

## Effect of *Urtica dioica* L Extract on Quantitative Morphometric Alterations of Liver Parenchymal Cells in STZ Diabetic Rats

### Efecto del Extracto de *Urtica dioica* sobre Alteraciones Morfométricas Cuantitativas de las Células del Parénquima Hepático en Ratas STZ Diabéticas

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**SUMMARY:** Diabetes is associated with several structural and functional liver abnormalities that affect glycogen and lipid metabolism. In this study, an attempt was made to evaluate the effects of hydroalcoholic extract of *Urtica dioica* leaves on Quantitative morphometric changes in parenchymal cells of the livers in STZ diabetic rats. Thirty male Wistar rats were allocated in 3 groups: normal, diabetic and treatment. Hyperglycemia was induced by 80 mg/kg Streptozotocin intraperitoneally. One week after the injection of STZ, the third group received the hydroalcoholic extract of *Urtica dioica* at 100 mg/kg/day over four weeks. After five weeks, the animals were sacrificed and whole livers were removed. Liver specimens were used for quantitative morphometric analyze after hematoxylin and eosin staining. All data are shown as means plus standard errors of means and were analyzed using One-Way ANOVA test at  $P < 0.05$ . The mean area of hepatocytes, nuclei and nucleolus had a decrease in periportal zone and an increase in perivenous zone in the diabetic and treatment groups. The increase of hepatocyte area in perivenous zone and reduce of nucleus area in periportal zone was significant in the diabetic group in comparison with control group ( $P < 0.05$ ), but were not significant between treatment and diabetic group. This study showed that administration of 100 mg/kg/day of *Urtica dioica* leaves extracts after induction of diabetes can cause a little modulating in the main morphometric indices of liver such as area of hepatocytes, nuclei and nucleolus in periportal and perivenous zones.

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**KEY WORDS:** Diabetes; *Urtica dioica*; Liver; Hepatocyte; Morphometry.

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## INTRODUCTION

Diabetes is a chronic disease with a relatively high prevalence in many populations across the world (Jerrold, 2000). Diabetes is associated with several structural and functional liver abnormalities that affect glycogen and lipid metabolism (Sanchez *et al.*, 2000; Koyuturk *et al.*, 2005; Bolkent *et al.*, 2004). The liver plays a central and crucial role in the regulation of carbohydrate metabolism. Thus it uses glucose as a fuel and also has the ability to store it as glycogen, and it synthesizes this from noncarbohydrate precursors (gluconeogenesis) (Levinthal & Tavill, 1999).

Despite the availability of many synthetic drugs a large number of diabetic patients seek herbal medication to

relieve the symptoms of the disease (Bennett & Brown, 2000; Ryan *et al.*, 2001).

*Urtica dioica* L. (*U. dioica*) is a plant belong to the plant family Urticaceae. This herb is widely used in folk medicine for improving certain diseases such as diabetes (Kavalali *et al.*, 2003; Roman Ramos *et al.*, 1992; Petlevski *et al.*, 2003; Farzami *et al.*, 2003), rheumatoid arthritis, hypertension and allergic rhinitis (Mittman, 1990; Sezik *et al.*, 1997; Riehemann *et al.*, 1999).

The inhibitory, antioxidative, antidiabetic and antitoxic effects of *U. dioica* on the liver in diabetes have

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been investigated (Petlevski *et al.*; Daher *et al.*, 2006; Onal *et al.*, 2005; Kanter *et al.*, 2005; Ozen & Korkmaz, 2003, Lebedev *et al.*, 2001).

However, quantitative morphometric studies on parenchymal cells of the liver due to *U. dioica* in diabetes have received less attention. Therefore, in the present study an attempt was made to evaluate the effects of hydroalcoholic extracts of *Urtica dioica* leaves on quantitative morphometric changes in parenchymal cells of the liver in Streptozotocin-induced diabetic rats.

