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SHORT COMMUNICATION

Thujone corrects cholesterol and triglyceride profiles in diabetic rat model

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Thujone, which is the major constituent in *Salvia* sp. (Lamiaceae), was found to correct the lipid profile (cholesterol and triglycerides) in diabetic rats. Oral treatment with thujone ($5\,mg\,kg^{-1}$ body weight dose) significantly adjusted cholesterol and triglyceride levels in diabetic rats ($p \leq 0.05$) to normal levels compared to diabetic untreated rats. This provides a premise in the field of finding new agents to treat diabetic complications.

Keywords: thujone; monoterpenes; diabetes mellitus; cholesterol; triglycerides

1. Introduction

Currently, diabetes mellitus is an important medical problem in developed and developing countries. Diabetes is ranked seventh among the leading causes of death and third when all its complications are taken into account (Trivedi, Mazumdar, Bhatt, & Hemarathi, 2004). The main characteristics of diabetes mellitus are polydipsia, polyuria, polyphagia, weight loss, muscle weakness, and hyperglycaemia (El Batran, Gengaihi, & El Shabrawy, 2006). Diabetes usually leads to persistent hyperglycaemia, dyslipedemia and reactive oxygen species formation that would result in life-threatening complications (Fowler, 2008; Punitha, Vasudevan, & Manoharan, 2006). Lowering serum lipid levels through dietary or drug therapy seems to be associated with a decrease in the risk of vascular diseases and related complications (Ahmed, Lakhani, Gillet, John, & Raza, 2006).

Currently available anti-diabetic treatments have several side effects prompting continuous search for new treatments particularly from natural sources (Kasiviswanath, Ramesh, & Kumar, 2005). The World Health Organization recommends the identification and development of new safer orally administrated natural agents for treating diabetic metabolic dysfunctions (Kasiviswanath et al., 2005). In this study, we employed experimentally induced diabetic rats to investigate the effect of orally administered $5\,mg\,kg^{-1}$ thujone over a 28 day period on

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serum cholesterol and triglycerides levels. Thujone is a monoterpene that occurs mainly as a mixture of alpha and beta diastereoisomers in many plants such as *Artemisia absinthium*. L. (Asteraceae), *Salvia officinalis* L. (Lamiaceae) (sage), *Thuja occidantalis* L. (Cupressaceae) and others. Thujone is commonly used as a flavouring substance in food stuff and beverages (Hold, Sirisoma, Ikede, Narahadhi, & Casida, 2000). *Salvia* sp. (Lamiaceae), which includes about 900 species, are widely spread throughout the world, some of which are economically important since they have wide use as spices and flavouring agents in perfumery and cosmetics. *Salvia officinalis*, or sage, is reported to have a wide range of biological activities, including anti-oxidant and hypoglycemic properties (A. Eidi & M. Eidi, 2009). Different countries all over the world allow the use of determined concentrations of thujone in food stuff and beverages, while others abandon its use due to its toxicity. In one of the studies showed to find out the thujone oral LD50 in rats it was found to be 192 mg kg^{-1} body weight. In a further study, thujone was administered to rats by gavage at doses of 0, 5, 10 or 20 mg kg^{-1} body weight day^{-1} six times per week for 14 weeks. There were three deaths in females and one in males associated with convulsions at the top dose level (European Committee, 2003). In our study, the rats were orally teated with 5 mg kg^{-1} thujone for 28 consecutive days which comprised a safe, non-convulsant dose, in addition, none of the teated rats died due to thujone treatment.

2. Results and discussion

The effect of thujone on lipid profiles of alloxan-induced diabetic rats was evaluated after oral administration over four consecutive weeks. The results are shown in Figure 1.

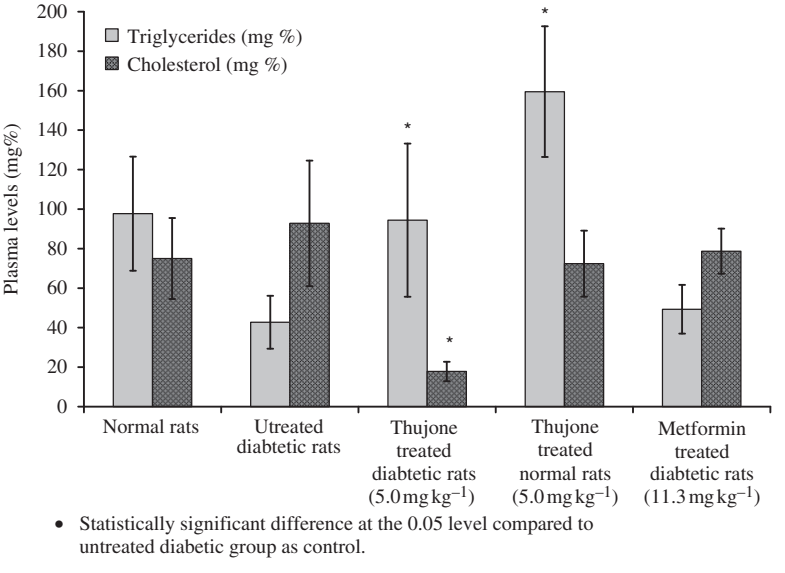

Figure 1. The correcting effect of thujone (5 mg kg^{-1} body weight) on serum cholesterol and triglycride profiles of alloxan-induced diabetic rats.
Notes: Error bars represent SD values of an average of six readings. *Statistically significant difference at the 0.05 level compared to the untreated diabetic group as control.

