

# Antidiabetic effect of hydroalcoholic extract of *Carthamus tinctorius* L. in alloxan-induced diabetic rats

Sedigheh Asgary<sup>1</sup>, Parivash Rahimi<sup>2</sup>, Parvin Mahzouni<sup>3</sup>, Hossein Madani<sup>2</sup>

<sup>1</sup>Department of Basic Sciences, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. <sup>2</sup>Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. <sup>3</sup>Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

**Background:** *Carthamus tinctorius* L. (*Compositae*) has been used in Iranian traditional medicine for treatment of diabetes. In this study, anti-diabetic effect of its hydroalcoholic extract was compared with that of glibenclamide. **Methods:** Male white Wistar rats were randomly allocated into four groups of six each: nondiabetic control; diabetic control; diabetic treated with hydroalcoholic extract of *Carthamus tinctorius* (200 mg kg<sup>-1</sup> BW); diabetic rats treated with glibenclamide (0.6 mg kg<sup>-1</sup> BW). Alloxan was administered (120 mg kg<sup>-1</sup> BW), intraperitoneally to induce diabetes. Fasting blood samples were collected three times, before injection of alloxan, two weeks and six weeks after injection of alloxan and fasting blood sugar (FBS), Hb A1C, insulin, cholesterol, LDL-C, HDL-C, VLDL-C, triglyceride, alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured each time. **Results:** FBS, triglyceride, cholesterol, LDL-C and VLDL-C had a meaningful decrease in diabetic rats treated with *Carthamus tinctorius* and diabetic rats treated with glibenclamide as compared with diabetic rats with no treatment. Insulin level increased significantly in diabetic groups received treatment (glibenclamide or *Carthamus tinctorius* L) in comparison with diabetic group with no treatment. The histological study revealed size of islets of Langerhans enlarged significantly consequentially as compared with diabetic rats with no treatment. The extract appeared non toxic as evidenced by normal levels of AST, ALP and ALT. Effects of administrating glibenclamide or extract of *Carthamus tinctorius* L on all biochemical parameters discussed above showed no difference and both tend to bring the values to near normal. **Conclusion:** These results suggested that the hydroalcoholic extract of *Carthamus tinctorius* possesses beneficial effect on treatment of diabetes.

**Key words:** Alloxan, *carthamus tinctorius* L., diabetes, glibenclamide, hydroalcoholic extract

## INTRODUCTION

*Carthamus tinctorius* L. (safflower) is said to be indigenous to Iran, northwest India and possibly different parts of Africa.<sup>[1]</sup> The medicinal parts are the flowers, seeds and the oil extracted from its embryos. *Carthamus* L. is a genus belonging to the *Compositae* family. It has six species in Iran.<sup>[2-4]</sup> In popular and traditional medicine, its flowers and seeds have been used as a flavoring agent and a purgative, respectively.<sup>[5]</sup> The effects of flower extract have been reported, including increase of peripheral blood flow, antibacterial activity, inhibition of platelet aggregation, increase in the beating amplitude of cultured myocardial cell sheet, elicited central depressant activity, anti-inflammatory action, and inhibition of tumor promotion in mouse skin carcinogenesis.<sup>[6]</sup> However, the antioxidant activity of this plant has not been well studied and the major components for the antioxidant activity are not known yet. In addition, the antioxidant actions of petal extract of safflower against formation of lipid peroxidation is revealed.<sup>[6,7]</sup>

The scavenging activities of the extract of safflower petals with various colors showed the order of orange, yellow and white from high to low. This order is consistent with the contents of carthamin, which is a pigment of orange color and is found highest in orange petals and lowest in white petals. There was also a relationship between free radical scavenging activity and carthamin content in the petal extracts of safflower. These results suggest that the petal extract of safflower has free radical scavenging activity and carthamin is one of the major active components.<sup>[7,8]</sup>

