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Effect of *Urtica dioica* L. (Urticaceae) on Testicular Tissue in STZ-induced Diabetic Rats

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Abstract: *Urtica dioica* L. (Stinging nettle) has already been known for a long time as a medicinal plant in the world. This histopathological and morphometrical study was conducted to determine the effects of the hydroalcoholic extract of *Urtica dioica* leaves on testis of streptozotocin-induced diabetic rats. Eighteen male Wistar rats were allocated to equally normal, diabetic and treatment groups. Hyperglycemia was induced by Streptozotocin (80 mg kg^{-1}) in animals of diabetic and treatment groups. One week after STZ injection (80 mg kg^{-1}), the rats of treatment group received the extract of *U. dioica* (100 mg/kg/day) IP for 28 days. After 5 weeks of study, all the rats were sacrificed and testes were removed and fixed in bouin and after tissue processing stained with H and E technique. Tubular cell disintegration, sertoli and spermatogonia cell vacuolization and decrease in sperm concentration in seminiferous tubules were seen in diabetic and treatment groups group in comparison with control. External Seminiferous Tubular Diameter (STD) and Seminiferous Epithelial Height (SEH) significantly reduced ($p<0.05$) in the diabetic rats compared with controls and these parameters in the treatment group were similar to diabetics animals. This study showed that hydroalcoholic extract of *Urtica dioica* leaves, after induction of diabetes; has no treatment effect on seminiferous tubules alterations in streptozotocin-induced diabetic rats.

Key words: *Urtica dioica*, seminiferous tubules, diabetes, morphometry, streptozotocin, testis, rat

INTRODUCTION

Diabetes mellitus is a disease due to abnormality of carbohydrate metabolism and it is mainly linked to low blood insulin level or insensitivity of target organs to insulin (Maiti, 2004).

Histopathological and histomorphometric alterations in seminiferous tubules have reported in streptozotocin-induced diabetic animals (Paz and Homonnai, 1979; Sexton and Jarrow, 1997; Ali *et al*., 1993; Anderson and Thliveris, 1986; Altay *et al*., 2003; Sainio-Pollanen *et al*., 1997; Tarleton *et al*., 1990; Cameron *et al*., 1985).

Furthermore, diabetes increases apoptosis in testicular germ cells either in mice (Sainio-Pollanen *et al*., 1997; Cai *et al*., 2000).

In recent years, there has been renewed interest in plant medicine for the treatment against different diseases (Rao *et al*., 2003; Ladeji *et al*., 2003). Isolated studies screened various plants having "folk medicine reputation" by biochemical test for this antidiabetogenic effect (Vats *et al*., 2002).

Urtica dioica (*U. dioica*), commonly known the stinging nettle, is a plant that grows in plenty in many countries like Iran, Greece and Turkey. It has a long history of use in traditional medicine, as well as being used for food (Bnouham *et al*., 2003). The evidences of its usefulness properties are as an analgesic (Manganelli *et al*., 2005), antihyperglycemic (Farzami *et al*., 2003; Kavalali *et al*., 2003; Petlevski *et al*., 2003; Mehmet *et al*., 2005), antioxidant (Daher *et al*., 2006), antihyperlipidemic (Schottner *et al*., 1997) and antithrombotic agent (Hryb *et al*., 1995).

The treatment effects of *U. dioica* in preventing from complications of diabetes on reproductive male system have not been shown clearly. Therefore, this study was performed to determine the treatment effects of the hydroalcoholic extract of *Urtica dioica* leaves on histopathological and morphometrical alterations of seminiferous tubules in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

This Experimental study was conducted in the Faculty of Medicine, Golestan (Gorgan) University of Medical Science. Approval for this study was acquired

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from the Animal Care and Ethics Committee of the Golestan University of Medical Sciences.

Plant material: *Urtica dioica* L. (Urticaceae) leaves were collected from cultivated plant, from suburb of Gorgan, northern Iran (Golestan, Iran) and taxonomically identified in the Department of Pharmacognosy, Mazandaran University of Medical Sciences. A voucher specimen (5-77-1) was deposited in the herbarium of Mazandaran University.