## MATERIAL AND METHOD

**Experimental design.** Leaves of *Urtica dioica* L. (Urticaceae) were collected from cultivated plants, in the suburb of Gorgan, northern Iran (Golestan province, Iran) in 2006 and taxonomically identified at the Department of Pharmacognosy, Mazandaran University of Medical Sciences. A voucher specimen (5-77-1) deposited in the herbarium of Mazandaran University.

Powder of *U. dioica* leaves was percolated by hydroalcoholic (60°) solvent for 48 hours. The extract was filtered and concentrated under vacuum at 40°C to make a jellied material. In addition to thin layer chromatography and purity tests (foreign matter, total ash, acid-insoluble ash, and water insoluble ash) for qualitative analysis, monosaccharide-linked spectrophotometric assay were carried out to determine the concentration of polysaccharides in *U. dioica* leaves for standardization of the extract. The results of phytochemical analysis revealed the presence of high percentages of tannins and steroids and low percentage of flavonoids, carotenoids and saponins in the leaves of *U. dioica*.

Thirty male 8-10 postnatal Wistar rats with a weight of 125-175 gram were used for this study. Ethical approval and animal care were in accordance with the principles of the regulations in use at the Gorgan University of Medical Sciences. The rats were housed in groups of three in standard animal cages and kept under standard laboratory conditions at the facilities of the Gorgan University of Medical Sciences.

The animals had free access to pelleted rat chow and tap water. In the experiments, ten rats were allocated to each group according to the following schema:

Group I. Control rats. Intraperitoneal Saline (IP) for four weeks.  
Group II. Diabetic rats. 80 mg/kg STZ IP in one dose and saline IP for four weeks.  
Group III. Treatment group: 80 mg/kg STZ IP and 100 mg/kg *U. dioica* over four weeks.

Hyperglycemia was induced by intraperitoneal injection of Streptozotocin, purchased from Sigma (St. Louis, Mo., USA), at a dose of 80 mg/kg-body weight, dissolved in distilled water just before use, to overnight fasted rats. In the third group, after one week, the diabetic rats (blood glucose range of above 250 mg/dl) were administered at 100 mg/kg-body weight (Kavalali *et al.*) with a hydroalcoholic extract of *U. dioica* leaves daily over four weeks.

All animals were deeply anesthetized with ether five weeks after the beginning of the experiment. Then, the livers were removed and fixed in natural buffered formaldehyde fixative. Sections of hepatic tissue were obtained from the left lateral and right posterior lobes and sliced at 5-mm thickness and embedded in paraffin wax after overnight machine processing for histological examination. Hematoxylin-and-eosin-stained sections (Bancroft & Gamble, 1990) at 5- $\mu$ m thickness at 30- $\mu$ m distance were used for morphological and morphometric analyze.

**Morphometric measurements.** Hepatocyte area measurements were performed using an Olympus BX-51T-32E01 research microscope connected to a DP12 Camera with 3.34-million pixel resolution and Olysia Bio software (from: Olympus Optical Co. LTD, Tokyo-Japan) in zone 1: liver cells near the portal area (Z1: periportal), and zone 3: hepatocytes in the centrilobular regions of the hepatic lobule (Z3: perivenous).

For each hepatocyte, the total cellular area, nuclear area, and nucleolar area were measured. The outline of each hepatocyte was measured after taking an image with a 40X objective. A separate measurement for nuclei and nucleoli was performed, using the same methodology with a 100X oil objective. At least 50 hepatocytes from each zone (total 100) were measured in each liver. For each chosen hepatocyte some parameters such as hepatocyte area and perimeter, nucleus area and perimeter, nucleolus areas, long and short axes of nucleus were measured with Olysia Bio software and then other parameters obtained from these data with SPSS software. The following variables were used Zaitoun *et al.*, 2006; Silva *et al.*, 2006):

Area: the total area of hepatocytes, nuclei and nucleoli in mononuclear cells.

Perimeter: perimeter of whole hepatocytes.

Diameter: diameter of nucleus (mean axis lengths).

Long axis: long axis of the nucleus.

Short axis: short axis of the nucleus.