The results indicate that thujone significantly ($p < 0.05$) decreased serum cholesterol levels compared to diabetic untreated rats. Similarly, the level of triglyceride also increased significantly in the diabetic treated group to the diabetic untreated group. Interestingly, thujon did not significantly alter cholesterol levels in normal rats.

It could be speculated that thujone lowers cholesterol levels in a similar mechanism to statins that inhibit HMG-CoA reductase (Kee, Livengood, Carter, Mckenna, & Cafiero, 2009). In conclusion, thujone has potently corrected the levels of serum cholesterol and triglycerides by decreasing the former and increasing the latter in alloxan-induced diabetic rats. According to what is mentioned above, our finding provides thujone as a lipid profile-correcting agent in diabetic rats helps in the treatment of diabetes mellitus in such aspect.

3. Experimental

3.1. *Chemicals and biochemical kits*

Thujone, as a mixture of alpha (70%) and beta (20%) isomers, was purchased from Fluka Co. (France), alloxan monohydrate, metformin and glucose anhydrous were purchased from Sigma Co. (St. Louis, USA). The biochemical kits for glucose, cholesterol and triglycerides determination were obtained from Lab. Kits (Barcelona, Spain).

3.2. *Animal models*

Thirty albino male rats (*Rattus norvegicus* UJ-1) of average weight of 175 ± 25 ($\pm$SD, standard deviation) grams were selected for this study. The experimental rats were provided and maintained by the Department of Biological Sciences at the University of Jordan. Rats were fed with pellet diet and tap water ad libitum. The procedures involving animals and their care conform to the international guidelines and principles of Laboratory Animal Care. Rats were kept for one week under ambient environment of humidity, temperature and light for acclimatisation before experimentation.

3.3. *Induction of diabetes*

Alloxan monohydrate (150 mg kg^{-1} body weight) was freshly dissolved in double-distilled water (1 mL) and immediately injected intraperitoneally in 8 h fasted rats. The rats were not allowed to eat but had a free access to drinking water ad libitum over 2 days. Subsequently, the process was repeated under the same circumstances. The diabetic animals were allowed to drink 5% glucose solution over a 24-hour period after the injection to overcome drug-induced hypoglycemia (Rajasekaran, Sivagnanam, & Subramanian, 2005). After 5 days, the experimental rats were fasted for 7–8 h, and blood was collected retro-orbitally. Then blood sera were obtained after immediate centrifugation (4000 rpm for 10 min) on which biochemical parameters were evaluated. Rats of fasting blood glucose level >150 mg% were considered diabetic and consequently enrolled in our study for subsequent steps.

Diabetic rats were then divided into four groups and maintained on standard pelleted diet and water ad libitum.

3.4. *Preparation of administered doses*

Equal quantities of thujone (5 mg kg^{-1} body weight) and tween 20 were mixed together and completed to 100 mL with normal saline (0.9% w/v NaCl). The resulting solution was stirred for 15–30 min and stored at 4°C.

3.5. *Study protocol*

Diabetic rats of similar weights and fasting blood glucose levels were clustered into four groups (six rats per group) as follows:

- Treatment group: Diabetic rats were administered appropriate volumes of thujon-tween 20 as normal saline solution equivalent to 5 mg thujone kg^{-1} body weight (*ca* 1 mL) as a single oral daily dose.
- Untreated control group: Diabetic rats were administered appropriate volumes of tween 20 as normal saline solution equivalent to 5 mg tween 20 kg^{-1} body weight (*ca* 1 mL) as a single oral daily dose.
- Positive control group: Diabetic rats were administered appropriate volumes of metformine-containing normal saline solution equivalent to 11.3 mg metformin kg^{-1} body weight (*ca* 1 mL) as a single oral daily dose. This was calculated based on the recommended daily human dose of 850 mg for a 75 kg adult (Skim et al., 1999).
- Normal rats group that were not administered any treatments: Normal rats group were administered appropriate volumes of thujon-tween 20 as normal saline solution equivalent to 5 mg thujone kg^{-1} body weight (*ca* 1 mL) as a single oral daily dose.

The experiments were conducted over four consecutive weeks during which all experimental groups had free access to pellet diet and water.

3.6. *Blood sampling*

Rats were mildly anesthetised prior to sampling. Blood samples (1–2 mL) were withdrawn from the inner canthus of the rat eye into heparinised capillary tubes. They were immediately centrifuged at 4000 revolution per minute for 10 min, subsequently, cholesterol and triglycerides levels were measured in blood sera. Biochemical measurements were conducted employing UV-1600 UV–Vis spectrophotometer and as recommended by the manufacturers.

3.7. *Statistical analysis*

Data presented as means ± SD. Analysis of variance (ANOVA) test was performed to test the significance of difference. The difference was considered significant at the level of $p \leq 0.05$.

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