

Full Length Research Paper

Hypoglycemic and hematological effects of aqueous extract of *Thymus serpyllum* Linn. in alloxan-induced diabetic rabbits

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This study was designed to evaluate the effect of aqueous extract of *Thymus serpyllum* Linn. on blood glucose level, body weight, and some hematological parameters of alloxan induced diabetic rabbits for a period of one month. It was found that the aqueous extract significantly ($P < 0.01$) reduced the blood glucose level in diabetic rabbits. This decrease in blood glucose level was comparable to the effect of standard drugs glibenclamide and acarbose. The aqueous extract also maintained the body weight of alloxanized rabbits. Significant increase was observed in erythrocyte sedimentation rate (ESR) and monocytes level in the diabetic treated rabbits as compared to the diabetic control non-treated group. ESR and monocytes level were significantly increased, whereas red blood cells (RBCs), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), neutrophils, hemoglobin (Hb) level, and platelets were significantly decreased in diabetic control non-treated rabbits, while these parameters in aqueous extract treated diabetic rabbits were comparable with normal control group. In conclusion, oral administration of aqueous extract of *T. serpyllum* produced hypoglycemic effects in alloxan-diabetic-rabbits, protected weight loss, and ameliorated diabetic-induced hematological disturbances in rabbits.

Key words: Diabetes, hematological parameters, hypoglycemia, *Thymus serpyllum* Linn.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that leads to other serious metabolic disorders as the disease progresses. Various hematological parameters and the immune system were also reported to be altered during the course of this disease (Mansi and Lahham, 2008). Anemia also resulted in diabetic patients due to the hemolysis of red blood cells (RBCs) (Kennedy and Baynes, 1984). It has been reported that, ingestion of medicinal plants or drugs can alter the normal hematological values (Ajagbonna et al., 1999). Therefore, hematological parameters could be an important tool in

the assessment of deleterious effect of drugs, as well as medicinal plants (Yakubu et al., 2007). Traditional plant medicines are used throughout the globe for the treatment of various types of diseases, including diabetes (Nagappa et al., 2003). The exploitation of medicinal plants by man for the treatment of various diseases has been in practice since ancient times. Over the last few decades, the reputation of herbal remedies has increased globally due to its therapeutic efficacy and safety (Hakim et al., 2007). Herbal drugs are widely prescribed today because of their minimal adverse effects and low costs (Mahesar et al., 2010). Researches on medicinal plants are very popular in the medical, as well as biological sciences, because of their availability and increase usage throughout the world. Most of these plants have not been

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identified and fully authenticated for their proper use in specific diseases (Watts et al., 1997). Recently, many plants have been studied for various biological activities, including CNS activities (Alamgeer et al., 2012).

Medicinal plants used to treat hypoglycemic or hyperglycemic conditions are of considerable interest for ethno-botanical community (Mansi and Lahham, 2008). For quite some years now, plants have been recommended for the treatment of diabetes (Jung et al., 2006). Many plants have been studied for their anti-diabetic potential (Maqsood et al., 2009).

Thymus serpyllum (wild thyme), belonging to the family Labiatae is locally known as Tumuro in Gilgit-Baltistan, Pakistan. In Pakistan, it is located at mountains of Gilgit-Baltistan, Kashmir, and Jamu. *Th. serpyllum* has been traditionally used in numerous diseases. It is used by the local peoples in weak vision, complaints of liver, suppression of urine and menstruation (Qureshi, 2007). *T. serpyllum* has anti-diabetic potential, because of its α -glucosidase inhibiting activity (Gholamhoseinian et al., 2008).

Moreover, *T. serpyllum* has been reported to show antioxidant activity (Pandey et al., 1996), and antioxidants have been shown to provide protection against the cytotoxic effect of reactive oxygen species, and their role in diabetes has been demonstrated (Cunningham, 1998). Current synthetic drugs used for the treatment of diabetes produce serious adverse effects (Williams and Pickup, 1991); moreover, a lot of money and time are required for a new drug to be in the market after appropriate clinical trials, therefore, there is a need to explore and characterize more of these abundant natural plants for the management of various ailments like diabetes.

This study was conducted to investigate the hypoglycemic, as well as hematological effects of *T. serpyllum* Linn. in alloxan-induced diabetic rabbits.

MATERIALS AND METHODS

Chemicals and drugs

Alloxan monohydrate was procured from Sigma Chemicals Co. Glibenclamide and acarbose were obtained from Biorax Pharmaceuticals, Islamabad and Bayer Pharmaceuticals, Karachi, Pakistan, respectively.

