

LAMIUM ALBUM OR URTICA DIOICA? WHICH IS MORE EFFECTIVE IN DECREASING SERUM GLUCOSE, LIPID AND HEPATIC ENZYMES IN STREPTOZOTOCIN INDUCED DIABETIC RATS: A COMPARATIVE STUDY

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Abstract

Objectives: Diabetes mellitus, the most common endocrine disorder, is defined by hyperglycaemia. *Urtica dioica* or stinging nettle is known to have antidiabetic effects. *Lamium album* or non stinging nettle is shown to have some beneficial effects such as antioxidant, and cytoprotective properties. The purpose of this study was to compare the effects of hydroalcoholic extract of *L. album* and *U. dioica* on serum glucose, lipids and hepatic enzymes level in streptozotocin induced diabetic rats.

Methods: Thirty-two male Wistar rats were randomly assigned into four groups; normal control, diabetic control, diabetic treated with *U. dioica* (100 mg/kg/daily), diabetic treated with *L. album* (100 mg/kg/daily) for 28 days. Serum glucose, cholesterol, triglyceride (TG), alanin transaminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST) were measured.

Results: *U. dioica* and *L. album* extracts caused significant decrease ($p < 0.05$) in serum glucose level in diabetic rats. Compared to diabetic control, both extracts significantly decreased serum cholesterol, ALT, AST and ALP ($p < 0.05$). The level of serum TG in diabetic rats treated with *U. dioica* was significantly lower than that of animals treated with *L. album* ($p < 0.05$).

Conclusion: it seems that administration of *U. dioica* and *L. album* extracts in diabetic rats may have similar lowering effects on the level of serum glucose, cholesterol and hepatic enzymes, albeit *U. dioica* might be more effective in improving serum TG as compared with *L. album*.

Key words: Diabetes, Glucose, *Lamium album*, Lipids, Rats, *Urtica dioica*

Introduction

Diabetes mellitus, the most common endocrine disorder worldwide, is defined by hyperglycemia, which is associated with insulin deficiency, insulin resistance, or both. The effects of diabetes mellitus contain impaired metabolism of carbohydrate, lipid and protein, as well as damage of different organs (Giacco and Brownlee, 2010; Robertson, 2004).

The precise reason of diabetes mellitus has not been elucidated and a likely chain of events involved in it includes oxidative stress, genetic susceptibility, viral infection, autoimmunity and inflammatory reactions (Van Belle et al., 2011). The number of diabetic patients is growing as a result of ageing, population increase, industrialization, increasing prevalence of obesity and reduced physical activity (Wing et al., 2001). It has been estimated that the number of diabetic patients would increase worldwide around 300 million by the year 2025 (King et al., 1998). Despite extensive researches on this condition, new approaches on early diagnosis, treatment of diabetes or prevention of diabetes complications are still highly needed to enhance public health and reduce health care costs and mortality. Streptozotocin (STZ) is extensively used to induce diabetes mellitus in experimental models such as rat. STZ- induced diabetic rats represent a diabetic condition very similar to type I diabetes (Lenzen, 2008).

In addition to hyperglycemia, impaired metabolism of lipid (dyslipidaemia) is also a general characteristic of diabetes such as increased level of serum triglyceride (TG) and low-density lipoprotein (LDL) and decreased level of high-density lipoprotein (HDL) (Feingold et al., 1992; Ghorbani, 2013). It is indicated that the hyperglycemia or dyslipidaemia simply cause oxidative stress resulting in cellular damage of different organs such as liver, kidney and pancreas (Kroger et al., 2011; Poitout and Robertson, 2002; Robertson, 2004). It has been shown that the level of serum hepatic enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) is increased in diabetic rats, indicating the enhanced release from damaged hepatocytes due to diabetes- induced oxidative stress (Maritim et al., 2003; Shafiee-Nick et al., 2012).

In the recent years, in an attempt to find safer and more effective antidiabetic drugs, much attention has been focused on the identification and use of natural plant extracts as substitutes for the synthetic compounds. Some herbs have beneficial effects in the treatment of diabetes complications (Abedinzade et al., 2013; Adaramoye et al., 2012).

