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The Effects of *Diplotaenia Turcica* Root Extract on Sperm Parameters and Reproductive Hormones in Streptozotocin Induced Diabetic Rats

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Abstract: This study was conducted to determine the effects of *Diplotaenia turcica* root extract on sperm parameters and reproductive hormones in streptozotocin (STZ) induced diabetic rats. The study was performed on a total of 42 male rats divided into 6 groups of equal numbers. Single-dose physiological saline was administrated intraperitoneally to Group 1. STZ 45 mg/kg was administered intraperitoneally to Group 2. *Diplotaenia turcica* root extract 100 mg/kg was administrated through gastric gavage for 28 days to Group 3. *Diplotaenia turcica* root extract 200 mg/kg was administrated through gastric gavage for 28 days to Group 4. STZ 45 mg/kg administrated intraperitoneally to Group 5. In addition, *Diplotaenia turcica* root extract 100 mg/kg was administrated through gastric gavage for 28 days. STZ 45 mg/kg administrated intraperitoneally to Group 6. Also, *Diplotaenia turcica* root extract 200 mg/kg was administrated through gastric gavage for 28 days. Reproductive hormones and sperm parameters were analyzed. In Group 2, it was determined that sperm motility and density and reproductive hormone values were significantly lower when compared to group 1, and the abnormal sperm rate was significantly higher when compared to Group 1. Testosterone levels in Groups 3 and 4 were significantly higher than Groups 2, 5, and 6. It was determined that the 100 mg/kg dose of *Diplotaenia turcica* root extract, which is given also to the diabetic group, creates an improvement in sperm parameters and the hormone testosterone, but the 200 mg/kg dose does not have the same effect. As a result, we can recommend the 100 mg/kg dose of *Diplotaenia turcica* root extract in patients with diabetes.
Keywords: *Diabetes, Diplotaenia turcica root extract, Male rat, Reproductive hormones, Sperm parameters.*

Streptozotosin Kaynaklı Diyabetik Sıçanlarda *Diplotaenia Turcica* Kök Ekstraktının Sperm Parametreleri ve Üreme Hormonları Üzerine Etkileri

Özet: Bu çalışma, Streptozotosin (STZ) kaynaklı diyabetik sıçanlarda *Diplotaenia turcica* kök ekstraktının sperm parametreleri ve üreme hormonları üzerindeki etkilerini belirlemek amacıyla yapıldı. Çalışma eşit sayıda 6 gruba ayrılan toplam 42 erkek rat üzerinde yapıldı. Grup 1'e intraperitoneal olarak tek doz serum fizyolojik uygulandı. Grup 2'ye intraperitonal yolla STZ 45 mg/kg uygulandı. Grup 3'e 100 mg/kg *Diplotaenia turcica* kök ekstraktı 28 gün boyunca gastrik gavajla uygulandı. Grup 4'e 200 mg/kg *Diplotaenia turcica* kök ekstraktı 28 gün boyunca gastrik gavajla uygulandı. STZ 45 mg/kg, Grup 5'e intraperitonal olarak uygulandı. Ek olarak *Diplotaenia turcica* kök ekstraktı 100 mg/kg, 28 gün boyunca gastrik gavaj yoluyla uygulandı. STZ 45 mg/kg, Grup 6'ya intraperitonal olarak uygulandı. Ek olarak *Diplotaenia turcica* kök ekstraktı 200 mg/kg, 28 gün boyunca gastrik gavaj yoluyla uygulandı. Üreme hormonları ve sperm parametreleri analiz edildi. Grup 2'de sperm motilitesi ve yoğunluğu ile üreme hormonu değerlerinin Grup 1'e göre anlamlı derecede düşük olduğu ve anormal sperm oranının Grup 1'e göre anlamlı derecede yüksek olduğu belirlendi. Grup 3 ve 4'ün testosteron düzeyleri, Grup 2, 5 ve 6'ya göre oldukça yüksekti. Diyabetli gruba ilave olarak verilen *Diplotaenia turcica* kök ekstraktının 100 mg/kg'lık dozunun sperm parametrelerinde ve testosteron hormonunda bir iyileştirme oluşturduğu, ancak 200 mg/kg'lık dozunun aynı etkiyi oluşturmadığı tespit edildi. Sonuç olarak, *Diplotaenia turcica* kök ekstraktının 100 mg/kg dozunu, diyabetli hastalarda önerebiliriz.
Anahtar Kelimeler: *Diplotaenia turcica kök ekstraktı, Diyabet, Erkek Sıçan, Sperm Parametreleri, Üreme hormonları.*

Introduction

Since ancient times, people have benefited from wild plants as a source of health and nutrition. Identical plants were named differently across regions, and these local discrepancies can render it difficult to work with these plants. For instance, giant fennel is the general name given to the *Ferula* (Umbelliferae) species mentioned in regions such as Helige, Helis, Helizan, Kerkur, Siyabo, and Siyabu. There exist approximately 20 *Ferula* species in Turkey. The two types, *Ferula orientalis* and *Ferula*

rigidula, are generally called Siyabo, Siyabu, or Çakşır in Van and the surrounding provinces. *Ferula rigidula Diplotaenia cachrydifolia* is a species that grows in eastern Anatolia (Baytop, 1984). Once the plant, known as *Diplotaenia cachrydifolia* and growing in high, humid ground, was examined taxonomically it was understood as *Diplotaenia turcica* (Pimenov et al., 2011).

