

An Investigation into the Effects of Alcoholic Extract of *Alhagi Maurorum* on Lipid Profiles In Streptozotocin-Induced Diabetic Male Rats

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Abstract

Disorders in Lipid production are one of the most common problems associated with diabetes seen in approximately 40% of patients. In this study, the effects of alcoholic extract of *Alhagi maurorum* on the serum levels of lipids in Streptozotocin-induced diabetic rats are investigated. For the purpose of this experimental research, 42 male Wistar rats were divided in 6 Groups of seven: the control, diabetic sham and 4 experimental groups. Diabetic sham received 70 mg/kg Streptozotocin once at the beginning of the experiment; the experimental groups 1 and 2 daily received 250 and 500 mg/kg *Alhagi maurorum* alcoholic extract respectively; the experimental groups 3 and 4 first received Streptozotocin once, and then a daily dose of 250 and 500 mg/kg extract. Oral administration of alcoholic extract continued over a period of two months. 48 hours after the last administration, blood samples were prepared and used for measurement of serum levels of triglycerides (TG), total cholesterol (TC), LDL cholesterol and HDL cholesterol. Serum levels of triglyceride and LDL Cholesterol in the diabetic sham compared to the control group showed a significant increase ($p < 0.05$). On the other hand, serum levels of triglyceride and LDL cholesterol in the experimental group 2 (500 mg/kg extract) compared to the control group demonstrated a significant decrease ($p < 0.05$). Also, serum total cholesterol concentration in the experimental group 1 (250 mg/kg extract) compared to the control group indicated a significant reduction, while HDL cholesterol increased significantly in this group ($p < 0.05$). A significant decrease was observed in the serum levels of triglyceride and LDL cholesterol in the experimental group 4 in comparison with diabetic sham, whereas concentration of HDL cholesterol in experimental Group 3 increased significantly ($p < 0.05$). Due to its antioxidant properties, alcoholic extract of *Alhagi maurorum* can reduce Streptozotocin toxicity leading to an improvement in Serum lipid profiles of diabetic patients.

Keywords: *Alhagi maurorum*, HDL, LDL, triglycerides, streptozotocin, total cholesterol, rat

Introduction

Cardiovascular disease, especially myocardial infarction (MI), is considered as the main cause of mortality and disability in the world, and a large percentage of these disorders are directly or indirectly related to lipid malfunction (Moghadam-Nia et al., 2016). Fortunately, various compounds show reasonable preventive effects in

the treatment of lipid disorders, and some can be used in the prevention of certain diseases (Moghadam-Nia et al., 2016). Diabetes often leads to functional and biochemical disorders in liver, including metabolic modification of carbohydrates, lipids, proteins and changes in the nature of antioxidants (Francés et al., 2010). Streptozotocin (STZ) is a natural compound produced by *Streptomyces achromogenes* (Ahangarpour et al., 2014). It has a strong anti-bacterial property, and is used in the treatment of pancreatic β - cells (Ahangarpour et al., 2014; Sayidi et al., 2013). STZ is an analog of N-acetyl glucose amine and is experimentally used to induce type I diabetes (Harald et al., 2007). It also causes an increase in lipid peroxidation in blood, liver and kidney (Morel and Chisolm, 1989). In fact, lipid disorder is one of the most common problems associated with diabetes, affecting about 40% of diabetic patients (Kasper et al., 2002). Diabetes induces systemic disorders through basic changes in plasma lipid levels increasing risk of atherosclerosis and cardiovascular disease (Kasper et al., 2002). One of the main common problems of diabetics is the disorder in lipid metabolism resulting in the elevation of fatty acid mobilization in adipose tissue and the increase in the serum levels of free fatty acids (Kasper et al., 2002). These free fatty acids enter hepatocytes and esterify in lipolytic process to form triglycerides (Kasper et al., 2002). Also, the increase in the level of free radicals, the reduction of lipid peroxidation and the elevation of antioxidants are seen during diabetes (Wolf, 1993; Desco et al., 2002), and lipid peroxidation results in an increase in triglyceride levels (Mamdouh et al., 2003).