Preparation of extract of *Urtica dioica*: The dried and powered of *U. dioica* leaves (400 g) were percolated by Ethanol (45%) solvent. In briefly the dried leaf of *U. dioica* (by using hot air 35-40°C) powdered by mechanical milling. Prelinering maceration during 5 h was done and the product percolated and mixing during 48 h. The extract was filtrated (0.8 Micron) and spray dried in a lab plant SD4 spray drier (lab plant ltd, England).

Animals: Eighteen male Wistar rats (body weight 125-175 g) were obtained from Pastor Institute. The rats were housed in groups of three in standard animal cages and kept under standard laboratory conditions in Gorgan University of Medical Sciences. Animals had free access to rat pelleted chow and tap water.

Experimental design: The rats were divided into three groups. Each group was included six animals:

Group 1: Normal control rats: Animals received intraperitoneal (ip) saline
Group 2: STZ-induced diabetic rats: Animals received 80 mg kg^{-1} STZ (ip)
Group 3: Treatment group, one week after intraperitoneal injection of 80 mg kg^{-1} STZ, animals received i.p. injection of 100 mg kg^{-1} (Kavalali *et al*., 2003) *U. dioica* leaves extract for 4-week. The animals were sacrificed at 35th day of experiment

Hyperglycemia (blood glucose range of above 200 mg dL^{-1} (Rasal *et al*., 2006) was induced with single i.p. injection of streptozotocin (STZ) with a single dose of 80 mg kg^{-1} body weight dissolved in distilled water just before overnight fasting.

Glucose concentration in the blood of the tail vein of the rats was measured with an Accu-Check Active blood glucose monitor test strip (Jackson-Guilford *et al*., 2000).

Glucose tolerance test: Intraperitoneal Glucose Tolerance Test (GTT) was performed on 16 h fasted rats using 2 granıs glucose/ kg-body weight. In all groups, blood was collected from the animals by tail snipping at 0, 30, 60 and 120 min after glucose load. Glucose tolerance test was performed at the beginning of study and on 7th and 35th days of experiment in control, diabetic and treatment groups.

Tissue processing: After five weeks from the beginning of the experiment, all animals in three groups were deeply anesthetized with chloroform. After cervical dislocation, the left testis of each experimental rat was extracted and fixed in bouin's fixative. Slices at 4 mm thickness dehydrated with a graded series of ethyl alcohol and embedded in paraffin wax after overnight automatical processing.

Ten sections of each specimen, taken from the left testis, hematoxylin and eosin stained sections (Bancroft and Stevens, 1990) at four μm thickness with 300 μm distance were used for morphometric analyses. The picture of each section was taken by using the Olympus BX-51T-32E01 research microscope connected to DP12 Camera with 3.34 million pixel resolution and Olysia Bio software (from: Olympus Optical Co. LTD., Tokyo-Japan) under magnification of 100 and 400x. Twenty seminiferous tubules in stage VI-X (Hess, 1999) were measured in each section.

Morphometric study: A morphometric study for each chosen seminiferous tubule that included external Seminiferous Tubular Diameter (STD) and Seminiferous Epithelial Height (SEH) were measured by Olysia Bio software.

Statistical analysis: General linear model and repeated measures were used to analyze the data of glucose.

The data are presented as the Mean±SEM. Statistical significance was tested by one-way analysis of variance (ANOVA) by the statistical packages SPSS Version 11.5. A probability value of less than 0.050 ($p<0.050$) was considered statistically significant according to the Tukey Honest Significant Difference (HSD) test.

RESULTS

Blood glucose concentrations and weight: The Mean±SEM of blood glucose concentrations, at the beginning of study were 84.5±1.3, 95.3±4.5 and 87.8±4.6 mg dL^{-1} in control, diabetic and treatment groups, respectively. The range of blood glucose concentration after injection of STZ is depicted in Table 1. The Mean±SEM of blood glucose concentration level in control, diabetic and treatment groups was 88.5±3.3, 475.2±39.6 and 391.8±35.7 mg dL^{-1} in the day 35.

