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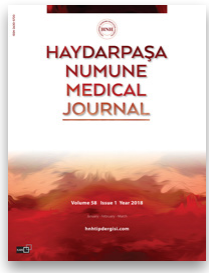

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ORIGINAL ARTICLE

Investigation of Possible Antidiabetic Effects of *Potentilla Fulgens* in Diabetic Rats and Comparison with Other Antidiabetics

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Abstract

Introduction: The current antidiabetic drugs have adverse side effects and the effects may decrease overtime depending on continuous use. In recent years, phytochemicals of natural plant origin, which show antidiabetic properties and have fewer side effects, have been the subject of research. However, studies and clinical studies on the antidiabetic and hypoglycemic effects of *Potentilla fulgens* are still not enough. We aimed to examine the antidiabetic effects of *P. fulgens* in diabetic rats and to contribute to new treatment approaches by comparing them with other antidiabetics.

Methods: In this study, rats were divided into seven groups, one control and six diabetic groups as seven rats in each group. The rats in which diabetes was induced by streptozotocin were sacrificed after treatment with two different doses of intraperitoneal and intragastric *P. fulgens* and standard antidiabetic drugs, metformin and gliclazide for 3 weeks.

Results: Intraperitoneal administration of *P. fulgens* significantly improved the activity of liver enzymes related to fasting blood glucose levels and carbohydrate metabolism. Intragastric 450 mg/kg/day *P. fulgens* did not show adequate antidiabetic effects. However, *P. fulgens* administered twice the usual dose (900 mg/kg/day) caused significant antidiabetic effects. Compared with metformin and gliclazide, it was found that *P. fulgens* had similar effects at high doses.

Discussion and Conclusion: According to our findings, *P. fulgens* improves the activity of liver enzymes related to blood glucose and glucose metabolism in diabetic rats and has significant antidiabetic effects.

Keywords: Diabetes mellitus; gliclazide; metformin; Potentilla fulgens.

Diabetes is a chronic metabolic disease that can lead to serious complications accompanied by deficiencies in carbohydrate, lipid, and protein metabolism due to deficiency in insulin secretion or resistance to insulin in target tissues [1–6]. It can be seen in all age groups [2]. Changing nutrition and lifestyle, obesity, and the sedentary working life increase its incidence [3]. This disease, which is accompanied by acute and chronic complications, can significantly reduce the quality of life and may cause permanent impairment in vital organs [4–6].

Despite the presence of insulin and various oral hypoglycemic drugs in its treatment, it still remains a medical and social problem due to its serious complications. Pharmacological agents used to prevent or reduce complications may also have adverse side effects, as well as decreased efficacy overtime, depending on continuous use [7]. Furthermore, the effects of pharmacological treatment approaches are limited, and at high doses, hypoglycemia,

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liver toxicity, lactic acidosis, and diarrhea may develop [7, 8].

The cost of diabetes treatment is very high. It is estimated that the cost per person per year is about 3800–4400 USD [9]. Some natural phytochemicals with less side effects in recent years have been the subject of research to reduce the financial burden of diabetes treatment and improve the quality of life [10–14]. Especially in India, it is reported that Potentilla fulgens, used in various diseases such as peptic ulcer, oral ulcer, diarrhea, and cancer, is antidiabetic [12, 13]. Every new drug that will be available for diabetes treatment will enrich the treatment options, but it can create an alternative option against side effects.

In this study planned in the light of the above information, investigation of the possible antidiabetic effects of *P. fulgens* in diabetic rats and the relationship with carbohydrate metabolism-related liver enzymes was aimed. We also compared *P. fulgens* with other antidiabetics such as metformin and gliclazide to determine whether it would be an alternative option in the treatment of diabetes.

Materials and Methods

This study was carried out in the laboratories of the University Science and Technology Application and Research Center after approval of the University Ethics Committee's Local Ethics Committee dated September 10, 2013.

Experimental Animals

A total of 49 adult male Wistar albino rats weighing 240–290 were procured from the University Health Science Research and Application Center. Animals were fed with standard rat chows and water ad libitum in stainless steel cages in rooms under alternate cycles of 12 h of light, and 12 h of dark, at 22±2°C and 55–60% humidity throughout the experiment.