One of the most important medicinal plants is *maurorum* which belongs to the Fabacea family and Fabales order. Fabacea comprises approximately 730 genera and 19,400 species (Shakiba et al., 2016). Some phytochemicals found in *Alhagi maurorum* include essential oils, phenolic compounds, carbohydrates, proteins, alkaloids, terpenoids, saponine, glycosides, steroids and tannins (Shakiba et al., 2016; Yaghoubian et al., 2013). These compounds are responsible for the medical properties of *Alhagi maurorum*. *Alhagi flavanon* glycosides include Alhagidin, Alhagitin and resins, and their Flavonoids include Quercetin and Catechin, all of which have antioxidant properties (Yaghoubian et al., 2013). Flavonoids, especially Quercetin, are mostly effective in the treatment of rheumatism, dementia, hypertension, fever, vomiting, constipation, pain, infections, asthma, diabetes, neurological disease, chest pain, stomach pain, diarrhea, nausea, heart disorders and respiratory diseases. They also have anti-inflammatory, anti-apoptotic, antispasmodic, appetite stimulant, diuretic, analgesic, antibacterial and strong antioxidant properties (Jaimandetal., 2011; Derakhshanian et al., 2013).

Alhagi maurorum aqueous extract has protective effects on inflammatory diseases induced by free radicals (Srivastava, 2014). In addition, ethanolic extract of *Alhagi maurorum* aerial parts is used in the prevention of stomach ulcers. It also shows anti-diarrheal activity and inhibitory effect on the calcium channel (Srivastava, 2014).

It has been reported that anti-oxidants protect liver against damage caused by toxins through inhibiting the production of free radicals (Gargoum, 2013). Such liver protection may be associated with the activities of phenolics and flavonoids found in *Alhagi maurorum* extract (Gargoum, 2013). Studies have shown that some flavonoids such as Quercetin and catechin can dramatically protect beta cells (Mansourabadi, 2014). Some of these anti-diabetic effects of flavonoids are related to the reduction in inflammation caused by Streptozotocin and

consumption of fatty food (Mansourabadi, 2014). It has been reported that carbon tetrachloride reactivate strichloromethyl free radical in the liver, and this free radical leads to self-oxidation of fatty acids present in membrane phospholipids, culminating in morphological and functional changes in the cell membrane. These free radicals initiate lipid peroxidation pathways, which attack and destroy polyunsaturated fatty acids (Gargoum, 2013). On the other hand, studies show that *Alhagi maurorum* protection of liver from injuries caused by various oxidative toxins is the result of flavonoids and phenolic compound activities (Gargoum, 2013; Anar and Mutaliyeva, 2013).

One of the adverse effects of lipid malfunction is cardiovascular disease seen in diabetes. Due to the side effects of chemical drugs used against diabetes, finding new drugs with fewer side effects is urgently required. Moreover in the composition of such drugs, the use of medicinal plants utilized in traditional medicine for treatment of various diseases must be considered. In the present study, therefore, the effects of *Alhagi maurorum* alcoholic extract on lipid malfunction induced by Streptozotocin were investigated in diabetic male rats.

Materials and Methods

Animals

In This experimental study, 42 mature Wistar rats weighing 200 ± 10 g in the age range of 2.5 to 3 months were used. They were divided into 6 groups: control group, left untreated, the diabetic sham, received a single dose of 70 mg/kg Streptozotocin at the beginning of the experiment, the experimental groups 1 and 2, daily received 250 and 500 mg/kg *Alhagi maurorum* alcoholic extract for 2 months respectively, and the experimental groups 3 and 4, first received a single dose of 70 mg/kg Streptozotocin followed by a daily dose of 250 and 500 mg/kg extract for 2 months respectively (Gulzar, 2015; Salama, 2016; Suthar, 2016). Streptozotocin was injected intraperitoneally, while the extract was administered orally. All the groups were kept at 20-22°C under 12- h light/ dark cycle and adequate humidity with unlimited access to water and standard prepared food (Ashraf et al., 2014).