Plant

The selected plant was collected from the mountains of the village, Shikyote, district Gigit-Baltistan, Pakistan. It was identified and authenticated by Dr. Shair Wali, Assistant Professor of Botany, Karakoram International University, Pakistan. A voucher specimen was preserved at the Faculty of Pharmacy, University of Sargodha, Pakistan, with voucher number TS.1155 for future reference. Plant material was shade dried and powdered with a Chinese herbal grinder. The powder was then packed in cellophane bags and was stored in the refrigerator at 4°C.

Extraction

The powdered plant was extracted by cold maceration. Briefly, the powder was soaked in distilled water for 48 h with occasional shaking. It was passed through Muslin cloth and then filtered through the filter paper. The extract was dried and lyophilized. It was preserved in glass bottles, labeled and stored in the refrigerator at 4°C.

Animals used

Adult rabbits (*Oryctolagus cuniculus*) of either sex weighing about 1.20 to 1.50 kg were used in the study. They were housed at standard conditions of temperature ($23 \pm 12^\circ\text{C}$), humidity ($55 \pm 15\%$), and 12 h light (7.00 to 19.00), and were provided with a free access to a balanced rabbit's diet consisting of green leaves, fodder, pulses (*Medicago sativa*), and water *ad libitum*. All the rabbits were kept randomly into different groups. The study protocol was approved by the local ethical committee. Animals were used in accordance with the National Institute of Health (NIH) guide for the care and use of laboratory animals.

Induction of diabetes

After an overnight fasting, rabbits were made diabetic with a single intravenous injection of 150 mg/kg body weight (b.w.) of alloxan monohydrate dissolved in isotonic saline (Akhtar et al., 2002; Khosla et al., 1995). After 72 h of alloxan administration, induction of diabetes was confirmed by measuring the blood glucose level. Rabbits with blood glucose level between 250 to 300 mg/dl were considered diabetic and were employed for further studies (Olajide et al., 1999).

Collection of blood samples

Blood was collected through the ear vein, before and after the administration. The rabbit was restrained using a rabbit stand and blood was collected from one of the ear marginal vein. The pricked site was pressed with cotton swab soaked with spirit to protect the rabbits against infection. The blood samples were collected for the estimation of hematological parameters from jugular vein of the rabbits in ethylenediaminetetraacetic acid (EDTA) K_3 tubes, because these parameters were determined from fresh un-clotted blood.

Biochemical analysis

Blood glucose level was measured by Optium Xceed Glucometer using glucose oxidized optium kits (Abbott Laboratories, USA). Hematological parameters of fresh collected blood from rabbits were measured using hematological analyzer.

Effect of aqueous extract of *T. serpyllum* Linn. on blood glucose level and body weight of diabetic rabbits

Rabbits were divided into five groups of six animals each. Groups 1 and 2 served as untreated normal and diabetic control, respectively and were administered orally 2% aqueous gum tragacanth solution daily for 30 days. Groups 3 and 4 received orally 600 $\mu\text{g}/\text{kg}$ body weight of glibenclamide and 3 mg/kg body weight of acarbose, respectively daily for 30 days. Group 5 was administered 500 mg/kg body weight of aqueous extract of *T. serpyllum* daily for 30 days. Blood glucose levels and weights of all rabbits in each group were

