). In the first study, the efficacy of essential oil was higher than that of the total extract in reduction of visceral pain. Here we provide further evidence for the antinociceptive effect of Teucrium polium in a third pain model in rats (tail flick model); our data also support the notion that the antinociceptive effect of this plant is produced, at least partially, by its essential oil. Recent study has demonstrated the antinociceptive properties of 1,8-Cineole and beta-pinene, which have been found in high levels in our essential oil, in rodents (Liapi et al, 2007)

Traditionally, Teucrium polium is used by the native inhabitants in the Mediterranean countries for its hypoglycemic activities (Dafni et al., 1984; Ali-Shtayeh et al., 2000; Abu-Irmaileh and Afifi, 2003). Hypoglycemic activity has been reported for the flavonoids as well as the volatile oil (Al-Hader et al., 1994; Talpur et al., 2005) in animal models of diabetes. However, Afifi et al, reported that Teucrium polium did not result in a decrease of blood glucose levels in normal and hyperglycaemic rabbits (Afifi et al, 2005). Our findings in this work, unexpectedly, further deviate from the results of previous studies in that the essential oil of Teucrium polium produced an increase in the plasma glucose levels. Further investigations are needed to identify the mechanism of the essential oil of Teucrium polium in producing this effect.

Treatment of normal rats with essential oil of *T. polium* aerial parts induced a significant and dose-dependent reduction of total serum cholesterol as compared with control; no change in triglyceride levels in treatment groups was observed. In previous study, the aqueous extract of *T. polium* given i.p. at doses of 50–200 mg/kg markedly reduced the serum levels of cholesterol and triglycerides in hyperlipidemic rats. This effect was suggested to be related to presence of flavonoids in this plant (Rasekh et al, 2001; Shahraki et al, 2007). It has been reported that the antihyperlipidemic properties of Teucrium polium is attributed to the flavonoids (Jahromi & Ray, 1993; Rasekh et al, 2001; Kaviarasan & Pugalendi, 2009). This may in part explain why the essential oil of *T. polium* had no effect on triglycerides as the essential oils are usually free of flavonoids. Our results, however, indicate that other components, in addition to the flavonoids, present in the essential oils are involved in reducing cholesterol levels.

In another study, diabetic rats that were fed *T. polium* (50 mg/kg) for a month presented increased levels of cholesterol and triglyceride (Shahraki et al, 2007). It is obvious from previous works and our data that the routes of administration, in addition to the type of *T. polium* extracts, play a major role in the determining the effects on the lipid profile.

Some concerns over the adverse effects of the crude extract of *T. polium* on human and animal liver have been raised. Cases of severe hepatotoxicity due to *T. polium* have been reported (Mattei et al, 1995; Starakis et al, 2006; Savvidou et al, 2007; Chitturi & Farrell, 2008). Liver damage occurred after intermittent and continuous use of the herb; Liver histology may reveal a picture of acute or chronic hepatitis (Vasileiado et al,). Cases of severe acute hepatitis, related to another plant of identical genus, *Teucrium chamaedrys* (4, 5), have been reported. However, a study on the effects of crude and EtOAc extracts of *T. polium* during a 4-week study period revealed no hepatotoxicity (reference).

Our histopathological findings (data no shown), with biochemical measurements, reveal hepatotoxic effects for the essential oil of *T. polium* administred for 21 days. However, it is not known from our data the first incidence (during the 21 days) of the hepatotoxic effects. This finding may explain why the high doses of essential oil of *T. polium* failed to cause any changes in the levels of cholesterol and glucose.

CONCLUSION

In conclusion, our data presented in this paper demonstrate a number of Pharmacological effects of the chronic administration of the essential oil of *T. polium* in naïve rats. The essential oil increased and decreased the levels of plasma glucose and cholesterol respectively. The essential oil also produced an anti-nociceptive effects, and hepatotoxicity. Further studies are needed to determine possible mechanisms of action of the *T. polium* essential oil.

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