ELISA reader (Multiskan Go Thermo Scientific), air-cooled microcentrifuge (SL20R Thermo Scientific), blood glucose meter and strips (Contour TS Bayer), electronic scales (Sartorius Basic), precision balance (Precisa XB 220 A), homogenizer (IKA Labortechnik Ultra-Turrax T25), deep freezer (Vestel), operation set (Kruuse), and automatic pipettes were used.

Chemicals

The chemicals used in the research were procured from the firms indicated in parentheses: *P. fulgens* extract (Xi'an Yuensun Biological Technology Cooperation Ltd.), diethyl ether and streptozotocin (Sigma-Aldrich), metformin (Bilim Pharm), and gliclazide (Servier Pharm). Glucose-6-phosphatase dehydrogenase (G6PD), glucose-6-phosphatase, hexokinase (HK), and pyruvate kinase (PK) activities (Bio Vision) were measured by a colorimetric method. Fructose level was measured by (Bio Vision) a fluorometric method.

Experimental Diabetes

Body weight and fasting blood sugar of all animals were measured before the study. Streptozotocin (55 mg/kg) prepared in citrate buffer (0.1 M and pH 4.5) was injected intraperitoneally (IP) to induce diabetes. The control group was only given the placebo (citrate buffer) through IP route. 48 h after injection of streptozotocin, fasting blood sugars were measured in blood samples taken from the tail veins of rats. Rats with fasting blood glucose levels >300 mg/dL were included in diabetic groups.

Experimental Groups

Wistar albino rats were divided into seven groups of seven animals each:

1. Control group: Rats in this group were fed with water and standard laboratory rat chows for 6 weeks without restriction.
2. Diabetic control group: Seven rats with diabetes were fed with water and standard laboratory rat chows for 6 weeks without any restriction as in the control group and no other treatments were applied.
3. Gliclazide group: Diabetic rats in this group were treated with intragastric 5 mg/kg/day gliclazide for 6 weeks.
4. Metformin group: Diabetic rats were given intragastric 500 mg/kg/day metformin for 6 weeks.
5. *P. fulgens* group (PIP): Diabetic rats received a single dose of 450 mg/kg sterile *P. fulgens* extract injections through intraperitoneal route, and they were sacrificed after 72 h.
6. *P. fulgens* group (P450): Diabetic rats in this group were given intragastric 450 mg/kg/day *P. fulgens* extract for 6 weeks.
7. *P. fulgens* group (P900): Diabetic rats were treated with intragastric *P. fulgens* extract at daily doses of 900 mg/kg for 6 weeks. All groups were fed after approximately 12 h of hunger at the end of the 6th week.

Preparation of *P. Fulgens* Extract

Each gram of *P. fulgens* powder was mixed in 2 ml of 2% ethanol. It was then held in boiling water bath for 10 min to sterilize the mixture and they were allowed to cool. The cooled solution was placed in glass tubes and centrifuged at 2000 rpm for 10 min. The resulting supernatant was calculated at a dose of 450 mg/kg in the PIP group and injected through intraperitoneal route, while the other two

groups received the drug through oral route.

Termination of the Study

6 weeks later, and, after approximately 12 h of fasting, the anterior wall of the rats' abdomen was opened with an incision under ether anesthesia, and the heart was reached from the diaphragm and blood sample was obtained through puncture, and then, the rats were sacrificed. Without delay, livers were removed and washed with 0.9% cold saline, then stored at –80°C until the day of measurement to determine the levels of enzymes involved in glucose metabolism.

Preparation of Liver Homogenates and Determination of Enzyme Levels

To prepare liver homogenate, 9 ml of phosphate buffer solution was added onto 1 g of tissue. Tissue samples were smashed with an air-cooled mechanical homogenizer and centrifuged at 3000 rpm for 5 min to obtain supernatants. In the samples of supernatants, G6PD, glucose-6 phosphatase (G6P-az), glucokinase HK, PK, and fructose-1,6-diphosphatase activities were measured using colorimetric and fluorometric methods and appropriate kits at our University Science and Technology Application and Research Center Laboratory.

Statistical Analysis

Statistical evaluations were performed using the (Statistical Package for the Social Sciences 22.0) package program. All values were expressed as mean±standard deviation. Since the number of data in each group was <30, non-parametric statistical analysis methods were used to evaluate the findings. Mann–Whitney U-test was used in the analysis of two independent groups. Kruskal–Wallis ANOVA test was used for non-parametric tests in the analysis of >2 independent groups. Wilcoxon matched-pairs test was used in the analysis of two dependent groups.

