



# Hepatoprotective and Hypolipidemic Effects of *Carthamus tinctorius* oil in Alloxan-induced Type 1 Diabetic Rats

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## ABSTRACT

**Introduction:** Hepatoprotective and hypolipidemic effects of *Carthamus tinctorius* Linn. (Safflower) seed oil was investigated in diabetic rats.

**Methods:** Diabetes was induced by administration of 120 mg/kg alloxan monohydrate. The seed oil of safflower at dose of 200 mg/kg was administered as single dose per day to diabetic rats for a period of 28 days. The effect of oil on blood glucose level was measured in the diabetic rats. Serum lipid profile [total cholesterol (TC), triglycerides (TGs), low density (LDL) and high density lipoprotein (HDL) and enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were also determined.

**Results:** Levels of blood glucose, TC, TGs, LDL, ALT, AST and ALP decreased and HDL increased in alloxan induced diabetic rats after treatment with 200 mg/kg safflower seed oil for 28 days.

**Conclusion:** The present study demonstrates that seed oil of safflower seems to be useful for the prevention of diabetes complications.

### *Implication for health policy/practice/research/medical education:*

The present study demonstrates that safflower seed oil might to be useful for the prevention of diabetes complications including hepatotoxicity and hyperlipidemia.

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## Introduction

Diabetes mellitus is a disease in which homeostasis of carbohydrate, protein and lipid metabolism is improperly regulated by hormone insulin resulting in elevation of fasting and postprandial blood glucose levels (1). The major chronic complications associated with diabetes include retinopathy, neuropathy, nephropathy, and atherosclerotic coronary artery disease and peripheral atherosclerotic vascular disease (2). According to recent estimation, the global population is approaching the midst of a diabetes pandemic. By the year 2010 the total number of people worldwide with diabetes is predicted to reach 239 million (3). Besides hyperglycemia, several

other factors like hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis. Despite the great strides that have been made in the understanding and management of this disease, the graph of diabetes-related mortality is rising unabated. Although a numbers of synthetic drugs are available in the market diabetes and its related complications still remain uncontrolled. On the other hand, traditional medicinal plants have been used successfully since ancient times by physicians and laymen to treat diabetes and its related complications, presenting a stirring prospect for the expansion of an alternative way of treatment of diabetes (4,5). Liver is a big organ that its main function is managing and controlling carbohydrates,

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lipids, and proteins metabolism. Maintaining normal blood glucose levels by taking and storing glucose in form of glycogen (glycogenesis), cleavage of glycogen into glucose (glycogenolysis), and forming glucose from non-carbohydrate sources such as amino acids (gluconeogenesis) are some other functions of liver (6). Various studies have shown that alloxan has deleterious effects on liver and kidney (7). Disruption in liver function that is demonstrated with increasing in alanine and aspartate aminotransferases (ALT & AST) have been reported one week after alloxan injection. These enzymes are measured for investigating liver function (8). Aminotransferases are the markers of the healthy hepatocytes. ALT is mainly found in the liver but AST, other than liver, is found in some other organs, so it is a less-specific marker for liver. Liver has a major role for maintaining post-prandial normal glucose concentration and it is the main site of insulin clearance (9).

*Carthamus tinctorius*, commonly known as safflower, false saffron or dyers saffron belongs to the family asteraceae and since centuries it has been grown from China to Mediterranean regions, but now is grown for commercial purposes in Pakistan, India, USA, Ethiopia, Mexico, Kazakhstan, Argentina, Australia, Spain, Turkey, Canada and Iran (10). Safflower is an oilseed crop in the Compositae that is valued for its oils rich in unsaturated fatty acids. The major fatty acid in safflower oil is linoleic acid (80%) (11). *Carthamus tinctorius* L extracts and oil are important in drug development with numerous pharmacological activities in the world. It is a useful plant in painful menstrual problems, post-partum hemorrhage and osteoporosis. *C. tinctorius* has recently been shown to have antidiabetic activities. Caryophyllene, p-allyltoluene, 1-acetyoxytetralin and heneicosane were identified as the major components for *C. tinctorius* flowers essential oil (12). This study was designed to investigate the Hepatoprotective and Hypolipidemic effects of *Carthamus tinctorius* Linn seed oil in diabetic rats.

