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The Extract of *Lamium album* and *Urtica dioica* Increase Serum Insulin-Like Growth Factor 1 Level in Streptozotocin-Induced Diabetic Rats

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Abstract

Background: Diabetes mellitus is defined by hyperglycemia. Antidiabetic effects of *Urtica dioica* have been shown. *Lamium album* or nonstinging nettle is known to have useful impacts such as antioxidant and cytoprotective properties.
Objectives: The aim of the present study was to evaluate the serum concentration of insulin-like growth factor 1 (IGF-1) in diabetic rats given *U. dioica* and *L. album* extracts to distinguish any relationship between IGF-1 level and these plant extracts administration.
Methods: In this experimental study, 32 male rats divided into four groups; normal, diabetic, diabetic treated with *U. dioica* (100 mg/kg/daily), diabetic treated with *L. album* (100 mg/kg/daily) for 28 days. Fasting blood sugar (FBS) and IGF-1 concentrations were measured. One way ANOVA followed by the Tukey post hoc test was used for comparison between groups. In each group, FBS level among different times was compared using repeated measure ANOVA. Analysis was done using SPSS software version 22.
Results: FBS level significantly increased in diabetic rats compared with control rats ($P < 0.0001$) but *L. album* and *U. dioica* decreased this level ($P < 0.0001$). Serum IGF-1 in diabetic rats was significantly lower than normal control rats ($P < 0.0001$), however both *L. album* and *U. dioica* caused significant increase in serum IGF-1 in diabetic rats ($P < 0.0001$ and $P = 0.03$ respectively)
Conclusions: *L. album* and *U. dioica* might increase the level of serum IGF-1 in diabetes; with regard to insulin like activity of IGF-1, this might be viewed as a further support of positive influence of these plant extracts on this disease.

Keywords: Diabetes, *Lamium album*, Insulin-Like Growth Factor 1, *Urtica dioica*

1. Background

Diabetes mellitus, the most common endocrine condition worldwide, is defined by hyperglycemia resulting from insulin deficit, insulin resistance, or both. The effects of diabetes mellitus include impaired metabolism of carbohydrate, lipid and protein affecting many organs such as liver, brain [1, 2].

The number of diabetic patients is increasing as a result of aging, population growth, industrialization, increasing rate of obesity and reduced physical activity [2-4]. In an estimation made by the world health organization (WHO), the total number of diabetes patients would be increased to about 370 million by the year 2030. Diabetes imposes a significant and growing burden on the Iranian people, and the healthcare system [5, 6]. Despite extensive studies on this disease, new approaches associated with effective therapeutic interventions with low side effect and costs would be welcomed [5, 7].

It has been reported that insulin directly increases liver synthesis of IGF-1 [8, 9]. IGF-1 could increase absorption of glucose and fatty acids into the peripheral tissues [10, 11]. It is suggested that the decrease in IGF-1 might play an important role in diabetes [10, 12].

Some studies have shown the useful effects of medicinal plants in improving diseases such as diabetes, menopause and many others [7, 12, 13].

U. dioica is known to have useful anti diabetic, antihypertensive [14], antioxidant [15] and anti-inflammatory [16, 17] effects. Another little known herb, *L. album* (also called white dead nettle or non-stinging nettle) is a member of Lamiaceae species and grows widely in European, African, and Asian countries such as Iran [18]. Antiproliferative, anti-inflammatory [19] antioxidant and free radical scavenging effects of *L. album* have been proposed

[19, 20].

Since the much lower cost and minimal side effects of medicinal plants and in order to evaluate other potential important effects of *U. dioica* and *L. album*, our objective was to determine the serum concentration of IGF-1 in diabetic rats given *U. dioica* and *L. album* extracts to see if there is any relationship between IGF-1 level and these plant extracts administration.

We hypothesized that IGF-1 improvement in this study could be viewed as a further support of positive influence of these plant extracts on diabetes.