Results

The Effects of *P. fulgens*, Gliclazide, and Metformin on Changes in Body Weights of Diabetic Rats

Although diet and water consumption of diabetic rats significantly increased compared to control group and antidiabetic treatment groups, body weights decreased by 3.1% at week 1, 13.2% at week 2, and 23.2% at week 3 when compared to baseline (day 1) (p<0001). Weight loss in diabetic rats receiving *P. fulgens*, gliclazide, and metformin treatment was much less limited when compared with their baseline body weights, but they did not completely return to normal dependent of reduced feed consumption (Tables 1, 2).

Table 1. The effects of Potentilla fulgens, gliclazide, and metformin on daily consumption of rat chows and water for 3 weeks (Since rats were sacrificed 3 days after administration of Potentilla fulgens, PFIP group was not included in this table)

	Consumption of rat chows (g/d)			Water consumption (ml/day)		
Groups	**1st Week**	**2nd Week**	**3rd Week**	**1st Week**	**2nd Week**	**3rd Week**
Control	25.3±3.3	30.1±3.9	34.9±5.7[c]	28.5±3.4	32.3±5.1[a]	36.1±5.7[c]
Diabetic	48.9±5.7	76.5±4.3[a]	95.8±4.6[a,b]	58.3±4.9	72.3±5.1[c]	80.7±4.4[b,c]
PF450	38.3±6.3	42.5±5.1[a]	38.7±5.3[b]	60.1±5.1	68.3±5.1[a]	70.6±3.9[d]
PF900	44.2±6.2	32.8±4.7[a]	30.3±6.1[c]	50.2±6.3	48.3±5.1	41.8±4.8[a,b]
Gliclazide	42.2±5.5	38.8±4.7	23.3±3.1[b,c]	31.2±5.1	30.3±5.1	29.4±5.1
Metformin	32.2±5.5	27.8±4.7	21.3±6.1[a,b]	30.6±4.1	26.3±3.1[a]	25.1±4.7[a]

[a]: When compared with the 1st week values p<0.05; [b]: When compared with the 2nd week values p<0.05; [c]: When compared with the 1st week values p<0.001; [d]: When compared with the 1st week values p<0.01.

Table 2. The effects of Potentilla fulgens, gliclazide, and metformin on changes in average body weights within 3 weeks in control and diabetic rats (Since rats were sacrificed 3 days after administration of Potentilla fulgens, PFIP group was not included in this table)

Weeks	Control	Diabetic	PF450	PF900	Gliclazide	Metformin
Baseline	248±5.2	257±6.3	251±4.9	259±5.7	255±6.4	261±5.7
1st Week	271±4.8[a]	249±5.7[a]	247±4.3	252±4.6	248±4.9[a]	257±4.4
2nd Week	295±6.4[b]	223±6.4[b,d]	235±5.1[a]	261±5.3	257±5.1	260±3.9
3rd Week	307±6.2[c,d]	198±6.2[c,d,e]	228±4.7[b,d]	273±6.1[a]	260±6.3	263±4.8
Changes	+%24.1	-%23.2	-%9.2	+%6.2	+%1.9	+%0.07

[a]: When compared with the baseline value p<0.05; [b]: When compared with the baseline value p<0.01; [c]: When compared with the baseline value p<0.001; [d]: When compared with the 1st week values p<0.01; [e]: When compared with the 2nd week values p<0.05.

The Effects of *P. Fulgens*, Gliclazid, and Metformin on the Levels of Hepatic G6PD in Diabetic Rats

Liver G6PD levels in diabetic rats were reduced by about 50% compared to baseline (p<0.001, Fig. 1). The liver G6PD levels in the diabetic rats (PIP) treated with *P. fulgens* returned to normal in respective percentages of rats in the PF900 (94%), gliclazide (85%), metformin (80%), and PF450 (65%) groups (p<0.001, p<0.001, p<0.001, p>0.001, and p<0.01, Fig. 1).