Urtica dioica, as a medicinal plant, is known to have beneficial effects against hyperlipidemia, hypertension, hyperglycemia (Farzami et al., 2003; Ziyat et al., 1997). Additionally, the antioxidant activity of *U. dioica* has been suggested (Gulcin et al., 2004).

Lamium album is also called white dead nettle; because of the lack of stinging hairs, which are normally found in stinging nettles (Lamium, 2006; Pashazadeh and Rezaei, 2013), it is a member of the genus of Lamiaceae and grows widely in European, African, and Asian countries (such as Iran). It has been reported that *L. album* possesses a variety of activities such as antiproliferative, anti-inflammatory, antioxidant, and free radical scavenging effects (Matkowski and Piotrowska, 2006). In addition, the role of *L. album* in improving the fat metabolism has been suggested (Ninomiya et al., 2006).

The present study aimed at comparing the effects of *L. album* and *U. dioica* on serum glucose, lipids and hepatic enzymes level in streptozotocin-induced diabetic rats.

Materials and Methods

Animals

Adult male Wistar rats with 250-300 g body weight were used in this experimental study. The rats were housed in a controlled room

(22-26 °C) with free access to their relevant diet and water. The research was conducted in accordance with the internationally accepted principles for laboratory animal use and cares as found in the US guidelines (NIH publication #85-23, revised in 1985). The study was approved by the ethical committee at Guilan University of medical sciences.

Induction of experimental diabetes

After overnight fasting, diabetes was induced by single dose injection of STZ (which was purchased from Sigma — Aldrich Diagnostic Ltd , PubChem CID: 29327), 60 mg/kg body weight freshly prepared in 0.1M Citrate buffer, pH =4.5 intraperitoneally (i.p.). On the 3th day after STZ injection, fasting blood glucose was measured by glucometer and diabetic rats were verified by blood glucose >300 mg/dL.

Experimental design

A total of thirty two rats were included in the present study. The rats randomly were assigned into four groups (eight in each group) as follows: normal rats ; receiving daily (i.p.) saline, diabetic rats; receiving (i.p.) daily saline, diabetic rats treated daily with 100 mg/kg (i.p.) of hydroalcoholic extract of *U. dioica*, diabetic rats treated daily with 100 mg/kg (i.p.) of hydroalcoholic extract of *L. album* . Treatment was begun after 3 days of diabetes induction and all four groups of rats were kept for 28 days on their respective exposures. On the 14th day, fasting blood glucose was measured. After 28 days, fasting whole blood samples were taken from vein of the tail. The serum samples were separated immediately and to determination the level of glucose, ALT, AST, ALP, total cholesterol, TG, LDL and HDL (by enzymatic methods using "Pars Azemoon" commercial kits ; manufactured in Tehran, Iran under the license of German Herb company).

Plant material and extraction

Plant material

Aerial parts of *U. dioica* and *L. album* were collected from suburbs of Rasht during spring season and confirmed by Dr Ghasemnezhad, Department of Horticulture, Faculty of agriculture, Guilan University. The voucher specimen 105183 was deposited in the Herbarium of the Department of Botany, Faculty of Agriculture, Guilan University. Preparation of the extracts was performed as previously described by Ahangarpour et al. (2012). In brief, the aerial parts of the both nettles were dried in the shade. Polyphenolic phase was extracted using solvent system (methanol, acetone, H₂O; 3.5/3.5/3 containing formic acid%1) for 30 minutes on shaker at room temperature; this process was repeated three times. Eventually the polyphenolic phase was obtained by removal of ethyl acetate over vacuum at low temperature.

Statistical Analysis

Values are presented as mean ±SEM. Values were compared between groups using one way ANOVA followed by student T-test. P<0.05 was regarded as statistically significant. Analysis was performed using SPSS software version 16.

Results

Effect of *L. album* and *U. dioica* on serum glucose

The serum glucose in diabetic rats was significantly higher than normal rats on the 0th, 14th and 28th days (p<0.05) (Table1). *U. dioica* and *L. album* caused significant decrease (p<0.05) in serum glucose on the 14th and 28th days in diabetic rats (table1). The level of serum glucose did not differ remarkably between two groups of diabetic rats exposed to *U. dioica* and *L. album* extracts.

Table 1: Effect of Lamium album and *Urtica dioica* on serum glucose in normal and streptozotocin-induced diabetic rats.