Preparation of alcoholic extract

Aerial parts of *Alhagi maurorum* were collected and after scientific approval by botanical experts, washed three times in tap water and twice in distilled water, and dried in the shade. Following milling by Wiley mill (Model 4-GMI, Germany); 100 g powder was mixed in 1 liter of 70% ethanol for an hour. After filtration, it was concentrated under reduced pressure of 40 degrees using a rotary evaporator (Buchi, Model 462, Germany), and the extract was freeze dried in a Lyophilizer. For oral administration, different concentrations of extract were prepared in distilled water (Sheweita et al., 2016).

Extract administration, blood sampling, enzymatic assays and histological studies

Streptozotocin drug was carefully weighed by a digital scale. To induce diabetes, 70 mg/kg Streptozotocin dissolved in Physiological serum was intraperitoneally injected after 12 hours of overnight fasting (Vinagre et al., 2010; Gajdosik et al., 1999). 5 days after injection of STZ, blood samples were taken by glucometer to determine

glucose level, and so its level was recorded. Rats with glucose levels over 250 Mg/dl were considered diabetic (Pouraboli et al., 2014; Nohtani and Pouraboli, 2016). A daily dose of 250 or 500 mg/kg alcoholic extract was gavaged to each rat in Experimental groups 2, 1, 3 and 4. Daily feeding of extract was performed at 9-10 o'clock in the morning using a feeder (Golzar, 2015; Salama, 2016; Suthar et al., 2016).

At the end of the experiment and 48 hours after the last gavages, animals were weighed, and direct blood sampling from heart was carried out under anesthesia with ether. Using 5 ml syringes, 3 to 5 ml blood was taken from each animal. Blood samples were kept in laboratory condition for 20 minutes; they were centrifuged for 15 minutes at 5000 rpm; serum was separated from the clot, and freezed at -20 °c to be tested for biochemical parameter (MoghadamNia et al., 2016).

Serum cholesterol and triglyceride levels were measured by enzymatic colorimetric method (Shirali et al., 2012). In general, total cholesterol was measured by enzymatic colorimetric method, LDL cholesterol by Friedewald method, HDL cholesterol by colorimetric method and triglyceride by enzymatic method with special kits and auto analyzer (Moghadam-Nia et al., 2016; Fadairo and Otite-Douglas, 2015; Zarei et al., 2014).

Statistical Analysis

The results were statistically analyzed using SPSS software (version 16) and data was statistically examined by the ANOVA test. Tukey HSD test was used to study significant differences, and the level of statistical significance was set at $p < 0.05$. Serum levels of triglycerides, total cholesterol, LDL -cholesterol and HDL cholesterol were presented as the Mean \pm SEM.

Results

The mean serum concentration of total cholesterol showed a significant decrease in the experimental group 1 (250 mg/kg *Alhagi maurorum* alcoholic extract alone) in comparison with the control group ($P < 0.05$; table 1).

The mean level of triglycerides in diabetic sham group (70 mg/kg Streptozotocin) compared to the control group indicated a significant increase ($P < 0.05$; table 1), while in experimental group 2 (500 mg/kg extract) it was declined significantly, and in experimental group 4 (500 mg/kg extract and Streptozotocin) it indicated a significant reduction compared to the diabetic sham group ($P < 0.05$; table 1).

The mean level of LDL cholesterol concentration increased significantly in the diabetic sham group compared to the control group, while it was declined in experimental group 2 in comparison with the control, and in experimental group 4 compared to the diabetic sham as well ($P < 0.05$; table 1).

Statistical Comparison of mean HDL cholesterol concentration showed a significant increase in the experimental group 1 (250 mg/kg extract alone) compared to the control group, and in experimental group 3 (250 mg/kg alcoholic extract and Streptozotocin) compared to the diabetic sham group ($P < 0.05$; table 1).