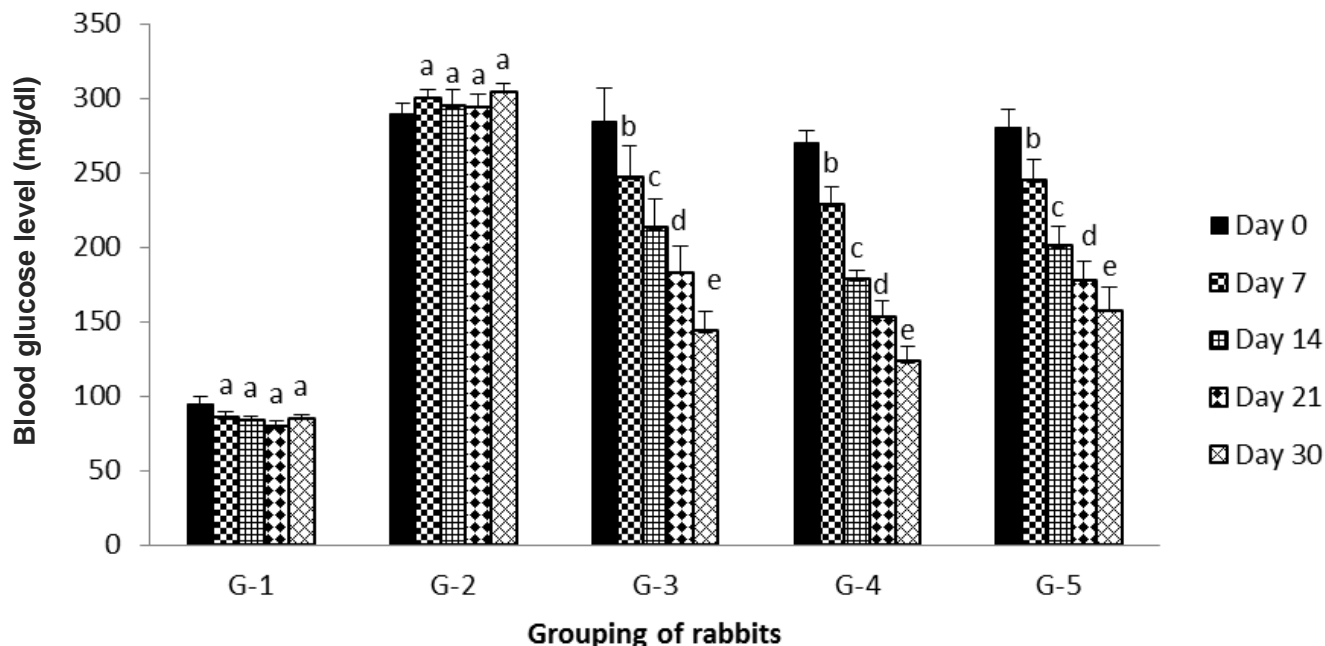


Figure 1. Blood glucose level of rabbits treated for one month.

^aP < 0.05, ^bP < 0.01, ^cP < 0.001, ^dP < 0.0001 and ^eP < 0.00001 compared to 0 h, G-1 = Normal control, G-2 = Diabetic control, G-3 = Glibenclamide treated, G-4 = Acarbose treated, G-5 = Aqueous extract treated.

Table 1. Weight (Mean \pm SEM) of normal control, diabetic control, glibenclamide, acarbose and aqueous extract of *T. serpyllum* treated diabetic rabbits for 30 days.

Time (day)	Normal control (2% gum tragacanth mean weight, kg)	Diabetic control (2% gum tragacanth mean weight, kg)	Glibenclamide (600 μ g/kg (b.w.) mean weight, kg)	Acarbose (3 mg/kg (b.w.) mean weight (kg)	Aqueous extract (500 mg/kg (b.w.) mean weight (kg)
0 day	1.41 \pm 0.073	1.6 \pm 0.078	1.65 \pm 0.11	1.34 \pm 0.103	1.42 \pm 0.037
7 th day	1.46 \pm 0.092 ^a	1.58 \pm 0.068 ^a	1.69 \pm 0.117 ^{ab}	1.38 \pm 0.098 ^b	1.43 \pm 0.036 ^{ab}
14 th day	1.460 \pm 0.09 ^{ab}	1.56 \pm 0.063 ^{ab}	1.69 \pm 0.118 ^{ab}	1.43 \pm 0.102 ^a	1.44 \pm 0.038 ^{ab}
21 th day	1.49 \pm 0.089 ^a	1.53 \pm 0.075 ^b	1.706 \pm 0.12 ^a	1.45 \pm 0.11 ^a	1.46 \pm 0.040 ^{ab}
30 th day	1.463 \pm 0.094 ^a	1.5 \pm 0.073 ^c	1.71 \pm 0.121 ^a	1.46 \pm 0.104 ^a	1.47 \pm 0.037 ^a

Data is expressed as Mean \pm SEM significant at P < 0.05, versus control where ^aP < 0.05, ^bP < 0.01, ^cP < 0.001 and ^dP < 0.0001, the values sharing the same superscript letters in the same column are not significant to each other.

checked at days 0, 7, 14, 21, and 30 (Ramesh et al., 2006; Maciejewski et al., 2001).

Effect of aqueous extract of *T. serpyllum* Linn. on various hematological parameters of diabetic rabbits

Rabbits were divided into three groups of six animals each. Groups 1 and 2 served as untreated normal and diabetic control, respectively and were administered orally 2% aqueous gum tragacanth solution daily for 30 days. Group 3 was administered orally 500 mg/kg body weight of aqueous extract of *T. serpyllum* daily for 30 days. At the end of the month, the blood samples of all rabbits in each group were collected for the estimation of various hematological parameters (Babu et al., 2003). From the hematological parameters obtained, the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular

corpuscular hemoglobin concentration (MCHC) were calculated.