Groups	Serum glucose (mg/dl)		
	0th day	14th day	28th day
Normal	131± 6	96± 4.3	120± 7
Diabetic control	428± 11 ^a	439± 5.2 ^a	392± 8.6 ^a
Diabetic+ <i>Urtica</i>	405± 10 ^{a,b}	226± 6.6 ^{a,b}	206± 4.8 ^{a,b}
Diabetic+Lamium	408± 9 ^{a,b}	199± 3.1 ^{a,b}	191± 3.9 ^{a,b}

Each value is mean± S.E.M. for eight rats in each group.

^a p < 0.05 by comparison with normal rats.

^b p < 0.05 by comparison with diabetic rats.

Effect of Lamium album and *Urtica dioica* on serum lipids

The level of serum cholesterol remarkably increased on the 28th day in diabetic rats as compared to normal rats (p<0.05). However, both plant extracts caused remarkably decrease in serum cholesterol level on the 28th day of treatment in comparison to diabetic rats (p<0.05). There was no significant difference in the serum cholesterol level between diabetic rats treated with *U. dioica* and *L. album* extracts (Table 2) The serum LDL and LDL/HDL ratio significantly increased while serum HDL significantly decreased on the 28th day in diabetic rats relative to normal rats (p<0.05) (Table2). Compared to diabetic rats, both plant extracts significantly decreased serum LDL and LDL/HDL ratio while remarkably increased serum HDL (p<0.05). No significant difference was observed in the serum LDL, HDL and LDL/HDL ratio between diabetic rats treated with *U. dioica* and *L. album* (Table 2).

The serum TG significantly increased on the 28th days in diabetic rats relative to normal rats ($p < 0.05$) (Table 2). However, only *U. dioica* extract showed remarkably decrease in the level of serum TG when compared to diabetic rats ($p < 0.05$). The serum TG in the diabetic rats treated with *U. dioica* was significantly lower than diabetic rats treated with *L. album* extract ($p < 0.05$) (Table 2)

Table 2: Effect of *Lamium album* and *Urtica dioica* on serum cholesterol, LDL, HDL, LDL/HDL ratio and triglyceride in normal and streptozotocin-induced diabetic rats .

Groups	Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	LDL/HDL ratio	Triglyceride(mg/dl)
Normal	40±7	29.28± 5.04	41.14± 1.92	0.71	45±4
Diabetic control	80±6 ^a	118± 7.95 ^a	23.85± 2.64 ^a	5.13	77±7 ^a
Diabetic+ Urtica	52±8 ^{a,b}	54.4± 6.18 ^{a,b}	36.14± 1.81 ^{a,b}	1.5	52±6 ^{a,b}
Diabetic+Lam	56±6 ^{a,b}	66.28± 6.18 ^{a,b}	28.57± 1.81 ^{a,b}	2.35	60±8 ^a

Each value is mean± SD for eight rats in each group.

^a $p < 0.05$ by comparison with normal rats.

^b $p < 0.05$ by comparison with diabetic rats.

LDL: low-density lipoprotein

HDL: high-density lipoprotein

Effect of *L. album* and *U. dioica* on serum hepatic enzymes

There was a significant increase in the levels of serum AST, ALT and ALP on the 28th day in diabetic rats as compared to normal rats ($p < 0.05$) (Figure 1). Both plant extracts caused significantly decrease in the levels of serum AST, ALT and ALP on the 28th day of treatments of diabetic rats when compared to diabetic rats ($p < 0.05$) (Figure 1). There were no significant differences in the levels of serum AST, ALT and ALP between diabetic rats treated with *U. dioica* and *L. album* extracts (Figure 1).