## Material and Methods

### Preparation of safflower oil

The seed of safflower was collected during September 2013 from Isfahan province.

The plant was identified by Dr. L. Ghaem Maghami of Isfahan University of Medical Sciences and a voucher specimen (No. 2338) was kept in the herbarium of the Sciences Faculty. Seeds of *Carthamus tinctorius* (800 g) were hydrodistilled for 3 h in a Clevenger type apparatus. Five percent v/v of the resulting oil was prepared using saline solution of dimethylsulfoxide (DMSO) (13).

### Preparation of diabetic rats

Alloxan monohydrate, dissolved in saline, was injected to rats intra-peritoneally at dose of 120 mg/kg body weight. After 4 days, rats with marked hyperglycemia (serum glucose more than 200 mg/dl) were selected and used for

the study (14).

### Experimental design

Eighteen male Wistar rats with (200±20 g) were purchased from Pasteur Institute, Iran and were kept in animal house of Isfahan University. They were kept at 20±5 °C, relative humidity of 30±5% and light/dark cycle for 12 h. All animals were fed with rodent pellet diet and water was allowed ad-libitum under strict hygienic conditions. These rats were randomly divided into 3 groups with 6 rats per group, as follows: The rats in group 1 (C: controlled group) were administered 0.5 ml saline, group 2 (D: diabetic rats), group 3 (D+SO) diabetic rats receiving safflower oil at 200 mg/kg in saline. Treatment period was 28 days.

### Collection of samples

At the end of experiment, rats were sacrificed and their fasting blood was collected for the estimation of blood parameters. Serum was obtained immediately by centrifugation (15 min at 4000 rpm), which was used for the measurement of various biochemical parameters. All analyses were carried out within 24 h of blood collection.

### Statistical analysis

The results are expressed as the mean±standard deviation (SD) of triplicate analyses. All statistical comparisons were performed using a one-way analysis of variance (ANOVA) followed by a two-tailed t-test. Differences were considered significant at a p level of 0.05 or lower.

## Results

### Effect of safflower oil on FBG and serum lipid profile

Diabetes significantly increased serum FBG, TG, Cholesterol, VLDL and LDL concentrations in comparison with the control group. Treatment of diabetic animals with safflower oil significantly inhibited the increase in serum FBG, TG, Cholesterol, VLDL and LDL with the untreated diabetic animals. The treatment of diabetic animals with safflower oil also significantly inhibited decrease of serum HDL concentrations in comparison with the untreated diabetic animals (p<0.05; Table 1).

### Effect of safflower oil on serum ALT, AST and ALP activity

Serum ALT, AST and ALP activity as markers of liver function significantly (p<0.05) were increased in the untreated diabetic animals in comparison with the control group. Treatment of the diabetic animals with SO could significantly inhibit an increase of serum ALT and ALP activity in comparison with the untreated diabetic animals. Treatment by SO could maintain serum ALT and ALP activity of the treated animal at the same level as that of the control group (Table 2).

## Discussion

Alloxan administration produces diabetes status by destruction of pancreatic β-cells with changes in metabolic

**Table 1.** The effects of safflower oil (SO) on FBG, TC, TG, LDL-C, HDL-C and VLDL-C in experimental rats

Parameter	Control	Diabetic	Diabetic + SO
FBG (mg/dL)	88 ± 21*	356 ± 61	288 ± 46**
TG (mg/dL)	76.01 ± 15.56*	102.02 ± 21.01	72.02 ± 22.87*
TC (mg/dL)	73.00 ± 16.01*	117.09 ± 24.15	86.66 ± 23.24**
HDL (mg/dL)	36.64 ± 6.90*	29.57 ± 10.09	34.55 ± 9.46*
LDL (mg/dL)	19.61 ± 3.78*	71.58 ± 14.24	38.42 ± 9.91**
VLDL (mg/dL)	13.43 ± 4.33*	21.41 ± 5.05	13.90 ± 4.65*

Values are represented as mean ± SEM

\*Significant change in comparison with diabetic without treatment at p<0.05.

#Significant change in comparison with control at p<0.05.