RESULTS

Effect of aqueous extract of *T. serpyllum* on the blood glucose level and weight of diabetic rabbits

Aqueous extract of *T. serpyllum* significantly (P < 0.01) reduced the blood glucose level of diabetic rabbits treated for 30 days. The results were comparable with glibenclamide and acarbose. The aqueous extract and glibenclamide prevented weight loss in the diabetic rabbits as compared to diabetic control group during one month treatment, while the weight of rabbits treated with

Table 2. Various hematological parameters of normal control, diabetic control, and aqueous extract of *T. serpyllum* treated diabetic rabbits after 30 days of treatment.

Hematological parameter	Normal control (2% gum tragacanth)	Diabetic control (2% gum tragacanth)	Aqueous extract (500 mg/kg)
ESR (mm/1 st hour)	7.50 ± 0.76 ^b	21.66 ± 0.76 ^a	7.66 ± 0.76 ^b
Hb level (g/dl)	13.55 ± 0.70 ^a	8.76 ± 0.70 ^b	14.16 ± 0.70 ^a
Hct (PVC, %)	43.43 ± 2.13 ^a	40.43 ± 2.13 ^a	45.60 ± 2.13 ^a
MCV (fl)	81.5 ± 2.99 ^a	70 ± 2.99 ^b	85 ± 2.99 ^a
MCH (Pg)	28.01 ± 0.95 ^{ab}	26.3 ± 0.95 ^b	30.4 ± 0.95 ^a
MCHC (%)	33.46 ± 1.24 ^a	29.58 ± 1.24 ^b	34.13 ± 1.24 ^a
Platelets (10 ⁹ L ⁻¹)	299.33 ± 29.09 ^a	140.7 ± 29.09 ^b	305.8 ± 29.09 ^a
RBCs (10 ¹² L ⁻¹)	5.05 ± 9.46 ^a	4.5 ± 9.46 ^a	5.38 ± 9.46 ^a
TLC	6.7 ± 0.70 ^a	7.8 ± 0.70 ^a	7.8 ± 0.70 ^a
Eosinophils (%)	3.16 ± 0.78 ^a	3.16 ± 0.78 ^a	3 ± 0.78 ^a
Lymphocytes (%)	38.16 ± 3.04 ^a	34.83 ± 3.04 ^a	35.83 ± 3.04 ^a
Monocytes (%)	4.66 ± 1.16 ^b	5.33 ± 1.16 ^a	5 ± 1.16 ^{ab}
Neutrophils (%)	56 ± 4.77 ^b	47.83 ± 4.77 ^a	54.33 ± 4.77 ^a

Data is expressed as Mean ± SEM significant at P < 0.05, versus control where ^aP < 0.05, ^bP < 0.01, ^{ab}P < 0.001, the values sharing the same superscript letters in the same column are not significant to each other. TLC: tin layer chromatography; Hct: hematocrit; PVC: packed cell volume.

acarbose was significantly (P < 0.01) increased. The weights of rabbits of normal control group did not change significantly (Figure 1 and Table 1).

Effect of aqueous extract of *T. serpyllum* on various hematological parameters of diabetic rabbits

Monocytes and erythrocyte sedimentation rate (ESR) increased significantly (P < 0.05) and RBCs, MCV, MCHC, hemoglobin (Hb) level, neutrophils, and platelets decreased significantly in the diabetic control group as compared to the normal control. The aqueous extract increased the RBCs, Hb level, MCV, and MCHV and decreased the ESR and neutrophil percentage in diabetic treated rabbits. There was no significant change occurred in other hematological parameters of rabbits in any of the three groups (Table 2).

Statistical analysis

Data collected were subjected to analysis of variance (ANOVA) and difference between the means was determined by Tukey's Kramer LSD (least significant difference) test using R software. Values were represented as Mean ± standard mean of error (SEM) and values of P < 0.05 were considered significant