The Effects of *P. Fulgens*, Gliclazide, and Metformin on the Levels of Hepatic Glucose-6 Phosphatase in Diabetic Rats

In diabetic rats, liver glucose-6 phosphatase activity increased approximately 100% (p<0.001, Fig. 2). Glucose-6 phosphatase levels of diabetic rats treated with gliclazide and metformin returned completely to normal levels. *P. fulgens* showed its effect at different rates depending on dose and administration schedule. Glucose-6 phosphatase levels improved 82% in the PIP, 64% in the P900, and 50% in the PF450 groups (p<0.001, p<0.001, p<0.001, p>0.01, and p<0.01, respectively, Fig. 2).

The Effects of *P. Fulgens*, Gliclazide, and Metformin on Hepatic Glucokinase Levels in Diabetic Rats

In diabetic rats, hepatic glucokinase levels were reduced by about 55% (p<0.001, Fig. 3). Liver glucokinase levels of metformin-treated diabetic rats returned completely to normal levels, whereas gliclazide treatment provided 85% improvement (p<0.001, p<0.001, p<0.001, p>0.005, and p<0.05, respectively). However, in the PIP, P900, and P450 groups treatment with *P. fulgens* achieved improvements in the glucokinase activity in 76, 72, and 60% of the rats, respectively (p<0.001, p<0.001, p<0.001, p>0.005, and p<0.05, respectively (Fig. 3).

The Effects of *P. Fulgens*, Gliclazide, and Metformin on the Levels of Hepatic PK in Diabetic Rats

In diabetic rats, liver PK levels were reduced by about 55% (p<0.001, Fig. 4). The liver PK levels of the diabetic rats in the PIP and P900 groups treated with *P. fulgens* returned completely to normal; its levels improved at a rate of 85 and 76% in the gliclazide and metformin groups, respectively (p<0.001, Fig. 4). However, oral *P. fulgens* treatment at 450 mg/day did not show any significant improvement.

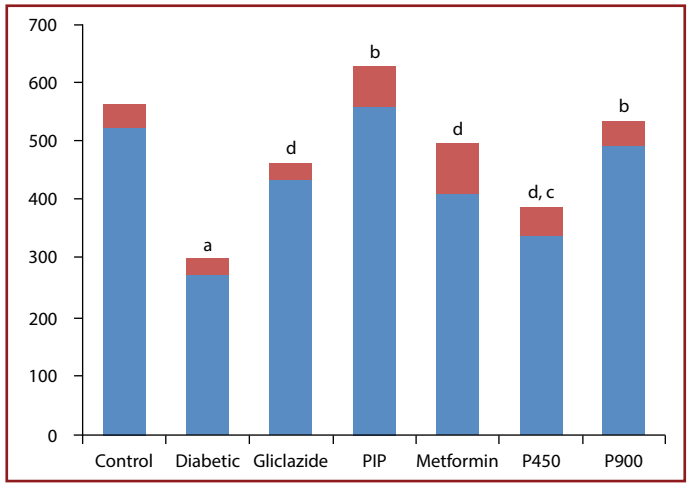

Figure 1. The effects of Potentilla fulgens, gliclazide, and metformin on hepatic glucose-6 phosphate dehydrogenase levels in diabetic rats.

a: When compared with the control group p<0.001; b: When compared with the untreated diabetic rats p<0.001; c: When compared with the control group p<0.05; d: When compared with the untreated diabetics p<0.05.

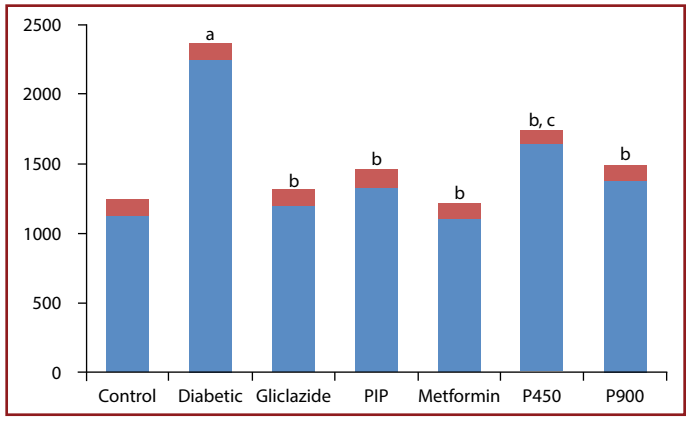

Figure 2. The effects of Potentilla fulgens, gliclazide, and metformin on hepatic glucose-6 phosphatase levels.

a: When compared with the control group p<0.001; b: When compared with the untreated diabetic rats p<0.001; c: When compared with the control group p<0.05.