Table 1: Blood glucose level (mg dL^{-1}) of rats in control, diabetic and treated groups in different days

	Blood glucose level (mg dL^{-1})			
Groups (n = 6)	Day 1	Day 7	Day 21	Day 35
Control	84.5±1.3	86.30±1.2	88.17±2	88.5±3.3
Diabetic	95.3±4.5	228.33±4.1	296.50±30.1	475.2±39.6*
Treated	87.8±4.6	381.40±2.5	290.50±20.2	391.8±35.7*

*p-value<0.001 compared to control group. Results are expressed as Mean±SE of the mean

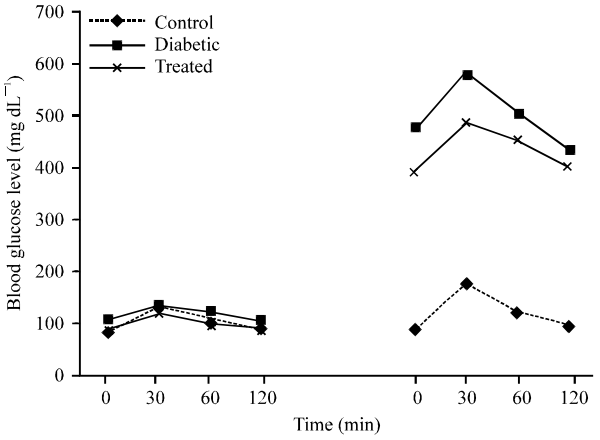

Fig. 1: Glucose Tolerance Test (GTT) of control, diabetic and treated rat groups at the beginning (left) and the 5th week of the study (right)

In control group, the Mean±SEM of blood glucose concentration did not show any changes. Statistically analysis showed that interaction between groups and days was significant ($p<0.001$).

The Glucose Tolerance Tests (GTT) at the beginning and 5th week of the study are shown in Fig. 1.

Body weight had a significant decrease in treated group. Testes weight was 2.05±0.04, 1.71±0.26 and 1.12±0.2 in control, diabetic and treated group that was significant ($p<0.05$) (Table 2).

Histopathological findings: The control group was shown normal spermatogenetic activity, normal seminiferous tubular structure and interstitial cells were normal.

But in STZ-induced diabetic group, disintegration of tubular cells, decrease cellularity, vacuolization of sertoli and spermatogonia cells were seen in most of seminiferous tubules. Also vasodilatation and congestion of capillaries were seen in interstitial tissue. In addition, spermatozoa were rarely seen in tubules in comparison with control group. Histopathological findings of treatment group were similar to diabetic group.

Morphometric results: The morphometric findings have been shown in Fig. 2.

Table 2: Average body weight, testes weight and relative testes weight in control, diabetic and treated rat groups

Variable	Control	Diabetic (STZ)	Treated (STZ-Urtica)
Body weight	228.60±10.5^{a,b}	143.00±10.6^{a}	112.30±10.6^{b}
Testes weight	2.05±0.04^{b}	1.71±0.26^{c}	1.12±0.2^{b,c}
Testes to body weight ratio	0.009±0	0.011±0.001	0.009±0.01
Relative testes weight	0.90±0.04	1.16±0.14	0.98±0.11

^{a}differences between control and diabetic groups, ^{b}differences between control and treated groups, ^{c} differences between diabetic and treated were significant ($p<0.05$, n = 6)

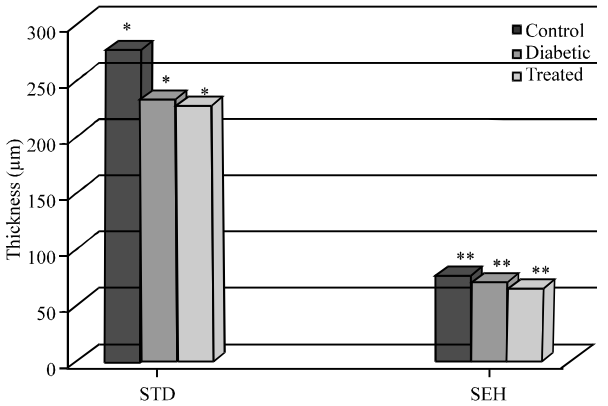

Fig. 2: Mean±SEM of external Seminiferous Tubular Diameter (STD) and Seminiferous Epithelial Height (SEH) in control, diabetic and treated groups (*,**$p<0.05$)