Table 1. Mean and standard deviations of triglycerides (TG), total cholesterol (Ch), LDL cholesterol and HDL cholesterol in different groups of rats.

Groups	TG (mg/dl)	Total cholesterol (mg/dl)	LDL	HDL
Control	85/57±4/57a	67/14±3/28	31/14±2/86a	21/57±2/43
Diabetic sham	236/14±22/57	70/86±4/28	36/42±3/28	23/42±2/58
Experimental 1	86/42±6/85	58/07±4/57b	37/42±3/28	24/22±3/72b
Experimental 2	60/21±5/14b	67/71±4/42	27/57±1/50b	21/28±1/72
Experimental 3	250±20/42	72±6/57	36/28±3/50	30±2/42c
Experimental 4	134/14±6/57c	71±6/85	30/28±2/28c	24/14±3/72

P<0.05diabetic sham group compared to the control group, P<0.05b the experimental groups 1 and 2 compared to the control group, P < 0.05c experimental groups 3 and 4 compared to the diabetic sham group. Diabetic control group peritoneally received 70 mg/kg Streptozotocin, experimental groups 1 and 2 daily received *Alhagi maurorum* alcoholic extract orally (250 and 500 mg/kg), experimental groups 3 and 4 first received Streptozotocin and then a daily dose of *Alhagi maurorum* extract orally (250 and 500 mg/kg).

Discussion

In this study, the protective effects of *Alhagi maurorum* alcoholic extract (250 and 500 mg/kg) on lipid malfunction caused by diabetes induced by Streptozotocin were investigated in adult male rats for 2 months, and the results were statistically compared to the different groups. Results showed that serum levels of triglycerides and LDL cholesterol increase significantly in the diabetic sham group receiving 70 mg/kg Streptozotocin compared to the control (Table 1). This means that Streptozotocin has a negative effect on the levels of these parameters. In contrast, triglycerides and LDL cholesterol levels decreased significantly in the experimental group 2 (500 mg/kg extract) compared to the control, while HDL cholesterol indicated a significant increase in the experimental group 1 (250 mg/kg extract) which reflects the positive effects of *Alhagi maurorum* extract on HDL cholesterol as well as LDL cholesterol and triglyceride concentrations (p< 0.05; Table 1).

There was a significant reduction in the serum levels of triglycerides and LDL cholesterol in the experimental group 4 (500 mg/kg *Alhagi maurorum* extract and Streptozotocin) compared to the diabetic sham, whereas HDL cholesterol increased significantly in the experimental group 3(250 mg/kg extract and Streptozotocin) compared to the diabetic sham (p < 0.05; Table 1). According to these results, *Alhagi maurorum* extract improves the negative effects of Streptozotocin on triglycerides and LDL cholesterol and boosts the serum level of HDL cholesterol.

High LDL-C level is seen in hereditary hyperlipidemiaand Hypercholesterolemia, uncontrolled diabetes mellitus, chronic renal failure and coronary heart disease (Dashty et al., 2013). Measurement of LDL cholesterol is specifically used to determine the extent of coronary artery disorders (Dashty et al., 2014). Conversely, studies have shown that for every 1 mg/dl increase in HDL-C, the risk of cardiovascular disease progression is reduced (Kapur et al., 2008). Over the past two decades, preclinical research has gained further insight into the nature of HDL-C metabolism, specifically with respect to the ability of HDL-C to promote reverse cholesterol transport (RCT) (Kapur et al., 2008). On the other hand, some anti-diabetic effects of flavonoids are due to the reduced inflammation

caused by Streptozotocin (Mohammad -Sadeghi et al., 2015). It has been shown that liver toxins exert their effects through production of free radicals, which lead to autoxidation of fatty acids found in the plasma membrane, and induction of physiological and functional changes in hepatocytes membrane (Abdellatif and Gargoum, 2014). In short, various liver toxic effects are associated with the cytochrome P450, which influence free radical activities and initiate lipid peroxidation (Abdellatif and Gargoum, 2014). West et al. (2000) reported that lipid peroxidation by malondialdehyde (MDA) is elevated in patients with type I and II diabetes. In fact, when saturated fatty acid chains are attacked by hydroxyl radicals, MDA is produced (Francés et al., 2010). According to some studies, pathophysiology of diabetes induced by STZ and production of oxidative stress which leads to systemic apoptosis in liver perform through the activity of P53/ERK or P53 intermediate signaling molecules (Francés et al., 2010).