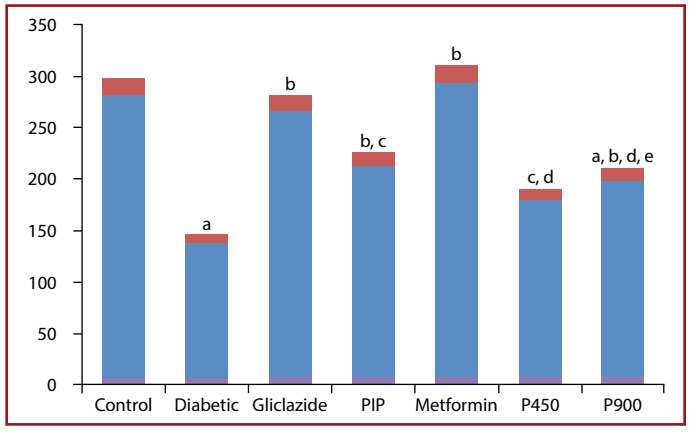

Figure 3. The effects of Potentilla fulgens, gliclazide, and metformin on hepatic glucokinase levels in diabetic rats.

a: When compared with the control group p<0.001; b: When compared with the untreated diabetic rats p<0.001; c: When compared with the control group p<0.05; d: When compared with the gliclazide group p<0.05; e: When compared with the metformin group p<0.01.

The Effects of *P. Fulgens*, Gliclazide, and Metformin on Hepatic Fructose 1,6-Diphosphatase Levels in Diabetic Rats

Liver fructose 1,6-diphosphatase levels increased approximately 61% in diabetic rats ($p<0.001$, Fig. 5). In the PIP, P900, and P450 groups treated with *P. fulgens*, fructose 1,6-diphosphatase levels returned to normal in 97%, 90%, and 70% of the diabetic rats, whereas gliclazide or metformin treatment improved liver fructose 1,6-diphosphatase levels in 92% and 72% diabetic rats, respectively ($p<0.001$, Fig. 5).

The Effects of *P. Fulgens*, Gliclazide, and Metformin on Fasting Blood Glucose Levels in Diabetic Rats

Fasting blood glucose levels in diabetic rats increased to approximately 4 times the normal values at the end of the 6th week ($p<0.001$, Fig. 6). Fasting blood glucose levels of the PIP group of diabetic rats treated with intraperitoneal *P. fulgens* returned completely to normal, while fasting blood glucose levels recovered in 46% and 12% of the diabetic rats in P900 and P450 groups, respectively. In diabetic rats treated with gliclazide and metformin, fasting blood glucose levels improved in 85 and 72% of diabetic rats, respectively ($p<0.05$, $p>0.05$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively, Fig. 6).

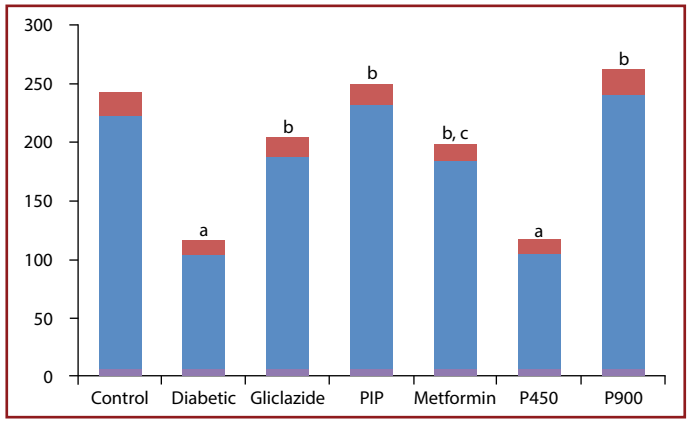

Figure 4. The effects of Potentilla fulgens, gliclazide, and metformin on hepatic pyruvate kinase levels in diabetic rats.

a: When compared with the control group $p<0.001$; b: When compared with the untreated diabetic rats $p<0.001$; c: When compared with the control group $p<0.05$.