Studies demonstrated that oxidative stress and free radical are the lead or supporting actor in pathogenesis of diabetic complications.<sup>[9,10]</sup>

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin. Although the etiology of this disease is not well defined, viral infection, autoimmune disease and environmental factors have been implicated. Diabetes is usually

accompanied by increased production of free radicals or impaired antioxidant defenses.<sup>[9-11]</sup>

From these facts, it is needed to find nutrients and food with effective antioxidant activity against oxidative damage to prevent various diseases. Recently, the use of functional foods and / or nutraceuticals has increased for preventing or treating many chronic diseases. This study is carried out to research on the anti-diabetic effect of hydroalcoholic extract from *Carthamus tinctorius* L. flowers on the alloxan-induced diabetic rats and comparing its effect with glibenclamide, an oral hypoglycemic agent which is also used in researches as a standard medication in treatment of diabetes.

## METHODS

### *Collection of Plant Material*

The plant material was collected during September 2006 from Isfahan province.

The plant was identified by Dr. L. Ghaem Maghami of Isfahan University of Sciences and a voucher specimen No.2338 kept in the herbarium of the Sciences Faculty. The flowers were removed and air dried at room temperature.

### *Preparation of Hydroalcoholic Extract*

The dried flowers were powdered with a blender and the ground samples were extracted twice with 70% ethanol for 24 h at room temperature.

The extract was filtered through Whatman No.2 filter paper and evaporated under the vacuum at 40°C and then further dried to a powder using a freeze-dryer at 50°C.

### *Animals*

Twenty four male Wistar rats weighing about 150-200 g obtained from Pasteur Institute, Tehran. The animals were housed in cages with filter tops under controlled conditions of 12 h light/dark cycle, 50% humidity and at 28°C. They were maintained on a standard pellet diet and water *ad libitum*.

Isfahan Cardiovascular Research Center Ethics Committee which is a member of office for human research protections, US department of health and human services, approved the present study, and the animals were handled according to guidelines of Isfahan University of Medical Sciences for Laboratory Animal Sciences for the care and use of laboratory animals.

### *Induction of Diabetes*

The rats were injected alloxan monohydrate dissolved in sterile normal saline at a dose of 120 mg kg<sup>-1</sup> body weight, intraperitoneally two weeks before starting the treatment. From the 48<sup>th</sup> h onwards fasting blood samples were collected from the rats and blood glucose was measured to know the induction of diabetes. Glucose level >250 was defined as diabetes.<sup>[12,13]</sup>

### *Experimental Design*

The rats were divided into four groups as follows after the induction of alloxan diabetes and each group comprised of 6 rats.<sup>[14,15]</sup>

Group 1: Non-diabetic Control rats given normal saline intraperitoneally daily to equalize stress induced by injections in all groups.

Group 2: Untreated diabetic control rats given normal saline intraperitoneally daily to equalize stress induced by injections in all groups.

Group 3: Diabetic rats given extract of *Carthamus tinctorius* L. 200mg/kg intra peritoneally daily.

Group 4: Diabetic rats given glibenclamide 0.6 mg/kg intraperitoneally daily.

### *Blood Sample Collection and Analysis*

Fasting blood samples were collected three times:

Time 0 was before injection of alloxan, Time 1 was two weeks after injection of alloxan and Time 2 was six weeks after injection of alloxan.

Fasting blood sugar (FBS), Hb A1C, insulin, Cholesterol, LDL-C, HDL-C, VLDL-C, triglyceride, alkaline phosphatase (ALP), alanine and aspartate transaminase (ALT, AST) were measured each time.

FBS, total cholesterol, triglyceride, LDL-C, HDL-C and VLDL-C were measured using DiaSys Kits from Germany which utilized the colorimetric method. Insulin was measured using Monobind Insulin Microplate Elisa test. HbA1C was analyzed by Biosystem kits (Barcelona, Spain) using chromatographic method. ALP, AST and ALT were measured by enzymatic method.