Hepatocyte area ratio: ratio of mean area of whole hepatocytes to the mean area of their nuclei.

Nuclear area ratio: ratio of the mean area of nuclei to the mean area of their nucleoli.

Cytoplasmic area: hepatocyte area minus the nuclear area

Area difference: nuclear area minus the nucleolar area.

**Statistical analyses.** Results were expressed as mean and standard errors of the means (SE) for ten animals in each group. Statistical analyses were performed with One-Way ANOVA followed by a post hoc test (Bonferroni) using of the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) Version 11.5 software. P values of less than 0.05 were considered to indicate statistical significance.

## RESULTS

The quantitative parameters of hepatocyte area, perimeter, cytoplasmic area, and the Nuclear/cytoplasmic ratio in hepatocytes of zone 1 and zone 3 in the treatment, diabetic and normal groups are given in Table I.

The means  $\pm$  SE of hepatocytes areas in Z1 were 258.81 $\pm$ 4.85, 257.45 $\pm$ 4.08 and 260.82 $\pm$ 4.92  $\mu\text{m}^2$  in the

treatment, diabetic and control groups and in Z3 265.07 $\pm$ 4.70, 277.77 $\pm$ 3.45 and 263.90 $\pm$ 4.80  $\mu\text{m}^2$  in Z3 in the treatment, diabetic and control groups, respectively.

The mean area of hepatocytes, nuclei and nucleolus had shown a decrease in Z1 and an increase in Z3 in the diabetic and treatment groups. The increase of hepatocyte area in Z3 and reduce of nucleus area in Z1 was significant in the diabetic group in comparison with control group (P<0.05), but were not significant between treatment and diabetic group.

Other morphometric findings are shown in Tables I, II and III. The mean of some parameters such as nuclear/cytoplasmic ratio, perimeter and diameter of nuclei, and area difference in diabetic group had shown a significant difference in comparing with control group (P<0.05), although these data were not significant between treatment and diabetic group.

Table I. Quantitative parameters of hepatocyte area, perimeter, cytoplasmic area and nuclear/cytoplasmic ratio in hepatocytes of zone 1 and zone 3 in normal, diabetic and treatment groups (n=10).

Groups	Hepatocyte area $\mu\text{m}^2$		Hepatocyte perimeter		Cytoplasmic area $\mu\text{m}^2$		Nuclear/cytoplasmic ratio	
	Z1	Z3	Z1	Z3	Z1	Z3	Z1	Z3
Control	260.82 $\pm$ 4.92	263.90 $\pm$ 4.80*	67.24 $\pm$ 0.67	68.09 $\pm$ 0.64	212.05 $\pm$ 4.58	216.11 $\pm$ 4.50	0.24 $\pm$ 0.00*	0.23 $\pm$ 0.00
STZ	257.45 $\pm$ 4.08	277.77 $\pm$ 3.45*	65.68 $\pm$ 0.51	69.02 $\pm$ 0.48	212.24 $\pm$ 3.54	228.78 $\pm$ 3.19	0.21 $\pm$ 0.00*	0.21 $\pm$ 0.00
STZ-Urtica	258.81 $\pm$ 4.85	265.07 $\pm$ 4.70	66.64 $\pm$ 0.60	68.07 $\pm$ 0.77	213.07 $\pm$ 4.28	216.31 $\pm$ 4.34	0.22 $\pm$ 0.00*	0.23 $\pm$ 0.00

Results are expressed as Mean $\pm$ SE of the mean (P value< 0.05). \*the treatment and diabetic groups were compared with control group.

Table II. Quantitative parameters of hepatocyte nuclei in zone 1 and zone 3 in the normal, diabetic and treatment groups (n=10).