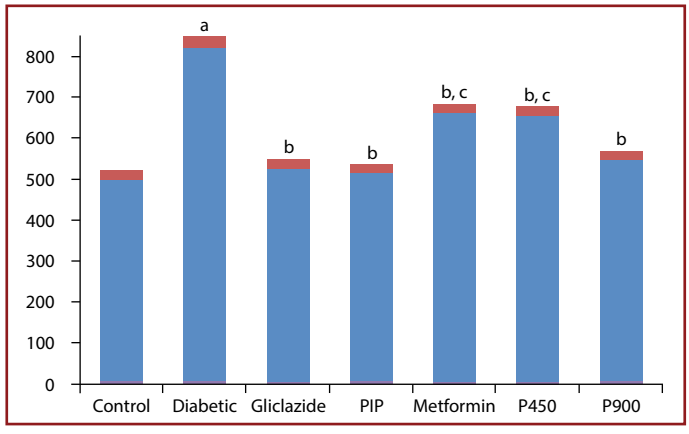

Figure 5. The effects of Potentilla fulgens, gliclazide, and metformin on hepatic fructose 1,6-diphosphatase levels.

a: When compared with the control group $p<0.001$; b: When compared with the untreated diabetic rats $p<0.001$; c: When compared with the control group $p<0.05$.

Discussion

Some of the many new bioactive phytochemicals isolated from plants show the same activity or have stronger effects than standard hypoglycemic and antidiabetic drugs used in the treatment of diabetes [15-17]. The World Health Organization recommends that traditional non-toxic, herbal treatments with no or lesser side effects and effective for diabetes treatment are to be considered as excellent candidates for oral therapy. Herbal treatment methods and plant researches have quickly begun to take place in the medical literature as alternative studies concerning diabetes and its complications [18-22].

In our study, we have taken into consideration the scientific research results made on this issue; extracts from the roots of *P. fulgens* plant grown in India have been investigated for possible antidiabetic effects in the experimental diabetic rat model and compared with standard antidiabetic drugs such as metformin and gliclazide.

Fasting blood glucose levels of streptozotocin-induced un-

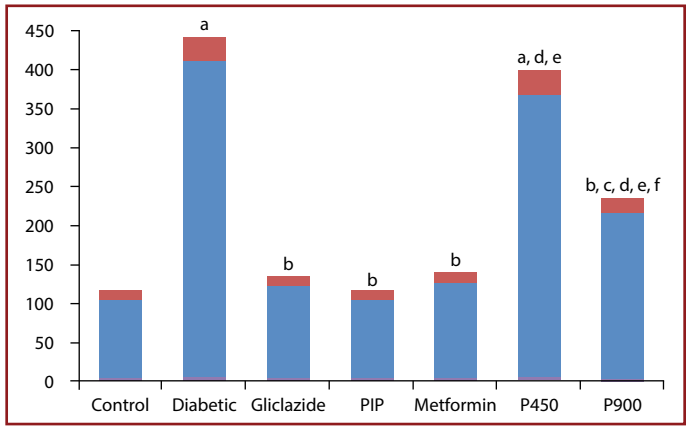

Figure 6. The effects of Potentilla fulgens, gliclazide, and metformin on fasting blood sugar levels in diabetic rats. a: When compared with the control group $p<0.001$.

b: When compared with the untreated diabetics $p<0.001$; c: When compared with the control group $p<0.05$; d: When compared with the gliclazide group $p<0.05$; e: When compared with the PIP group $p<0.01$, f: When compared with the metformin group $p<0.05$.

treated diabetic rats treated with without diabetes reached approximately 4 times the normal levels. Diabetic rats lose their body weight considerably, though they consume more chows. Low-dose intragastric *P. fulgens* (450 mg/kg/day) treatment did not prevent weight loss in diabetic rats. Weight loss in diabetic rats treated with high-dose intragastric *P. fulgens* (900 mg/kg/day), metformin, and gliclazide was slightly lower than untreated diabetic rats. However, feed consumption was lower in rats receiving antidiabetic treatment than in healthy rats due to decreased appetite.

6 weeks of intragastric low-dose *P. fulgens* therapy did not significantly alter fasting blood glucose levels in diabetic rats. Oral *P. fulgens* could only show its antihyperglycemic effect when given at high doses. However, when *P. fulgens* was given through IP route, its antihyperglycemic effect was slightly higher than that of metformin and gliclazide, and the fasting blood glucose level was fully normalized.