Seminiferous tubular diameter (STD): The Mean±SEM of external diameter of seminiferous tubules was 276.92±1.1, 233.04±1.22 and 227.43±1.60 micrometer in control, diabetic and treated groups, respectively. According to the data, STD in diabetic and treated groups were significantly lower than control group ($p<0.05$).

Seminiferous epithelial height (SEH): The Mean±SEM of seminiferous epithelial height was 76.59±0.54, 70.88±0.49 and 65.52±0.70 micrometer in control, diabetic and treated groups, respectively. SEH was decreased in diabetic animals in comparison with control group. This difference was significant ($p<0.05$). In other hand, SEH decreased in treated group in comparison with diabetic group ($p<0.05$).

DISCUSSION

This study revealed that the induction of diabetes in animals possesses histological alterations in seminiferous tubules, interstitial tissue and morphometrical indices such as STD and SEH changes in STZ-induced diabetic rats. Several studies have reported histopathological and morphometrical alterations in STZ diabetic rats (Paz and Homonnai, 1979;

Sexton and Jarrow, 1997; Ali *et al*., 1993; Altay *et al*., 2003; Sainio-Pollanen *et al*., 1997; Tarleton *et al*., 1990; Cameron *et al*., 1985; Ricci *et al*., 2009; Kianifard *et al*., 2011; Hassan and Moneium, 2001).

Tarleton *et al*. (1990) showed testicular histological changes included disorganization of maturation, malorientation of spermatids and hypospermatogenesis in diabetic animals.

Also, Ricci *et al*. (2009) reported that STZ induced diabetes caused frequent abnormal histology and seminiferous epithelium cytoarchitecture, altered spermatogenesis and a decrease in plasma testosterone levels.

Elsewhere, Kianifard *et al*. (2011) showed a reduction in testicular capsule diameter, seminiferous tubules and germinal epithelium height, increase of amorphous material of interstitial tissue, germ cell depletion, decrease in cellular population and activity and disruption of spermatogenesis in the untreated diabetic rats.

Indeed Anderson and Thliveris (1986) study reported that tubules of diabetic animals showed frequent thinning and permature desquamation of pachytene spermatocytes and early spermatids from the germinal epithelium. Also significantly decreased seminiferous tubule diameter and increased testicular blood vessel numbers were seen (Ali *et al*., 1993).

Altay *et al*. (2003) reported that six weeks after the IP streptozotocin injection with 40 mg/kg for 5 days, both the mean testicular and the seminiferous tubuli diameters were significantly decreased in diabetic rats compared with the control group. Furthermore, Hassan and Moneium (2001) reported that STZ- induced diabetes can cause germ cell depletion of seminiferous epithelium and malorientation of spermatid and thickened tubular walls in the diabetic group, also they showed a 18% reduce in the seminiferous tubular diameter and 28% increase in tubular lumen.

Diabetes appears to mimic the effects of ageing, inducing an increase in OS in the testes in which anti-oxidant enzymes are particularly abundant and relevant for the maintenance of testicular physiology (Mruk *et al*., 2002). The anti-oxidant defence systems in rat Leydig cells decrease with age (Cao *et al*., 2004) and in the total testes the SOD activity is age-dependent (Ricci *et al*., 2009). Other authors have demonstrated that the reactive oxygen species at, or below, physiological concentrations modulate adult rat Leydig cell function through a variety of actions such as decrease in steroidogenic enzyme activity and increase in OS and apoptosis (Gautam *et al*., 2006; Ricci *et al*., 2009).

Also, a study has shown reduce level of testosterone (Ricci *et al*., 2009). The decrease in testosterone levels could be related to the reduced testicular activity against toxic free radicals as indicated by the decreased activity of SOD.