Various studies on diabetes suggest that induction of diabetes by injection of STZ significantly increases serum levels of glucose, cholesterol, triglycerides, renal biomarkers (urea, uric acid and creatinine) and liver enzymes (AST, ALT and ALP) in diabetic mice relative to the normal group (Eidi et al., 2006). Also, it has been shown that the levels of LDL and VLDL in diabetic rats were significantly increased, while the level of HDL was significantly declined relative to the normal group (Kasiappan et al., 2006).

Diabetes is found with an increase in the synthesis of cholesterol resulting from an increase in the activity of HMGCOA Reductase (Kasiappan et al., 2006). Elevation of cholesterol in hyperlipidemic patients is probably due to an increase in cholesterol biosynthesis or a reduction in its clearance from blood (Kaviramasam et al., 2005). Similarly, an increase in the concentration of triglycerides is also seen in diabetic patients (Kasiappan et al., 2006). In these patients, a decrease in plasma lipoprotein lipase enzyme activity, a certain increase in the levels of triglycerides and VLDL are observed, and diabetes treatment by insulin decreases plasma triglyceride concentration through bringing lipoprotein lipase to the normal level (Kasiappan et al., 2006).

Over 50% of ethanolic *Alhagi maurorum* extract contains flavonoids, which is daily prescribed against aspirin at the concentration of about 100 mg/kg (Suthar et al., 2016). Studies demonstrate that the *Alhagi maurorum* extract interferes in liver enzymes, oxidation, tumors and hyperlipidemia (Suthar et al., 2016). Administration of aqueous or alcoholic extract of *Alhagi maurorum* to diabetic rats subjected to STZ showed that the ratio of LDL/HDL was improved, and the levels of TG, TC, and VLDL were declined (Sheweita et al., 2016). This improvement may be the result of lupeol, one of the components of *Alhagi maurorum* extract that plays an important role in normalization of lipid profile (Sheweita et al., 2016).

It has been shown that 4 week administration of *Alhagi* ethanolic extract induces an increase in the body weight (about 20%) and a reduction in the blood glucose level (about 52.5%) compared to the diabetic mice (Salama, 2016); the levels of total cholesterol, triglycerides, LDL are increased significantly, while HDL level in diabetic rats is reduced about 11.83 percent compared to the normal rats (Salama, 2016). Although *Alhagi* ethanolic extract decreases the levels of total cholesterol, triglycerides and LDL about 22.6%, serum concentration of HDL is increased (Salama, 2016). In addition, *Alhagi maurorum* extract reduces blood glucose level, elevates anti-

oxidancehepatic enzymes activities, inhibits free radicals, and reduces lipid malfunction and TD levels in diabetic rats (Sheweita et al., 2016). Moreover, 100 mg/kg *Alhagi maurorum* extract can reveal hepatic enzymes protection, the nature of MDA and GSH oxidation as well as the ratio of lipids (Al-Snafi, 2015). Sheweita et al. (2016) reported that *Alhagi maurorum* extract improves glucose level, lipid profiles and lipid functions in the diabetic rats (Peluso et al., 2016).

Conclusion

The present study was an attempt to show that oral administration of *Alhagi maurorum* alcoholic extract to the rat models with lipid malfunction can lead to desirable and beneficial changes. With more research to confirm our results, *Alhagi maurorum* extract diet supplementation in patients with lipid malfunction is recommended.

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