2. Methods

2.1. Animals

32 male Wistar rats with 250 - 300 g body weight and on average 8 weeks of age were used in this experimental study. Animals obtained from breeding and maintaining laboratory animal center of Guilan University of Medical Sciences. They were housed in the animal room under controlled lighting (12 hours light: 12 hours darkness) and temperature (22 - 26°C) conditions and had free access to a pelleted food and tap water.

This 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 present study was approved by the ethical committee at Guilan University of Medical Sciences (Rasht, Iran) (No: 5930069503).

2.2. Induction of Experimental Diabetes

After overnight fasting, diabetes induced by intraperitoneal (IP) injection of 60 mg/kg Streptozotocin (STZ) (Sigma-Aldrich Diagnostic Ltd, USA); freshly prepared in 0.1M citrate buffer pH = 4.5. On the 3th day after STZ injection, Fasting blood sugar (FBS) was calculated by glucometer (Accu chek, Roche, Germany) and diabetic rats were verified by FBS $\geq$ 300 mg/dL [7, 21].

2.3. Experimental Design

The rats were randomly allocated into four groups including eight rats in each group as follows; normal treated with daily citrate buffer, diabetic treated with daily citrate buffer , diabetic treated with *U. dioica* (100 mg/kg/daily), diabetic treated with *L. album* (100 mg/kg/daily) [7]. All injections were performed as IP.

Treatment was started three days after diabetes induction and all rats were administered IP to the related treatments for 28 days. On the 14th and 28th day, FBS was measured by glucometer. After 28 days, fasting blood samples were obtained from the vein of the tail using anticoagulant free tubes. Then serum of blood samples was separated using centrifuge at 800 $\times$ g for 5 minutes. The resulting sera were stored at -20°C until IGF-1 measurement. Serum IGF-I level was measured using ELISA kit (Hangzhou Eastbiopharm Co., China) and ELISA reader (Stat Fax, USA) in a single run.

2.4. Plant Material and Extraction

Aerial portions of *U. dioica* and *L. album* were obtained around the Rasht city (Guilan province) and the species were identified by the herbarium unit at school of agriculture (Guilan university, voucher specimen: 105183). Preparation of the extracts was performed as previously described [7]. Polyphenols were extracted from the powdered plants (200 g) according to the modified methods of Zhang et al. [22] and Zheng et al. [23].

2.5. Statistical Analysis

Data are presented as mean $\pm$ SEM or SD as appropriate. Data distribution was evaluated by Shapiro-Wilk test. Data were normally distributed and the groups had equal variances. One way ANOVA followed by the Tukey post hoc test was used for comparison between groups. In each group, FBS level among different times was compared using repeated measure ANOVA. $P < 0.05$ was regarded as statistically significant. Analysis was done using SPSS software version 22.

3. Results

3.1. Evaluation of FBS in Different Experimental Groups

FBS level significantly increased in diabetic rats relative to control rats ($P < 0.0001$). However, Hydroalcoholic extract of *U. dioica* and *L. album* caused remarkably decrease in FBS level in diabetic rats ($P < 0.0001$) (Table 1). In *U. dioica* and *L. album* groups, FBS level was significantly lower in the day 14 and the day 28 as compared with the day 0. ($P < 0.0001$) (Table 1). Also, In *U. dioica* and *L. album* groups, FBS level was significantly lower in the day 28 as compared with the day 14 ($P = 0.0003$ and $P = 0.04$ respectively) (Table 1).

3.2. Evaluation of Serum IGF-1 Level in Different Experimental Groups

Serum IGF-1 level in diabetic rats was significantly lower than normal control rats ($P < 0.0001$). Both *L. album* and *U. dioica* significantly increased serum IGF-1 level in diabetic rats ($P < 0.0001$ and $P = 0.03$ respectively) (Table 2).

