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Full Length Research Paper

Hypoglycaemic effect of *Thymelaea hirsuta* in normal and streptozotocin-induced diabetic rats

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The present study has investigated the effect of oral administration of the aqueous extract of *Thymelaea hirsuta* (*T. hirsuta*) on blood glucose levels in normal, glucose-hyperglycemic and streptozotocin (STZ)-induced diabetic rats. In normal rats, single oral administration of *T. hirsuta* lowered blood glucose levels significantly. It omitted significantly reduced the fasting glucose level in rats with oral glucose (2 g/kg) induced hyperglycemia. In STZ-induced diabetic rats, single oral administration of *T. hirsuta* also produced a significant decrease of blood glucose levels. The aqueous extract of *T. hirsuta* possesses both hypoglycaemic and antidiabetic effects in normoglycaemic and streptozotocin-induced diabetic rats. This may indicate the ethnopharmacological reason of the use of *T. hirsuta* in traditional medicine for treating diabetes.

Key words: *Thymelae hirsute*, hypoglycaemic activity, streptozotocin-induced diabetic rats, aqueous extract, oral administration.

INTRODUCTION

In spite of the introduction and extensive utilization of hypoglycaemic agents, diabetes and the related complications continue to be a major health problem worldwide. Currently, there are over 150 million diabetic patients in the world and this likely tends to increase to 300 million or more by the year 2025 (Zimmet, 2000). On the other hand, plant parts with hypoglycaemic effect are still prevalent in developing countries, where they have been used to alleviate the symptoms of diabetes for many centuries.

More than ca. 1200 plant species have been recorded to be used empirically worldwide for their alleged hypoglycaemic activity (Marles and Farnsworth, 1995; Oubre et al., 1997). This fact is attributed to the high cost and the lack of availability of current therapies for the majority of patients in developing countries. It is worth to state that phytotherapy is widely adopted by the Moroccan population (Bellakhdar, 1997; Ziyyat et al., 1997; Hassar, 1999). Study of the hypoglycaemic activity of medicinal plants is highly encouraged in order to discover new natural substances to be used in the treatment of diabetes (la Cour et al., 1995; Bhandari et al., 1998; Thompson Coon and Ernst, 2003).

Thymelaea hirsuta is a plant belonging to Thymeleaceae family commonly known as “Methnane” in Morocco. The aerial part of this plant is used as decoction in the treatment of diabetes (Ziyyat et al., 1997). *T. hirsuta* has been used in folk medicine for its Antimelanogenesis (Kawano et al., 2007), and Antioxidant (Djeridane et al., 2005) properties. The present study aims to evaluate the effect of *T. hirsuta* aqueous extract at a dose of 250 mg/kg on blood glucose in normal and diabetic rats.

MATERIALS AND METHODS

Plant material

T. hirsuta used in the present study, was selected from a large number of species sold in herb markets in Morocco. Both sellers and buyers (diabetic patients) were interviewed to gather information on the traditional uses and the methods of preparation and

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administration of this herbaceous plant. The plant was previously identified and authenticated by specialists of the plant Ecology Laboratory. Moulay Ismail University Meknes, Morocco.

Preparation of aqueous extract

T. hirsuta aerial parts were prepared according to the traditional method used in Morocco (decoction): 10 g powdered of the whole plant mixed with 100 ml of distilled water was boiled for 10 min followed by cooling for 15 min. Thereafter, the aqueous extract was paper filtered and water was removed under vacuum at a temperature below 50°C. The aqueous extracts were prepared daily, just before administration. The extracts obtained were then given orally to different groups of rats at a dose of 250 mg/kg body weight.

Animals

Male Wistar rats weighing 170 - 220 g, housed in standard environmental conditions of temperature, relative humidity and dark light cycle were used. They were fed with a standard diet and given adlibitum access to water.

Study on normoglycemic animals

Three groups of five rats each were fasted for 14 h. One group received the decoction that is administered by gavage at a dose of 250 mg/kg body weight (bw). The second group received distilled water and the third group received Glibenclamide 3 mg/kg body weight. Blood samples were drawn by puncture from the tail immediately before administration and 60, 120, 240 and 360 min later. For this procedure any reference should be added.