The male germ cells are damaged by the OS (Shrilatha and Muralidhara, 2007), however, the severe tubular damages we found are strongly correlated with the decreased amount of plasma testosterone levels. Therefore, it seems in STZ-induced diabetes the altered spermatogenesis is mainly due to the Leydig cell functional impairment which is show by the decreased plasma testosterone levels and the altered Leydig cell distribution in the testes (Ricci *et al*., 2009).

It is known that testosterone is one of the factors influencing the BTB possibly via the regulation of the levels of tight junction proteins, including occludin (Janecki *et al*., 1992; Chung and Cheng, 2001).

The decrease of morphometric indices such as STD in streptozotocin induced diabetic rats were reported by Altay *et al*. (2003) and other researchers (Anderson and Thliveris, 1986; Oksanen, 1975). In our study, the morphometric indices such as STD and SEH decreased in diabetic rats.

Furthermore, this study revealed that the administration of *Urtica dioica,* after induction of diabetes in animal model, possesses no effect against seminiferous tubules alterations and histomorphometric indices in diabetic rats.

In spite of our findings, some researchers reported that medicinal herbs have beneficial effects on reproduction in experimental diabetic rats (Mallick *et al*., 2007; Sangameswaran and Jayakar, 2008; Feng *et al*., 2001; Golalipour and Khori, 2007; Shalaby and Mouneir, 2010).

Feng *et al*. (2001) reported that *ligustrum* fruit extract protects the damaging effect of experimental diabetes on spermatogenesis. Furthermore, Sangameswaran and Jayakar (2008) have shown that methanolic extract of stem of *A. spinosus* L. has accelerated the process of spermatogenesis by increasing the sperm count and accessory sex organ weights (Sangameswaran and Jayakar, 2008). Also, other report indicated that herbal formulated drug named as MTEC consisting of aqueous-methanol extract of *Musa paradisiaca*, *Tamarindus indica*, *Eugenia jambolana* and *Coccinia indica* has a significant protective effect on testicular dysfunction in STZ induced diabetic rats (Mallick *et al*., 2007).

Indeed, Shalaby and Mouneir (2010) study was reported that, oral administration *Zingiber officinale* extract at 250 and 500 mg kg G1 b.wt. to diabetic male rats for 65 days alleviates the degenerative lesions which seen in the testes of diabetic rats and improve semen quality and quantity; reduce blood glucose level and increase serum insulin and testosterone levels.

In our study we did not observed treatment effects of *Urtica dioica* against seminiferous tubules alterations of diabetic rats. Lack of response to *Urtica* treatment could be due to firstly: low dosages of *Urtica* extract which we used in our study and secondly: high disruption of organ due to experimental diabetes.

The exact mechanism of the effect of herbal medicine including *U. dioica* is not clear. But there are some possible mechanisms as following.

The medicinal herb can cause a significant recovery in fasting blood glucose level and regeneration of beta cells as proposed earlier by our previous study (Golalipour and Khouri, 2007). The other possible mechanism is related to Oxidative Stress (OS). The oxidative stress is widely accepted as playing a key direct role in the pathogenic of various diabetic complications (Shrilatha and Muralidhara, 2007; Baynes and Thorpe, 1999; Aybek *et al*., 2008; Karim *et al*., 2011). A study has shown that diabetes induction is associated with consistent OS in rat testis from first week onwards which progresses with time. It is likely to contribute towards the development of testicular dysfunctions as the oxidative impairments accompanied by compromised antioxidant defences and protein carbonyls in testes (Shrilatha and Muralidhara, 2007). Regarding the several herbal medicine contains phenolic compounds, especially flavonoids which flavonoids generally have antioxidant potential (Hall and Cuppett, 1997).

CONCLUSION

Regarding to our results, we concluded that the administration of the hydroalcoholic extract of *Urtica dioica* leaves, after induction of diabetes, has no possible treatment effect against histomorphometric alterations in seminiferous tubules of streptozotocin-induced diabetic rats which this disability may be due to insufficient dosage of *U. dioica* or short time of treatment program.

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