**Table 2.** The effects of safflower oil (SO) on ALT, AST and ALP levels in experimental rats

Parameter	Control	Diabetic	Diabetic + SO
ALT (U/L)	37.72 ± 1.36	50.13 ± 3.80*	38. ± 4.59**
AST (U/L)	65.86 ± 1.81	122.02 ± 1.01*	108.02 ± 2.87**
ALP (U/L)	143.12 ± 1.21*	179.79 ± 2.15**	118.23 ± 2.4**

Values are represented as mean ± SEM

\*Significant change in comparison with diabetic without treatment at p<0.05.

\*\*Significant change in comparison with control at p<0.05.

variables as well liver functions (15). In the alloxan-induced diabetes mellitus, the rise in blood glucose is also accompanied by an increase in plasma cholesterol, triglycerides cholesterol, AST, and ALT levels (16,17). The diabetogenic effects of alloxan are partly attributed to the specific cytotoxic action mediated by reactive oxygen species generation leading to the damage of large number of  $\beta$ -cells accompanied by a decrease in endogenous insulin release. However, alloxan-administered rats became hyperglycaemic in a short period of time, followed by a hepatic glucose overproduction (18).

Medicinal plants and natural antioxidants with hypolipidemic effects could prevent or be helpful in reducing the complications of lipid profile seen in diabetic patients (19). The mechanism of hypolipidemic action of medicinal plants may also be due to the inhibition of glycation lipoproteins, enzymes and proteins that involve lipid and lipoprotein metabolism (20,21).

Safflower is especially attractive as an oilseed crop, given that its seed oils are rich in mono- and polyunsaturated fatty acids (22). The major fatty acid in safflower oil is linoleic acid (80%). Linoleic acid is a polyunsaturated essential fatty acid called omega-6 fatty acid. In physiological literature, it has been used in the biosynthesis of prostaglandins and reported to be rich in the lipids of cell membranes. There is evidence that free fatty acids play an important role in regulating animal insulin secretion response and glucose homeostasis. It was recognized in a previous study that elevated plasma free fatty acids had both stimulatory and inhibitory effects on insulin secretion. Elevated free fatty acids were proved to enhance glucose-stimulated insulin secretion in fasted rats. Prolonged

exposure to elevated fatty acids induced an impairment of animal insulin secretion in  $\beta$ -cells secretion function, whereas an acute exposure was found to enhance insulin secretion (23). In addition, saturated fatty acids induced lipoapoptosis in human  $\beta$ -cells, whereas unsaturated fatty acids had no effect. The insulinotropic effect of free fatty acids was profoundly influenced by the chain length and degree of saturation of individual fatty acids under certain circumstances. Long-chain and saturated fatty acids were more effective than medium-chain and unsaturated fatty acids (24).

*C. carthamus* oils may be exert their antihyperglycemic effect by potentiating plasma insulin action, secretion or its release from bound form. In diabetic status, lipoprotein lipase is not activated due to insulin deficiency resulting in hypertriglyceridemia and hypertriglyceridemia. This is in agreement with the fact that the glycemia level is the major determinant of total and very low-density lipoprotein cholesterol concentrations (25).

The liver is an important insulin-dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes. The increase in the activities of serum glutamic pyruvic transaminase (SGPT) (ALT), serum glutamic oxaloacetic transaminase (SGOT or AST) and ALP indicated that diabetes might be induced due to liver dysfunction. Therefore, increase in the activities of SGPT, SGOT and ALP, may be mainly due to the leakage of these enzymes from the cytosol of hepatic cells into the blood stream (26).

Treatment of alloxan diabetic groups with safflower oil for 28 consecutive days could restore the activities of the above enzymes to their normal levels. A possible explanation

for effects of safflower oil on the activities of AST, ALT and ALP in plasma and liver is that these treatments may inhibit the liver damage induced by alloxan.

### Conclusion

Findings of the present study clearly indicate that treatment with safflower oil is effective in its hepatoprotection and hypolipidemia in diabetic rats. It is very difficult to comment on the mechanism of hepatoprotective and hypolipidemic activities of safflower oil, since the study was not designed accordingly.

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### Authors' contributions

All the authors wrote the manuscript equally.

### Conflict of interests

The authors declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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