Study on glucose-loaded animals [Oral Glucose Tolerance Test (OGTT)]

The Oral Glucose Tolerance Test (OGTT) was performed on overnight fasting (14 h) normal rats. Distilled water, aqueous extract of *T. hirsuta* (250 mg/kg) and glibenclamide (3 mg/kg) were administered to three groups of rats, respectively. Glucose (2 g/kg) was fed 30 min after pretreatment with distilled water, *T. hirsuta* or glibenclamide. Blood glucose levels were measured at –30, 0, 60, 120, 180 and 240 min after glucose load to access the effect of extract on blood glucose levels of the glucose loaded animals. Blood glucose levels were determined by the glucose oxidase method using a reflective glucometer (Model On call plus, ACON laboratory, USA).

Induction of experimental diabetes

Diabetes was induced by a single intraperitoneal injection of a freshly prepared streptozotocin (STZ) solution (Sigma, St. Louis, MO, USA) (50 mg/kg in cold sodium citrate buffer 0.1 M, pH 4.5) to overnight fasted rats.

Diabetes was identified by polydipsia and polyuria along with measuring the non-fasting plasma glucose levels after 48 h of injection of STZ (Adolfo Andrade Cetto et al., 2000). Animals, which did not develop more than 250 mg/dl glucose levels, were rejected. The diabetic animals were classified into three groups, each of them with five rats. Group 1 as a control received distilled water, group 2 was given a standard oral hypoglycemic agent, glibenclamide (3 mg/kg bodyweight (bw), while group 3 received *T. hirsuta* extract.

Statistical analysis

All the data reported are expressed as mean ± S.E.M. Statistical analysis was performed using the Analysis of Variance (ANOVA) followed by Bonferroni post-tests. The values were considered to be significantly different when the p value was less than 0.05 compared to the respective control.

RESULTS

Blood glucose levels after single oral administration of *T. hirsuta* aqueous extract at a dose of 250 mg/kg are shown in Figure 1. In normal treated rats, a significant decrease in blood glucose levels was observed from the first to the fourth hour after administration ($p < 0.01$). However, after 6 h of administration, the decrease of blood glucose levels is less significant ($p < 0.05$). Glibenclamide treatment at a dose of 3 mg/kg produced a slight decrease in blood glucose levels after 1 h ($p < 0.05$). However, Glibenclamide caused significant drop in blood glucose levels 4 h after single administration ($p < 0.001$).

In the OGTT, the highest increase in serum glucose was observed in both treated and untreated rats after 30 min oral administration of glucose at 0 min (Figure 2). At 60 min, the percentage change in serum glucose in rats administrated with distilled water, 250 mg/kg body weight of aqueous extract or glibenclamide respectively. *T .hirsuta* at dose of 250 mg/kg produced a significant attenuation in the serum glucose ($P < 0.05$) at 60 min when compared to the control group, a significant drop in blood glucose levels was observed at 180 min ($p < 0.001$). Glibenclamide caused significant attenuation in serum glucose at 60, 120 and 180 min by ($P < 0.05$), ($P < 0.01$) and ($P < 0.001$) respectively when compared to the control group.

STZ administration at a dosage of 50 mg/kg bw to normal rats significantly elevated the blood glucose levels compared with rats injected citrate buffer alone as reported for albino rats (Gilman et al., 1990). In diabetic rats, the extract of *T. hirsuta* showed a significant hypoglycemic effect (Figure 3). The extract at a dose of 250 mg/kg bw produced a significant decrease in the plasma glucose level compared with the control; the effect was significant from 60 min with $p < 0.05$ and went down again with $p < 0.01$ at 120 and 240 min. The maximum effect was observed after 4 h. The glibenclamide group (3 mg/kg) produced a significant decrease compared to the control, with $p < 0.05$ at 60 min, going down to $p < 0.01$ at 120 and 240 min. These results provide evidence that there exists no significant difference between the plant extract well as between the glibenclamide group.