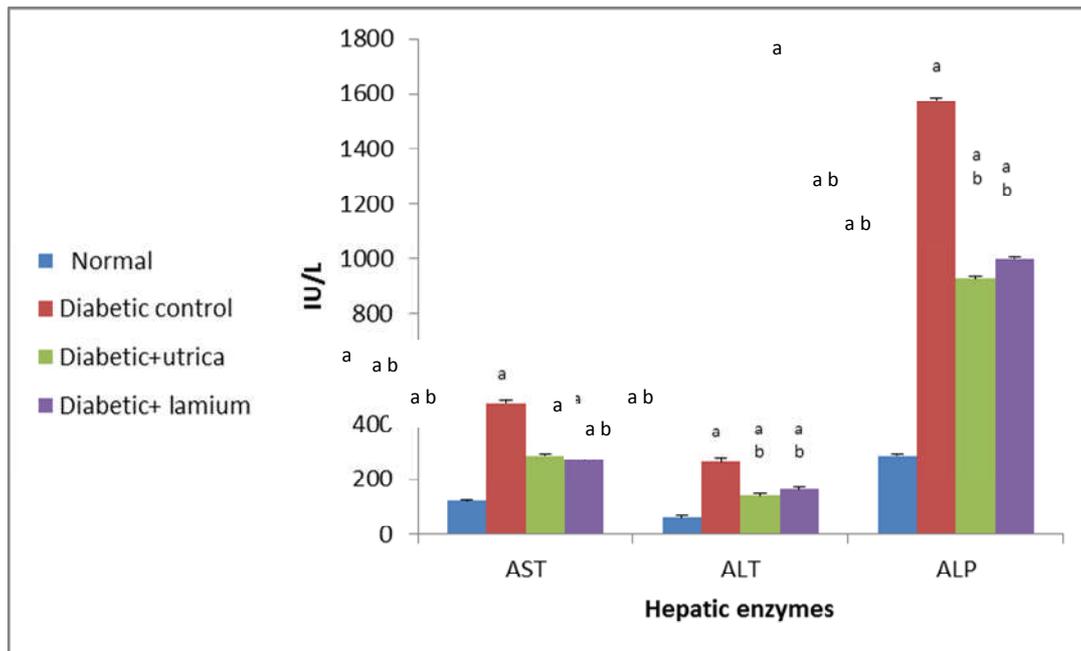


Figure 1: Effects of *Lamium album* and *Urtica dioica* on serum AST, ALT and ALP in normal and diabetic rats.

AST: aspartate transaminase, ALT: alanin trasaminase, ALP: alkaline phosphatase

Each value is mean± S.E.M. for eight rats in each group. ^a $p < 0.05$ by comparison with normal rats.

^b $p < 0.05$ by comparison with diabetic rats.

Discussion

For the first time, we reported the effects of *L. album* (non stinging nettle) on serum glucose, lipids and hepatic enzymes. Fasting blood sugar in diabetic rats is regarded as an indicator of diabetes condition. In the present study, the level of serum glucose in diabetic rats was about three times higher than normal rats three days after STZ injection. This finding is similar to Farzami et al. (2003) and Bnouham et al. (2003) study. The present study showed significant decrease in the level of serum glucose when diabetic rats were administered *L. album* (non stinging nettle) and *U. dioica* (stinging nettle) extracts. Although the serum glucose did not differ significantly between diabetic rats treated with *U. dioica* and *L. album* extracts. This finding is in agreement with that of Pashazadeh and Rezae (2013); Ahangarpour et al. (2012) and Bnouham et al. (2010) study where *U. dioica* showed hypoglycemic effect in diabetic rats. These results contrast the study conducted by Ozkol et al. (2013) where no significant hypoglycemic action of *U. dioica* was found. while we didn't examine the molecular mechanisms involved in this effect, it appeared that the hypoglycemic activity exhibited by the extract of *U. dioica* could attributed to the elevation of insulin secretion by pancreas (Farzami et al., 2003; Bnouham et al., 2003), the promotion of glucose uptake by forming individual glucose permeable pores (Domola

et al., 2010), the reduction of insulin resistance (Ahangarpour et al., 2012), the increased activity of Acetyl coenzyme A carboxylase as glucose sensor in support of insulin secretion and Nucleoside diphosphate kinase that involved in energy metabolism of the cells (Qujeq et al., 2011). More investigations indicating the potential molecular mechanisms involved in hypoglycemic action of *L. album* are needed.