Diplotaenia turcica grows in the east of Turkey, in Hakkari, Sirnak, Van, and Bitlis, and is widely used in traditional therapy. *Diplotaenia turcica* is a genus belonging to the family Umbelliferae (Apiacea) (Pimenov et al., 2011). In the Van region *Diplotaenia turcica* leaves are add in cheese products and several local dishes for smell and flavor. It was reported *Diplotaenia turcica* is used to protect against poisonous animal bites and is also good for rheumatism, blood sugar, blood pressure, labored breathing, and heart disease (Kaval et al., 2014).

Apart from surgical methods, different chemical agents used in pancreatic damage are used to create experimental diabetes. The most commonly used chemicals to create experimental diabetes today are streptozotocin (STZ) and alloxan (Kurcer et al., 2012; Gushiken et al., 2016). STZ was obtained from streptomyces achromagenes, a fungus species in 1950. It is an antibiotic with neoplastic, antineoplastic and diabetogenic properties (Pari et al., 2017). Due to the presence of glucose in the structure of STZ, the pancreas is taken into beta cells. STZ affects pancreatic beta cell DNA. After this effect, necrosis occurs as cell energy stores are consumed as a result of consumption of nicotinamide adenine dinucleotides and ATP from beta cells. In addition, due to the oxidant properties of STZ, it activates the xanthine oxidase system and increases the formation of hydrogenperoxide and hydroxyl radicals (Pabbidi et al., 2008).

It is known that *Diplotaenia turcica* is used especially by local people in patients with diabetes. People who use it say that it is good for diabetes. However, this situation is based on subjective opinions. It has been reported in previous studies that diabetes causes problems in sperm parameters, especially lowers sperm count and sperm motility, increases anarmol sperm count, and also decreases testosterone hormone, which directly affects sexual power (Artimani et al., 2018; Bal et al., 2011; Nelli et al., 2013; Rashid et al., 2015; Soliman et al., 2018). Problems in sperm parameters can be attributed to the polyunsaturated fatty acids found in the plasma membranes of the sperm because this leaves them vulnerable to reactive oxygen species (Rashid and Sil, 2015). Özdek et al. (2017) determined that the dose of 250 mg / kg *Diplotaenia turcica* root extract significantly reduced glucose levels compared to other treatment groups and the control group. Özdek et al. (2020) reported in another study that *Diplotaenia turcica* root extract significantly reduced pancreatic damage and decreased blood insulin levels in diabetic rats. The situation that lays the ground for conducting this study is to determine whether the above subjective opinion has a scientific basis and to reveal what effects the mentioned plant will have on sperm parameters and reproductive hormones that deteriorate after diabetes.

For this purpose, experimental diabetes was created with streptozotocin in the study., spermatogenic parameters were analyzed. In addition, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone hormone which directly affect spermatogenesis, were evaluated.

Materials and Methods

Plant material and extraction: The *Diplotaenia turcica* plant, which is the primary focus of the present study, was collected from the natural environment between May and June through a taxonomic examination. The removed root was first washed with water, then cut into small pieces and dried in a shaded medium, then pulverized using a grinder. 100 g was taken from the powdered plant root. It was kept in 96% 100 ml ethyl alcohol for 24 hours and then filtered. In the second step, the remaining filtrate was kept in 70% ethyl alcohol for 24 hours and filtered. Then both filtrates were combined and dried at 50 °C and 70 rpm on the evaporator. The remaining part was kept in a 40 °C water bath until it was completely dry (Farkhad et al., 2012).

Chemicals: The streptozotocin (STZ) was purchased from Sigma (Sigma-Aldrich Corp., St. Louis, MO, USA). The LH reagent kit (Ref No: 2P40-35), FSH reagent kit (Ref No: 7K 75-25), testosterone reagent kit (Ref No: 2P 13-23), Architect system concentrated wash buffer, Architect reaction vessels, Architect trigger solution and pre-triyer solution was purchased from the Abbott Laboratories Import Export and Trade Company (Abbott Lab. Distributor, Istanbul, Turkey).

Animals: In the present study 42 Wistar albino male rats (200-250 g in weight and 10-12 weeks old) were used. The animals were obtained from the Medical Faculty Research Laboratory at Van Yuzuncu Yıl University. The rats were kept under standard laboratory conditions during the study period. The rooms were regularly ventilated and the

cages were cleaned daily. Fresh feed and water were provided at all times.

Induction of diabetes in experimental animals: Firstly, the basal glucose levels of the rats were measured with a glucometer. Then, the STZ was dissolved in a cold citrate buffer (0.1 M, pH 4.5) and a single dose of 45 mg/kg was administered intraperitoneally. Diabetic rats having glucose levels >200 mg dL^{-1}, 72 h after administration of STZ were included in the study (Kumar et al., 2016).