External standardization was done with the central laboratory of the St. Rafael University Hospital of Leuven in Belgium. The results of two laboratories correlated highly.

**Histological Studies**

After the last blood sampling the whole pancreas was removed after sacrificing the animal and was collected in 10% formalin solution, and immediately processed by the paraffin technique. Sections were cut and stained by hematoxylin and eosin (H and E) for histological examination.<sup>[16]</sup>

**Statistical Analysis**

All the values were expressed as mean ± standard deviation. For comparison within groups Friedman test and Wilcoxon test and for comparison between groups, Kruskal-Wallis test and Mann-Whitney test are used. Differences between groups were considered significant at  $P < 0.05$  levels.

**RESULTS**

The extraction method used in this study yielded 8 ± 0.2 g safflower dried extract for each 100 g of the plant material.

**At Time 0:**

As shown in [Table 1] the levels of different biochemical parameters in serum of all four groups had no meaningful deference.

**At Time 1:**

FBS level was found to be significantly increased in diabetic control rats, diabetic rats treated with *Carthamus tinctorius* and diabetic rats treated with glibenclamide when compared to Time 0 and non-diabetic control group, and this was associated with a significant decrease in insulin level.HbA1C showed no meaningful change at this time.

Cholesterol, LDL-C and VLDL-c were significantly increased in diabetic control; diabetic rats treated with *Carthamus tinctorius* and diabetic rats treated with glibenclamide as compared to non diabetic control rats, and also in comparison with Time 0.

Diabetic control rats had lower level of HDL-C when compared with non-diabetic rats.

**Table 1: Different biochemical parameters levels in non-diabetic control, diabetic control, diabetic treated rats with *Juglans regia* and diabetic treated rats with glibenclamide (means ± SD)**

Parameters	Time	Non diabetic control	Diabetic control with no treatment	Diabetic group treated with <i>Carthamus tinctorius</i>	Diabetic group treated with glibenclamide
FBS (mg/dl)	0	95.5 ± 13.52	98.5 ± 12.43	98.5 ± 12.34	95.0 ± 3.0
	1	101.25 ± 26.22	299.0 ± 82.6*‡	260 ± 66.33*‡	240 ± 26.45*‡
	2	97.25 ± 12.78	492.4 ± 95.56†‡	130.8 ± 10.11§	122.33 ± 32.39§
Insulin (µU/ml)	0	13.12 ± 1.21	13.4 ± 1.26	13.6 ± 1.66	14 ± 1.35
	1	5.21 ± 1.61	5.27 ± 0.91*‡	5.08 ± 4.65*‡	6.6 ± 0.83*‡
	2	12.11 ± 1.72	4.86 ± 1.41†‡	13.7 ± 4.71§	12.5 ± 1.27§
HbA1c%	0	4.22 ± 0.22	4.25 ± 0.25	4.23 ± 0.23	4.03 ± 0.23
	1	4.3 ± 0.16	4.44 ± 0.63	4.96 ± 0.6	4.46 ± 0.66
	2	4.5 ± 0.21	6.9 ± 1.75†‡§	4.23 ± 0.32	4.16 ± 0.15
LDL-C (mg/dl)	0	14.75 ± 2.5	11.16 ± 2.22	14.96 ± 2.42	13.66 ± 1.52
	1	15.0 ± 1.82	20.2 ± 1.48*‡	33.16 ± 2.31*‡	22 ± 8.88 *‡
	2	16.25 ± 1.70	33.0 ± 3.36†‡§	20.16 ± 4.16†‡§	15.66 ± 3.21
HDL-C (mg/dl)	0	37.25 ± 1.70	37.5 ± 1.87	39.25 ± 1.07	37.0 ± 1.0
	1	40.25 ± 10.87	35.1 ± 6.08‡	48.16 ± 5.63	49.0 ± 21.93
	2	41.75 ± 6.39	33.33 ± 6.65‡	57.5 ± 14.69	42.33 ± 9.45
VLDL-C (mg/dl)	0	17.45 ± 3.54	16.8 ± 3.32	16.9 ± 3.42	19.26 ± 1.13
	1	15.15 ± 3.04	23.56 ± 11.97*‡	15.26 ± 1.25*‡	17.66 ± 7.85‡
	2	16.55 ± 2.34	30.5 ± 6.6*‡§	20.23 ± 7.29*‡	14.0 ± 3.12
Cholesterol (mg/dl)	0	61.25 ± 6.29	61.25 ± 6.18	64.5 ± 6.18	62.0 ± 7.21
	1	62.57 ± 3.20	127.5 ± 2.01*‡	93.8 ± 6.04*‡	100.0 ± 34.21‡
	2	64.5 ± 5.19	91.0 ± 14.73*‡§	91.16 ± 24.55§	60.33 ± 5.50
Triglyceride (mg/dl)	0	87.24 ± 17.72	83.9 ± 16.52	84.0 ± 16.62	96.33 ± 5.68
	1	85.75 ± 15.23	117.8 ± 59.87*‡	76.03 ± 6.58	88.33 ± 39.27
	2	82.75 ± 11.70	152.5 ± 33.04†‡§	101.16 ± 36.44	70.0 ± 15.62