In the present study, the level of serum cholesterol increased in diabetic rats. It is likely that STZ causes the increased β -oxidation stem of fatty acid and consequently the increased level of acetyl CoA; alternatively, it enhances the accessible substrate in the biosynthesis of cholesterol (Yakubu and Afolayan, 2009). The present study showed remarkable decrease in the serum cholesterol and LDL while significant increase in the serum HDL when diabetic rats were exposed to *L. album* and *U. dioica* extracts. Albeit the level of serum cholesterol, LDL and HDL did not significantly differ between diabetic rats treated with *U. dioica* and *L. album* extracts. These findings were consistent with those of Ahangarpour A et al. study (2012), who reported the *U. dioica* extract remarkably decreased the level of serum LDL and LDL/HDL ratio. Our results were in accordance with those of Shahraki et al. (2013) who found that the diabetic rats treated with *U. dioica* had a remarkable decrease in the level of serum total cholesterol, LDL compared with those of diabetic rats. Dahr et al. (2006) also showed that the extract of *U. dioica* reduced the level of LDL and cholesterol in hypercholesteromic diet male rats. Cholesterol is an essential structural element of the plasma membrane and of the plasma lipoproteins. In addition, steroid hormones, bile acids, and vitamin D are synthesized from cholesterol (Hanukoglu, 1992). High level of serum cholesterol is associated with the increased risk of atherosclerosis and cardiovascular diseases, mainly due to the oxidation of LDL; the major transporter of cholesterol in blood (Avci et al., 2006). LDL delivers cholesterol to the tissues such as artery walls and therefore drives atherosclerosis. In contrast, HDL takes part in the transport of cholesterol from the tissues to the liver for catabolism- a process that is known as reverse cholesterol transport- thus HDL is known to have anti-atherogenic effects and is inversely associated with the incidence of coronary atherosclerosis (Nofer et al., 2002). The LDL/HDL ratio has been suggested as an important predictor of coronary heart disease risk. Since the role of *U. dioica* and *L. album* in improving the fat metabolism (Ninomiya et al., 2006; Das et al., 2009), it appears that these plants can be useful in preventing diabetic-related problems and improving lipid metabolism in diabetics patients by decreasing serum cholesterol and LDL and LDL/HDL ratio (Cho et al., 2002).

Hypertriglyceridemia is considered as one of the diabetic indicators (Feingold et al., 1992). In the present study, STZ caused the increased level of serum TG. However, treatment with *U. dioica* extract caused remarkably decreases in the serum TG when compared to diabetic rats. The serum level of TG in the diabetic rats treated with *U. dioica* was significantly lower than diabetic rats exposed to *L. album* extract. Our result is in consistent with that of Shahraki et al. (2013) who reported that the treatment with *U. dioica* caused remarkable decreases in the serum TG concentration when compared to diabetic rats. However in contrast to our present study, Ahangarpour et al. (2012) showed significantly increased TG in diabetic rats treated with the *U. dioica*. since the significant decrease in the serum TG by *U. dioica* is suggestive of the antidiabetic effects of this plant extract (Ziyyat et al., 1997); This plant extract seems to be more effective in improving TG and fat metabolism as compared with *L. album*.

Serum hepatic enzymes are considered as an index of liver damage (Jung et al., 2006). In the present study, in agreement with the previous studies (Jung et al., 2006; Maritim et al., 2003), the level of serum AST, ALT and ALP increased in diabetic rats. On the other hand, treatment of the diabetic rats with *L. album* and *U. dioica* extracts showed significant decreases in the level of these enzymes in serum as compared to the diabetic rats. The level of serum hepatic enzymes did not significantly differ between diabetic rats treated with *U. dioica* and *L. album* extracts. This finding is in agreement with that of Kanter et al. (2005) study where *U. dioica* significantly decreased the level of hepatic enzymes in carbon tetrachloride-treated rats. This result contrasts a study conducted by Ahangarpour et al. (2012) where *U. dioica* with no change of serum ALP, remarkably increased the level of serum ALT. The beneficial effects of *U. dioica* and *L. album* on serum hepatic enzymes could be in part due to the antioxidant and cytoprotective properties of them (Gulcin et al., 2004; Kanter et al., 2005; Matkowski and Piotrowska, 2006; Pereira et al., 2013), although we didn't evaluate this complicated process and needs to be further investigated.

Conclusion

The present study has revealed that administration of *U. dioica* and *L. album* extracts in diabetic rats may have similar lowering effects on the level of serum glucose, cholesterol and hepatic enzymes, albeit *U. dioica* might be more effective in improving serum TG as compared with *L. album*. More research exploring the molecular mechanisms of *L. album* effects on diabetes would be welcomed.

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