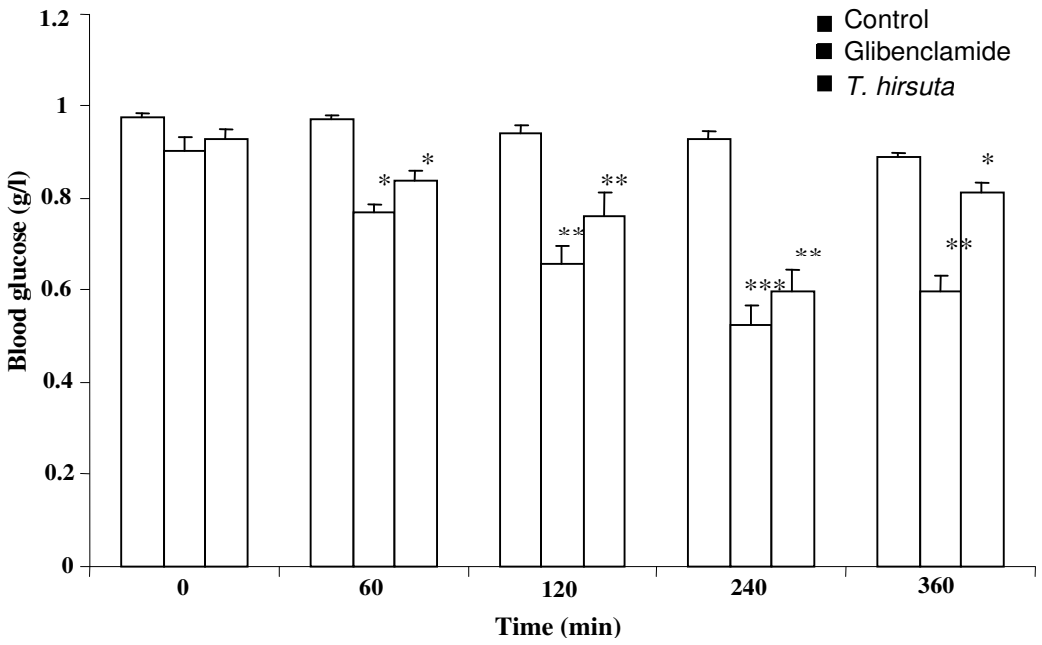

Figure 1. Plasma glucose levels over 6 h after single oral administration of *T. hirsuta* aqueous extract (250 mg/kg) in normal rats. Values are means"S. E. M. *P < 0.05; **P < 0.01; ***P < 0.001 vs. control (n = 5).

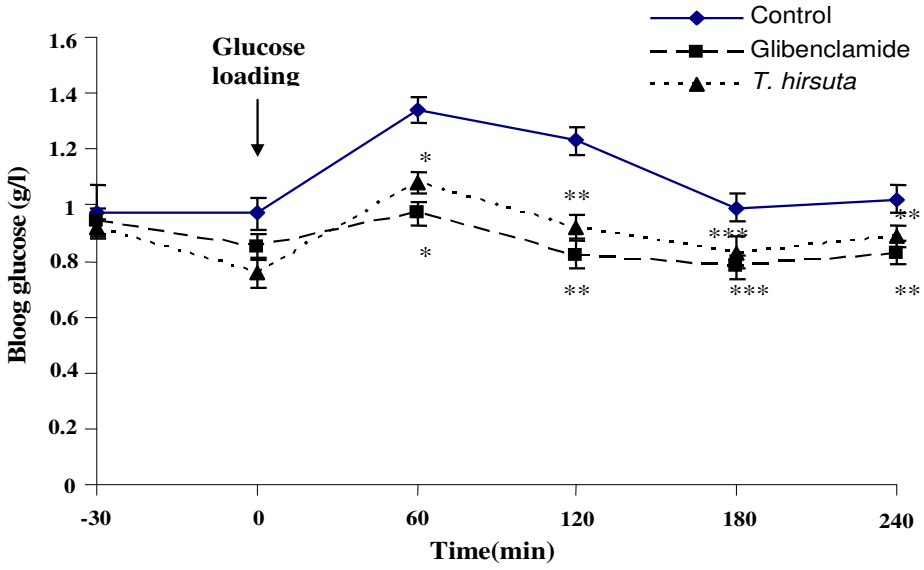

Figure 2. Effect of oral administration of 250 mg/kg of *T. hirsuta* aqueous extract on plasma glucose level of oral glucose loaded rats. Values are means" S. E. M. *P < 0.05; **P < 0.01; ***P < 0.001 vs. control (n = 5).

DISCUSSION

Our ethnopharmacological studies as well as our experimental pharmacological data confirm that *T. hirsuta* is traditionally used in Morocco for the treatment of diabetes type II and there exist a clear hypoglycaemic activity in our animal studies. The diabetes induction by STZ and the use of glibenclamide in this animal model were discussed previously (Adolfo Andrade Cetto et al., 2000).