Groups	Nucleus area ( $\mu\text{m}^2$ )		Nucleus perimeter ( $\mu\text{m}$ )		Diameter of nucleus		Long axis ( $\mu\text{m}$ )		Short axis ( $\mu\text{m}$ )	
	Z1	Z3	Z1	Z3	Z1	Z3	Z1	Z3	Z1	Z3
Control	48.76 $\pm$ 0.8	47.78 $\pm$ 0.	29.50 $\pm$ 0.2	28.89 $\pm$ 0.	7.75 $\pm$ 0.	7.56 $\pm$ 0.	8.15 $\pm$ 0.	7.96 $\pm$ 0.	7.35 $\pm$ 0.0	7.17 $\pm$ 0.0
	1*	80	6*	26	04*	06	05*	07	5	7
STZ	45.21 $\pm$ 0.8	48.99 $\pm$ 0.	27.59 $\pm$ 0.3	28.24 $\pm$ 0.	7.45 $\pm$ 0.	7.47 $\pm$ 0.	7.78 $\pm$ 0.	7.83 $\pm$ 0.	7.13 $\pm$ 0.0	7.12 $\pm$ 0.0
	5*	74	3*	26	06*	06	07*	07	7	6
STZ-Urtica	45.74 $\pm$ 0.9	48.76 $\pm$ 0.	28.56 $\pm$ 0.3	28.34 $\pm$ 0.	7.54 $\pm$ 0.	7.64 $\pm$ 0.	7.90 $\pm$ 0.	7.96 $\pm$ 0.	7.18 $\pm$ 0.0	7.31 $\pm$ 0.0
	6*	84	2	24	07	06	07*	07	7	7

Results are expressed as Mean $\pm$ SE of the mean (P-value< 0.05) \* the treatment and diabetic groups were compared with the control group

Table III. Quantitative parameters of nucleolar areas, area difference (nuclear minus nucleolar areas) and nuclear/ nucleolar ratio from hepatocytes in zone 1 and 3 in normal, diabetic and treatment groups (n=10).

Groups	Nucleolus area ( $\mu\text{m}^2$ )		Area difference ( $\mu\text{m}^2$ )		Nuclear / Nucleolar ratio	
	Z1	Z3	Z1	Z3	Z1	Z3
Control	5.25 $\pm$ 0.12	5.16 $\pm$ 0.13	43.51 $\pm$ 0.77*	42.62 $\pm$ 0.74	9.85 $\pm$ 0.22	9.87 $\pm$ 0.21
STZ	5.21 $\pm$ 0.14	5.32 $\pm$ 0.13	39.99 $\pm$ 0.77*	43.66 $\pm$ 0.69	9.25 $\pm$ 0.20	9.80 $\pm$ 0.22
STZ-Urtica	5.11 $\pm$ 0.15	5.25 $\pm$ 0.13	40.63 $\pm$ 0.86*	44.57 $\pm$ 0.76	9.67 $\pm$ 0.22	10.09 $\pm$ 0.20

Results are expressed as Mean $\pm$ SE of the mean (P-value< 0.05) \* The treatment and diabetic groups were compared with the control group.

## DISCUSSION

In the present study, we assessed the morphometric changes at light microscopy level using quantitative techniques and studied the effect of an *Urtica dioica* extract on the liver of diabetic rats.

This study showed diabetic morphometric parameters in hepatocytes reduce in periportal zone and increased in perivenous zone. According to our findings *Urtica dioica* leaf extracts can cause a little increasing in the main morphometric indices such as area of hepatocytes, nuclei and nucleolus in periportal zone and a little decreasing of those parameters in perivenous zone.

There are no comprehensive studies on the therapeutic effects of *U. dioica*. Also, most research on the liver in diabetes has focused on biochemical, physiological and histopathological changes. Besides, quantitative aspects of liver structure have received less attention.

Gunes *et al.* (1999) reported that *U. dioica* extract had no significant effect on histological changes in the liver of STZ induced diabetic rats. He observed cell infiltration, low-level sinusoidal congestion and hydropic degeneration in the STZ induced diabetic rats as well as *U. dioica* extract treatment group after inducing diabetes. Gunes *et al.* concluded that *U. dioica*, when used as a traditional medicine, has no effect on diabetes. Moreover, it causes some side effects in the liver.

On the other hand, several experimental studies have investigated the role of *U. dioica* in the prevention and therapy of liver disease.