Table 1. Effects of *Urtica dioica* and *Lamium album* on Fasting Blood Glucose Level in Different Experimental Groups

Group	Blood Glucose Level[a] (mg/dL)		
	day 0	day 14	day 28
Control	112 ± 9	89 ± 6	106 ± 7
Diabetic	530 ± 12[b]	515 ± 7[b]	499 ± 11[b]
U. dioica	390 ± 15[b,c]	255 ± 8[b,c,d]	211 ± 4.5[b,c,d,e]
L. album	422 ± 13[b,c]	220 ± 7.5[b,c,d]	200 ± 5[b,c,d,f]

[a]Values are presented as mean ± SEM.
[b]P < 0.0001 by comparison with control rats.
[c]P < 0.0001 by comparison with diabetic rats.
[d]P < 0.0001 by comparison with the day 0.
[e]P < 0.01 by comparison with the day 14.
[f]P < 0.05 by comparison with the day 14.

Table 2. Effect of *Urtica dioica* and *Lamium album* on Serum IGF-I Level in Experimental Groups at the End of Study

Group	IGF-I Concentration[a] (ng/mL)
Control	2863.6 ± 279
Diabetic	1027 ± 476[b]
Urtica	1555 ± 378[b,c]
Lamium	2211 ± 200[b,d]

[a]Values are presented as mean ± SD.
[b]P < 0.0001 by comparison with control group.
[c]P < 0.05 by comparison with diabetic group.
[d]P < 0.0001 by comparison with diabetic group.

4. Discussion

The present study was conducted to find out the effects of *U. dioica* and *L. album* on serum IGF-1 and FBS levels in STZ-induced diabetic rats.

The current study illustrated that serum IGF-1 level was reduced in diabetic rats. The relationship between serum IGF-1 and diabetes mellitus is still controversial [24-29]. In the studies conducted by Kim et al., Bereket et al., and Dunger et al. [8, 24, 25], low serum IGF-1 level in diabetes was observed. In these studies, subjects were children and adolescent with diabetes type 1, therefore it seems that low serum IGF-1 could be explained by intra portal hypoinsulinaemia [12, 24]. Our result was similar to above mentioned studies; it is mentionable that streptozotocin induces diabetes type 1 in rats [30]. In contrast, Kim et al. [31] and Rajpathak et al. [28] showed that serum IGF-1 was increased in diabetic patients. In these reports, diabetic patients were type 2 and as we know, diabetes type 2 usually is described by hyperinsulinemia. Since insulin directly increases hepatic production of IGF-1 [8, 9], elevated concentration of total or free IGF-1 might be relatively attributed to hyperinsulinemia [12].

The liver is the main source for IGF-1 production. Hepatic glucose metabolism is changed by diabetes and IGF-1 could improve glucose homeostasis [12, 28]. Some studies have shown that IGF-1 not only triggers glucose uptake in peripheral tissues, but also suppresses hepatic glucose production [12, 32, 33]. In addition, decrease in IGF-1 concentration in diabetes mellitus might affect lipid metabolism [12]. As mentioned previously, insulin can increase IGF-1 level [8, 9], so reduction in insulin concentration in diabetes mellitus may cause decrease in IGF-1 level [16, 19, 20, 28].

In the present study, *U. dioica* and *L. album* extracts increased serum IGF-1 level. Also, similar to the other studies, hypoglycemic effect of both plant extracts was seen. The beneficial outcome of *U. dioica* and *L. album* on serum IGF-1 and FBS might be in part due to increase in insulin secretion [14] and decrease in insulin resistance [34]. Although as one limitation, we didn't examine serum insulin level.

4.1. Conclusion

L. album and *U. dioica* could increase the level of serum IGF-1 in diabetes; with regard to insulin like activity of IGF-1, this might be viewed as a further support of positive influence of these plant extracts on this disease. More research discovering the molecular mechanisms involved in *L. album* special effects on diabetes is needed.

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Footnotes

Authors' Contribution: Korosh Khanaki and Mahmood Abedinzade designed the study, wrote the protocol, performed the interpretation of data; Mahmood Abedinzade wrote the first draft of the manuscript; Moslem Mohammadi read the first draft of the manuscript and wrote some valuable comments; Korosh Khanaki performed critical revision of the manuscript and managed the literature searches; Korosh Khanaki and Mahmood Abedinzade performed analysis and administrative, technical and material support; all authors read and approved the final manuscript.

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