\*Means differ significantly between Time 0 and Time 1 ( $P < 0.05$ )

†Means differ significantly between Time 0 and Time 2 ( $P < 0.05$ )

‡Means differ significantly in comparison with non-diabetic control group in each time ( $P < 0.05$ )

§Means differ significantly between Time 1 and Time 2 ( $P < 0.05$ )

Triglyceride increased at Time 1 in control diabetic group, but it was significant just in diabetic control rats which did not receive any treatment, and there was no significant difference of triglyceride levels between the groups which received treatment (*Carthamus tinctorius* or glibenclamide) and non diabetic control group. As shown in Table 2, ALP and AST significantly increased in diabetic rats as compared to non-diabetic rats and *Carthamus tinctorius* extract significantly inhibits the increase of ALP. Glibenclamide had not any significant effect on ALP at this time.

#### At Time 2:

Treatments with either *Carthamus tinctorius* or glibenclamide produced a significant decrease in FBS levels along with increase in insulin levels.

Serum cholesterol, triglycerides, LDL-C and VLDL-C levels were decreased by glibenclamide or extracts of *Carthamus tinctorius* due to treatment in comparison with Time 1.

The effect of *Carthamus tinctorius* on decreasing LDL-C level was remarkable when compared to control diabetic group ( $P < 0.05$ ), but still did not reach to the normal level.

Also, HDL-C level rose with either *Carthamus tinctorius* or glibenclamide, and showed no significant difference, when compared with non-diabetic group and Time 0.

HbA1C in diabetic control rats was found to be significantly higher when compared with non-diabetic rats ( $P < 0.05$ ).

In contrast, diabetic rats treated with *Carthamus tinctorius* and diabetic rats treated with glibenclamide

showed lower mean HbA1C, which had no meaningful difference when compared to non-diabetic group and Time 0.

Effects of administrating glibenclamide or extract of *Carthamus tinctorius* on all biochemical parameters discussed above showed no significant difference and both tend to bring the values to near normal.

As shown in Table 2, *Carthamus tinctorius* extract and also glibenclamide significantly inhibit the increase of ALP and AST as compared to diabetic group.

#### Results of the Histomorphometric Study:

Histopathological study of islets of Langerhans revealed that size of Langerhans islets in diabetic control group had a significant difference in comparison with non-diabetic control group ( $P < 0.05$ ).

There was no significant difference in size of Langerhans islets between the treated rats (with *Carthamus tinctorius* or glibenclamide) and non-diabetic control rats. [Table 2, Figure 1].