Onal reported that alpha-glucosidase inhibitor activity in *U. dioica* extract was conducted to identify a prophylactic effect for diabetes. The inhibitory effect of this plant's extract and some common antidiabetic drugs against the enzyme source (liver and small intestine) were researched (Onal *et al.*). Also Daher *et al.* has been reported that orally administered *U. dioica* extract, improve the blood lipid profile.

Moreover, some researchers reported that hyperglycemia is responsible for the development of oxidative stress via glucose auto-oxidation and protein glycation which is characterized by increased lipid peroxide production (MDA: malondialdehyde) and or decreased antioxidative defence (Petlevski *et al.*; Ozturk *et al.*, 1996; Singh *et al.*, 2000; Rajasekaran *et al.*, 2005; Rauscher *et al.*, 2000; Levy *et al.*, 1999).

Hyperglycemia may exhibit most of the diabetic complications through a decrease in the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and GST in the liver (Koyuturk *et al.*; Gunes *et al.*; Rajasekaran *et al.*; Rauscher *et al.*) and an increase in the lipid peroxidation and free radicals.

Cooperative defense systems that protect the body from free radicals damage include the antioxidant nutrients and enzymes (Rajasekaran *et al.*). The efficiency of this defense mechanism is altered in diabetes. Therefore, the ineffective scavenging of free radicals may play a crucial role in determining tissue damage (Wohaieb & Godin, 1987) and morphometric and pathologic changes among hepatic cells in diabetic liver.

In conclusion, this study showed that administration of 100 mg/kg/day of *Urtica dioica* leaves extracts after induction of diabetes can cause a little modulating in the main morphometric indices of liver such as area of hepatocytes, nuclei and nucleolus in periportal and perivenous zones.

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**GOLALIPOUR, M. J.; GHAFARI, S. & FARSI, M. M.** Efecto del extracto de *Urtica dioica* sobre alteraciones morfológicas cuantitativas de las células del parénquima hepático en ratas STZ diabéticas. *Int. J. Morphol.*, 27(4):1339-1344, 2009.

**RESUMEN:** La diabetes esta asociada con severas anomalías en la estructura y funcionamiento del hígado que afectan el metabolismo glicogénico y lipídico. En el presente estudio, se evaluó los efectos del extracto hidroalcohólico de *Urtica dioica*, observando los cambios morfológicos cuantitativos en las células del parénquima hepático de ratas diabéticas STZ. Se utilizaron 30 ratas Wistar, machos, conformando 3 grupos: normal, diabéticas y con tratamiento. Se indujo una hiperglicemia inyectando intraperitonealmente con 80 mg/kg de estreptozotocina. Una semana después de la inyección de STZ, el tercer grupo recibió el extracto hidroalcohólico de *Urtica dioica* en dosis de 100mg/kg/día por 4 semanas. Después de 5 semanas, los animales fueron sacrificados y sus hígados removidos. Las muestras de hígado fueron usadas para análisis morfológico cuantitativo y posteriormente teñidos con hematoxilina eosina. Los datos son mostrados como

promedios con sus respectivas desviaciones Standard y fueron analizados con un test de ANOVA con un p menor a 0,05. El área promedio de los hepatocitos, núcleos y nucléolos tuvieron una disminución en la zona periportal y un incremento en la zona perivenosa en los grupos diabético y con tratamiento. El incremento del área del hepatocito en la zona perivenosa y la reducción del área nuclear en la zona periportal fue significativa en el grupo diabético en comparación con el grupo control (p menor que 0,05), pero no fue significativo entre las ratas tratadas y el grupo diabético. Este estudio mostró que la administración de 100 mg/kg/día de extracto de *Urtica dioica* después de la inducción de diabetes puede causar una pequeña modulación en los índices morfométricos principales del hígado, tales como: área de los hepatocitos, núcleos y nucléolos en las zonas periportal y perivascular.

**PALABRAS CLAVE: Diabetes; *Urtica dioica*; Morfometría; Hígado; Hepatocito.**

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