DISCUSSION

Our study showed that *T. serpyllum* has antidiabetic

activity. Aqueous extract of *T. serpyllum* exhibited significant anti-hyperglycemic activity in alloxan induced hyperglycemic rabbits without significant change in their weights. It also shows that, *T. serpyllum* treatment might restore some altered hematological parameters of diabetic rabbits. Alloxan is a diabetogenic agent which induces diabetes by damaging the pancreatic β-cells leading to hyperglycemia (Szkudelski, 2001). This study correlates with previous research findings, in that the blood glucose level was significantly increased in untreated alloxanized rabbits. Alloxan induces damage and death of pancreatic islet-cells in several experimental animal models, thus causing DM and decreasing the secretion of insulin. The cytotoxic action of alloxan is mediated by reactive oxygen species. Alloxan has been reported to be a specific β-cytotoxic drug and acts by complexing with the metal ions in the islets (Akhtar et al., 2011). In this study, the aqueous extract of *T. serpyllum* significantly reduced the blood glucose level in alloxan induced diabetic rabbits. The results obtained were similar to those obtained by (Mahesar et al., 2010). It is possible that the plant may increase glucose removal from blood, decrease the release of glucagon or increase that of insulin, stimulate directly glycolysis in peripheral tissues, or reduce glucose absorption from the gastrointestinal tract (Marrif et al., 1995). In a study conducted in Iran, *T. serpyllum* demonstrated the α-glucosidase inhibitory effect *in vitro* (Gholamhoseinian et al., 2008). The α-glucosidase is an enzyme found in the brush border in the intestine and is responsible for the conversion of polysaccharides into simple sugars. The inhibition of this enzyme slows the elevation of blood sugar following carbohydrate meal and this is one of the

best strategies to decrease the postprandial rise in blood glucose level which may help to avoid the onset of late diabetic complications (Lebovitz, 1997). So, it can be concluded that the hypoglycemic effect of the aqueous extract might be due to the inhibition of α -glucosidase enzyme. Our study agrees with previous studies. *Tournefortia hartwegiana*, an α -glucosidase inhibiting plant produced the anti-hyperglycemic activity in alloxanized rats (Ortiz-Andrade et al., 2007). In another study, the fruit extracts of an α -glucosidase inhibitor plant, *Phaleria macrocarpa* decreased the blood glucose concentration of rats after treatment with 80% w/v sugar solution (Sugiwati et al., 2006). Antioxidant action of *T. serpyllum* has also been reported (Pandey et al., 1996). The antioxidant activity of the plant might also contribute towards the anti-diabetic effect of the aqueous extract by providing protection against the cytotoxic effect of free radicals generated by the alloxan or diabetes itself. This finding is in accordance with Gallo et al. (2005) and Wadood et al. (2007). This study indicates that aqueous extract of *T. serpyllum* might attenuate some disturbed hematological parameters of diabetic rabbits. It has been suggested that anemia associated with DM is due to the increased non-enzymatic glycosylation of RBC membrane proteins, which accompanies with hyperglycemia (Kennedy and Baynes, 1984). Moreover, the oxidation of these glycosylated membrane proteins and hyperglycemia in DM cause an increase in the production of lipid peroxides causing hemolysis of RBCs. Thus, increased RBC count of *T. serpyllum* treated rabbits might be due to the lowered lipid peroxide level in RBCs membrane leading to a decrease susceptibility of RBCs to hemolysis. Moreover, reactive oxygen species has also been suggested to play role in the mechanism of red cells damage (Rao et al., 2003). So, the antioxidant effect of the *T. serpyllum* might provide the protection of RBCs against free radical damage. In DM, the hemoglobin level is decreased, because the excess glucose produced in the body reacts with the hemoglobin to form glycosylated hemoglobin (HbA1c) (Sheela and Augusti, 1992). In this study, the hemoglobin level in diabetic control rabbits decreased, which is in accordance with previous studies (Mohammed et al., 2009). In diabetic treated rabbits, the Hb level was increased and it was due to the decreased level of blood glucose in that rabbits produced by the aqueous extract. The treatment with the *T. serpyllum* brought improvement in the platelets count which is advantageous in diabetes associated with bleeding tendencies. PCV, MCH, and MCHC were not significantly altered in diabetic treated rabbits as compared to normal control which is consistent with earlier studies (Akah et al., 2009). Lower values of red blood cells and associated parameters indicate the anemic conditions, while higher values than the normal range are suggestive of polycythemia (American Diabetes Association, 2000). So, it is clear from the data that aqueous extract may not have adverse effect on the bone marrow, kidney, and

hemoglobin metabolism as the substances, which significantly affect the values of RBC and associated parameters are believed to have harmful effects on the bone marrow, kidney, and hemoglobin metabolism (Young and Maciejewski, 1997).

Conclusion

The oral administration of aqueous extract of *T. serpyllum* demonstrated significant hypoglycemic effects in alloxan-induced diabetic rabbits, prevented body weight loss of diabetic animals and might ameliorate the diabetes induced hematological disturbances. This study calls for further investigation to isolate the active principal(s) and elucidate the exact mechanism of action of the plant extract.

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