## DISCUSSION

In our present experimental study, it was observed that safflower can reverse the metabolic disorders occurring in alloxan induced diabetic rats. Our findings indicate that FBS, triglyceride, cholesterol, LDL-C and VLDL-C had a meaningful decrease in diabetic rats treated with *Carthamus tinctorius* and diabetic rats treated with glibenclamide as compared with diabetic rats. Insulin level increased significantly in diabetic groups received treatment (glibenclamide or *Carthamus tinctorius* L) in comparison with diabetic group with no treatment. The desirable effect of the safflower extract on the liver is also considerable.

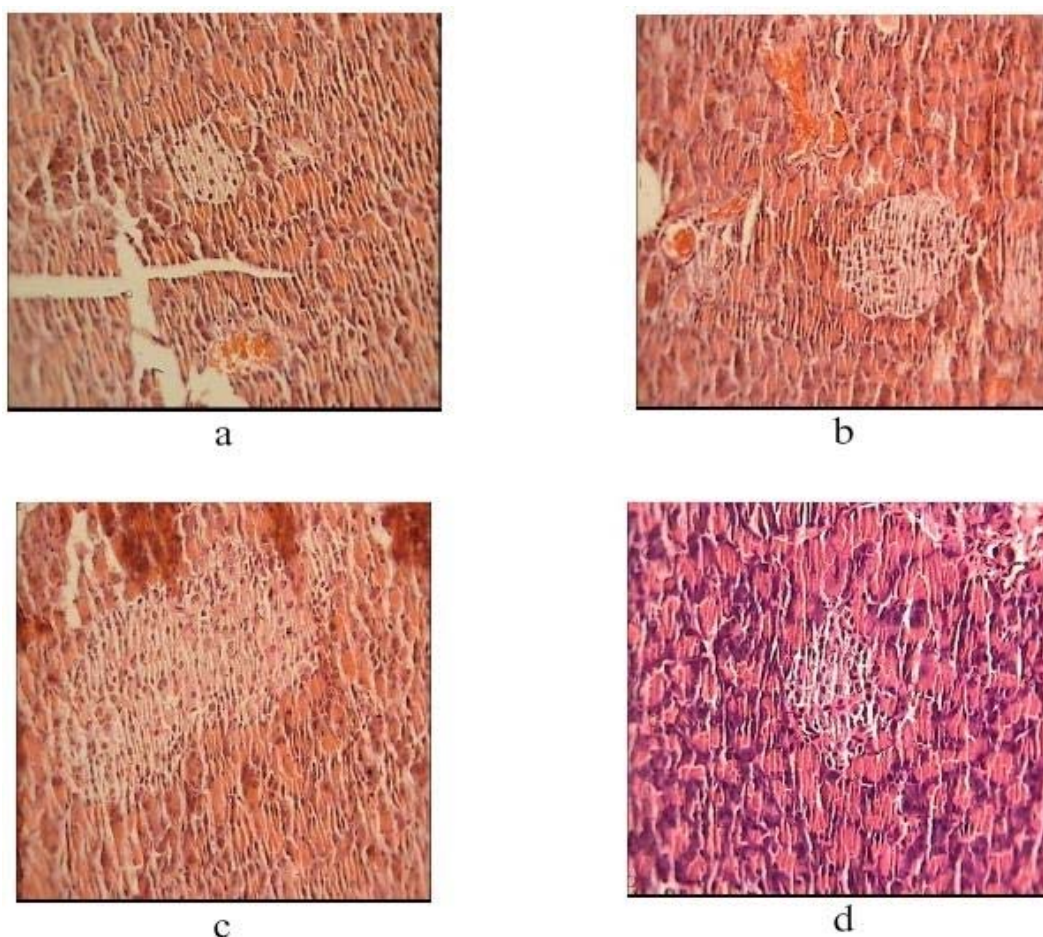
**Table 2: Different hepatic enzyme levels in non-diabetic control, diabetic control, diabetic treated rats with *Carthamus tinctorius* and diabetic treated rats with glibenclamide (means  $\pm$  SD)**