G6FD, G6F-ase, glucokinase, F1, 6DP-ase, and PK are known to be important enzymes involved in glucose metabolism [22-25]. G6FD is the rate-limiting key enzyme that enables the use of glucose in the pentose phosphate pathway and is responsible for the production of NADPH required for the antioxidant defense system. Previous studies have shown that liver G6FD activity is significantly reduced in diabetic humans and experimental animals [26, 27]. It has been reported that hyperglycemia decreases G6FD activity in the liver by increasing protein kinase activity, leading to an increase in oxidative stress. In addition, one of the major factors responsible for diabetic complications has been shown to be an increase in oxidative stress due to a decrease in G6PD activity [27]. G6F-ase and F1, 6DP-ase are important enzymes that play a role in the regulation of the gluconeogenic pathway. The increase in the activity of these gluconeogenic enzymes in untreated diabetic treatment leads to an excessive amount of hepatic glucose production and contributes to the elevated blood glucose levels [29].

In our diabetes-induced rats, liver G6FD decreased by 50%. In contrast, the G6F-ase level increased twice the control value, while the F1, 6DP-ase activity increased by approximately 61%. Our findings support literature. *P. fulgens*, metformin, and gliclazide treatment improved the decreased rate of liver G6PDH activity in diabetic rats and related increased G6P-ase levels at a certain rate. However, the strongest effect was detected in low-dose IP *P. fulgens* applied rats.

Glucokinase is a rate-limiting enzyme that regulates glycolysis. It performs postprandial function and its activity is increased with insulin. PK is another important enzyme of glycolysis. It converts phosphoenolpyruvate into pyruvic acid and provides its entry into mitochondria; thus, it contributes to energy production. Gupta et al., they found that glucokinase activity decreased in rats in which they had induced experimental diabetes [26].

In our study, liver glucokinase and PK activities also decreased significantly in diabetic rats. Thus, a reduction in the use of glucose in the liver and peripheral tissues of diabetics contributes to hyperglycemia. *P. fulgens* and other antidiabetics have significantly improved the reductions in diabetic glucokinase and PK activities. It has been understood that when compared among themselves the most potent effect of improving PK activity was intraperitoneally applied *P. fulgens*; however, metformin was more potent in improving glucokinase activity.

Metformin exerts its effect by increasing insulin sensitivity, especially in the liver and peripheral tissues, without inducing significant changes in insulin secretion. It has been shown that metformin reduces G6F-ase activity in the liver, limits glucose production, and has antihyperglycemic effects [28]. Metformin in this study significantly improved the reductions in liver G6PD and glucokinase activities of diabetic rats whether metformin demonstrates this positive effect directly or indirectly is open to speculation.

Alpha-glucosidase inhibitors show antihyperglycemic effects by reducing the absorption of fructose and glucose in the bowels [29]. In *P. fulgens* extracts, considerable amounts of five types of the terpenes, known as α-glycosidase inhibitors, have been found [29]. However, in our study, intraperitoneal dmnst of *P. fulgens* was much more effective than its intragastric administration. According to this surprising finding and literature information, we may think that *P. fulgens* shows antidiabetic effects with various mechanisms by stimulating insulin secretion, increasing insulin sensitivity, reducing intestinal absorption of fructose and glucose, and improving the activities of glucose metabolism-related enzymes, especially in the liver.

As a matter of fact, experimental evidence has been found that *P. fulgens* extracts increase insulin sensitivity in tissues, show antihyperglycemic effects, and increase glucose tolerance [30].

As a result, *P. fulgens* significantly improves adverse changes in the activities involving in the regulation of blood glucose levels in diabetic rats and liver enzymes related to carbohydrate metabolism; G6PD, glucose-6 phosphatase, glucokinase, PK, and fructose 1,6-diphosphatase. These positive effects of *P. fulgens* show that it may be an alternative in the treatment of diabetes because it exerts effects similar to those of gliclazide and metformin.

Ethics Committee Approval: This study was carried out in the laboratories of the University Science and Technology Application and Research Center after approval of the University Ethics Committee's Local Ethics Committee dated September 10, 2013.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: P.İ.; Design: E.T., P.İ., Y.K.; Data Collection or Processing: P.İ., E.T.; Analysis or Interpretation: P.İ., Y.K.; Literature Search: P.İ., E.T.; Writing: E.T.

Conflict of Interest: None declared.

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