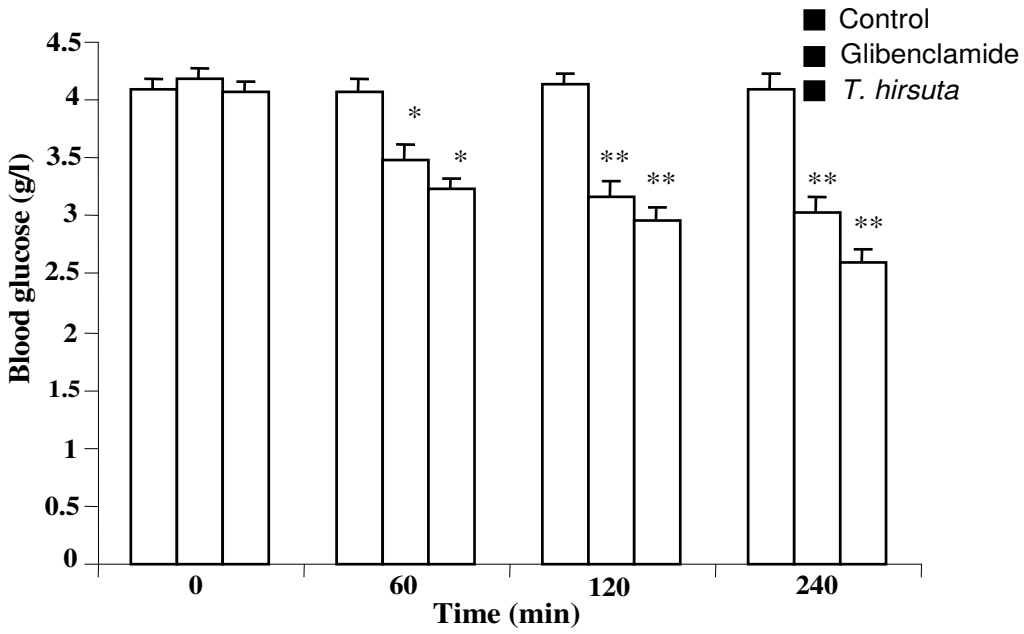

Figure 3. Plasma glucose levels over 4 h after single oral administration of *T. hirsuta* aqueous extract (250 mg/kg) diabetic rats. Values are means" S. E. M. *P < 0.05; **P < 0.01, control (n = 5).

The STZ-induction in adult animals produces a type 2 diabetes mellitus model. STZ selectively destroys the pancreatic insulin secreting β-cells, what leaves less active pancreatic cells and results in a diabetes mellitus (Ivorra et al., 1988; Sharma et al., 1997).

The acute hypoglycemic action of glibenclamide is the stimulation of the insulin release and the inhibition of glucagon secretion. Previous reported findings indicate the effectiveness of glibenclamide in moderate diabetic rats, and ineffectiveness in severe diabetic animals (Jackson and Bressler, 1981; Thompson Coon and Ernst, 2003). The β-cells which are not totally destroyed results a moderate diabetes and the hypoglycemic drugs like glibenclamide can stimulate those cells.

Results obtained in the present study showed that administration of the aqueous extract (250 mg/kg b.w.) of *T. hirsuta* to the fasted normal rats resulted a significant decrease in blood glucose level. The maximum hypoglycaemic activity of the plant was observed 4 h after treatment. Like the plant extract, glibenclamide also produced a significant reduction in the blood glucose level of fasted normal rats. The present findings appear to be in consonance with the earlier suggestion of Jackson and Bressler (1981) that sulphonylureas such as glibenclamide have extra-pancreatic hypoglycaemic mechanism of action secondary to their causing insulin secretion and the attendant glucose uptake into and utilization by the tissues.

In the oral glucose tolerance test, normal fasted rats treated with *T. hirsuta* extract at a dose of 250 mg/kg showed an inhibition of glucose increase compared with the control. This action could be due to a direct stimulation of insulin secretion.

In STZ induced diabetic rats, *T. hirsuta* showed a significant reduction $p < 0.001$, indicating similar effect as the reference drug, Glibenclamide. This antihyperglycemic action may be attributed to the potentiation of pancreatic secretion of insulin from existing β cells of islets or to the extrapancreatic mechanisms like enhanced transport of blood glucose to peripheral tissue, increased peripheral utilization of glucose via different enzymatic pathways.

Conclusion

The *T. hirsuta* possesses both hypoglycaemic and antidiabetic activities in normoglycaemic and STZ diabetic rats, respectively. This activity could be attributed to certain compounds of different nature present in *T. hirsuta*. Further investigations are in progress to isolate these active principles and to determine their mechanism of action.

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