Parameters	Time	Non diabetic control	Diabetic control with no treatment	Diabetic treated with <i>Carthamus tinctorius</i>	Diabetic treated with glibenclamide
ALP (U/L)	0	701.75 $\pm$ 61.30	697.3 $\pm$ 52.36	690.33 $\pm$ 49.06	674 $\pm$ 55.34
	1	607.5 $\pm$ 35.93	2407.6 $\pm$ 274.93*‡	825.33 $\pm$ 23.85	1333.3 $\pm$ 18.08*‡
	2	622.5 $\pm$ 20.61	2937.5 $\pm$ 381.60†‡	749.5 $\pm$ 49.52	704.33 $\pm$ 58.39
AST (U/L)	0	22.25 $\pm$ 5.5	16.16 $\pm$ 1.02	20.83 $\pm$ 11.68	28.33 $\pm$ 12.66
	1	29.0 $\pm$ 18.7	44.0 $\pm$ 6.89*	45.16 $\pm$ 17.97*‡	58.0 $\pm$ 8.54*‡
	2	26.5 $\pm$ 9.87	51.25 $\pm$ 2.62† ‡	39.66 $\pm$ 6.60	20.03 $\pm$ 9.45
ALT (U/L)	0	48.62 $\pm$ 8.21	45.33 $\pm$ 9.21	47.33 $\pm$ 8.71	53.33 $\pm$ 3.05
	1	60.16 $\pm$ 20.11	55.5 $\pm$ 12.76	42.2 $\pm$ 11.56	98.33 $\pm$ 30.98
	2	57.8 $\pm$ 13.77	51.0 $\pm$ 21.43	35.2 $\pm$ 28.84	52.83 $\pm$ 15.80

\*Means differ significantly between Time 0 and Time 1 ( $P < 0.05$ ).

†Means differ significantly between Time 0 and Time 2 ( $P < 0.05$ ).

‡Means differ significantly in comparison with non-diabetic control group in each time ( $P < 0.05$ ).



**Figure 1:** Cross-section of Langerhans islets in experimental groups (A) diabetic control group, (B) non-diabetic group, (C) diabetic group with *Carthamus tinctorius*, (D) Diabetic group with glibenclamide

**Table 3: Size of islets of Langerhans in four experimental groups**

Time	Non diabetic control	Diabetic control with no treatment	Diabetic treated with <i>Juglans regia</i>	Diabetic treated with glibenclamide	
Size of Langerhans islets (micron)	2	1.64 ± 0.3	0.62 ± 0.4*	2.19 ± 0.5	1.48 ± 0.6

\*Means differ significantly between diabetic control and non-diabetic control group ( $P < 0.05$ ).

The histological study revealed size of islets of Langerhans enlarged significantly consequentially as compared with diabetic rats with no treatment. Histopathological studies revealed that safflower and glibenclamide significantly improved the histological architecture of the islets of Langerhans. Other studies also established these findings.<sup>[8,17]</sup> Alloxan is known for its selective pancreatic islet  $\beta$ -cell cytotoxicity which has been extensively used to induce diabetes mellitus in animals. In the alloxan-induced diabetes mellitus the increase in blood glucose is accompanied by an increase in serum cholesterol and triglyceride levels. A significant increase in serum cholesterol and triglycerides observed in our experiment is in agreement with the findings of the aforementioned authors.<sup>[18,19]</sup> In our present experimental study it was observed that safflower

extract can reverse the metabolic disorders occurring in alloxan induced diabetes. Considering these effects on these lipid components, it can be assumed as a potential hypolipidemic agent, which will be a great advantage both in diabetic condition as well as the associated atherosclerosis or hyperlipidemic conditions. Antioxidants are a group of substances which significantly inhibit or delay oxidative processes, while often being oxidized themselves. Two main mechanisms of action have been proposed for antioxidants. The first is a chain-breaking mechanism, by which the antioxidant gives an electron to the free radical present in the system. The second mechanism involves removal of reactive oxygen species (ROS) and reactive nitrogen species (RNS) initiators by extinguishing chain-initiating catalysts.<sup>[8,19,20]</sup> Safflower constitutes a good source of anti-

oxidant compounds with free radical-scavenging potential<sup>[7,21]</sup> suggesting that it could be useful in prevention of diseases in which free radicals are implicated. Some studies have shown that flavonoids are able to decrease plasma glucose levels.<sup>[22]</sup> Previous studies revealed that quercetin promotes normalization of the level of glycemia and reduces high blood serum concentrations of cholesterol and LDL-C seen in alloxan-induced diabetic rats.<sup>[23]</sup> Quercetin inhibits glucose transporter (GLUT2), so diminishes glucose intestinal absorption.<sup>[24]</sup> Plant antioxidants are able to restore and regenerate pancreatic B cells.<sup>[18]</sup> The results from the studies on garlic, onion and fenugreek show that in diabetic rats treated with anti-oxidants the number of Langerhans islets has increased significantly.<sup>[13,25]</sup> Taking into accounts these results, we conclude that one of the mechanisms involved in hypoglycemic effect of *Carthamus tinctorius* is regeneration and restoration of Langerhans islets, thus elevating the insulin level. On the other hand, a clinically used glibenclamide is known to lower the blood glucose level by stimulating  $\beta$ -cells to release more insulin in alloxan-induced diabetic rats.<sup>[26,27]</sup> The increase in serum insulin levels suggested that safflower like glibenclamide enhances the secretion of insulin from the beta cells of the islets of Langerhans. Further, it has an ability to restore the protein breakdown and enhance the glycogenesis process in the liver of diabetic rats. The ALT and AST activities are known as cytosolic marker enzymes reflecting hepatocellular necrosis as they are released into the blood after cell membrane damage.<sup>[19,28]</sup> In the present study, therefore, both enzyme activities were used as indicators of hepatic damage. Table 2 shows the activities of AST and ALT in experimental rats. Compared with normal rats, diabetic rats showed more activities of serum AST and ALT. Hypercholesterolemia and hypertriglyceridemia have been induced in alloxan-induced diabetic rats.<sup>[8,29]</sup> In the present study in the alloxan-induced diabetic rats the increase in blood glucose is accompanied by significant increase in serum triglyceride, cholesterol, LDL-C, VLDL-C, HbA1c, ALP, AST and a decrease in serum insulin and HDL-C. The mechanism by plant extracts has been proposed to inhibit hepatic glucose production,<sup>[30]</sup> to inhibit intestinal glucose absorption<sup>[31]</sup> or to correct insulin resistance.<sup>[32]</sup> However, possibilities of other mechanisms to exert hypoglycemic effect cannot be ruled out. It may be summarized that the possible mechanisms by which safflower brings about its antihyperglycemic action may be through potentiation of pancreatic secretion of insulin from the intact  $\beta$ -cells of islets (which was clearly evidenced by the increased level of insulin in diabetic rats treated with safflower and glibenclamide) coupled with extra-pancreatic mechan-

isms like decreased glycogenolysis and enhanced glycogenesis by the liver and/or enhanced transport of blood glucose to peripheral tissues (as seen by the stimulatory effect on glucose uptake in rat diaphragm). With such evidence, it is possible to assume that safflower extract might stimulate the secretion of insulin from the beta cells by a mechanism similar to that of oral hypoglycemic agents by depolarization of islet membrane which consequently alters the change in ion flux.<sup>[14]</sup> In conclusion, we found that the petal extract of safflower is useful for treatment of diabetes and its complications. The petals of safflower might be an excellent antioxidant ingredient to protect damage induced by free radicals. Further clinical trials in diabetic patients are recommended for its crude extract and also its carthamin substance.

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