Experimental design: Permission was obtained from the Ethics Committee of Yuzuncu Yıl University before initiation of the present study (Authorization number: 2020/01).

The 42 male Wistar albino rats were randomly divided into six experimental groups.

1. Control group (n = 7): a single dose physiological saline was administered intraperitoneally.
2. Diabetes group (n = 7): STZ 45 mg/kg was administered intraperitoneally.
3. *Diplotaenia turcica* root extract (100 mg/kg) group (n = 7): *Diplotaenia turcica* root extract 100 mg/kg was administrated through gastric gavage for 28 days.
4. *Diplotaenia turcica* root extract (200 mg/kg) group (n= 7): *Diplotaenia turcica* root extract 200 mg/kg was administrated through gastric gavage for 28 days.
5. Diabetes + *Diplotaenia turcica* root extract (100 mg/kg) group (n=7): STZ 45 mg/kg was administrated intraperitoneally. In addition, *Diplotaenia turcica* root extract 100 mg/kg was administered through gastric gavage for 28 days.
6. Diabetes + *Diplotaenia turcica* root extract (200 mg/kg) group (n = 7): STZ 45 mg/kg was administrated intraperitoneally. In addition, *Diplotaenia turcica* root extract 200 mg/kg was administered through gastric gavage for 28 days.

At the end of the study the rats were fasted for 12 hours. Later, each rat was anesthetized using intraperitoneally 75 mg/kg ketamine. The intracardiac blood samples were retrieved after the anesthesia had taken effect. The blood samples were centrifuged at 3000 rpm for five minutes to remove the serums. These serums were used in hormonal evaluations. Furthermore, the cauda epididymis of rats was cut to retrieve semen and spermatological examinations were performed.

Measurement of serum testosterone, FSH, and LH levels: Testosterone measurements were performed on the Abbott Architect I4000 SR with the chemiluminescence microparticle immunological method using the appropriate calibrator, control, and kit. The obtained serum testosterone levels were given as nmol/L. Measurements of the serum FSH and LH levels were performed on the Abbott Architect I6200 SR with chemiluminescence microparticle immunological method using the appropriate calibrator, control, and kit. The FSH and LH values were given as mIU/L.

Obtaining semen and evaluation of spermatological features: After anesthesia was administrated to the rats, one of the testicles was removed from the scrotum through an incision. Efforts were made to remove the testicle before the body was cooled. For the motility examination, a microscope with a heating table set at 37 °C was used. In this examination, very dense semen was diluted in physiological saline at 37 °C and care was taken not to waste time in the motility examination. In the motility assessment, three different field evaluations were made under the microscope. Motility score was determined by taking the arithmetic averages of the motility percentages detected in these areas.

In the same cauda, the epididymis was sliced in 2 ml of physiological saline. Sperm density and abnormal sperm ratios were determined using a mixture obtained by slicing the cauda epididymis in 2 ml of physiological saline. To determine the abnormal sperm rate, eosin dye and semen were mixed in equal amounts, and froti was prepared from this mixture and allowed to dry in a short time. In these preparations, 200 sperms were counted, respectively. A thoma slide was used to determine sperm density. After the thoma slide was prepared, approximately 5-10 microliters of sperm suspension was left in both counting chambers. It was waited for 5 minutes for the sperm to collapse. Then 5 large squares were counted in both counting chambers (Aksu et al., 2015; Sonmez et al., 2005; Turk et al., 2008).

Statistical analysis: Descriptive statistics of the groups are given as mean and standard deviation. In reproductive hormones, the significance of the difference between the groups within the same parameter was evaluated with the Kruskal-wallis non-parametric test. Tukey post-hoc test (multiple comparison test) was used to determine which group caused the significant difference ($p < 0.05$). In sperm parameters, differences between groups were determined by post hoc Tukey's HSD test and one - way analysis of variance (ANOVA). All statistical data were evaluated using the SPSS program (SPSS for Windows, version 20.0).

Results

The FSH, LH, and testosterone levels of all groups are presented in detail in Table 1. It was determined the testosterone, LH, and FSH levels of the diabetes group were lower than the control group ($p < 0.012$ and $p < 0.001$). Furthermore, FSH and LH levels of the *Diplotaenia turcica* root extract (100 mg/kg) group did not present significant changes compared to those of the control group ($p > 0.05$). In addition, with the group given 200 mg/kg *Diplotaenia turcica*, the FSH and LH levels of the groups given diabetes + 100 mg / kg *Diplotaenia turcica* and Diabetes + 200 mg/kg *Diplotaenia*

turcica were lower than the control group and were similar to the diabetes group (p> 0.05).

When testosterone values were analyzed in detail, there was a significant decrease especially in diabetes and diabetes + *Diplotaenia turcica* groups (p <0.001). Although the testosterone values of the 100 mg/kg *Diplotaenia turcica* group increased partially compared to the control group, it was not significant (p> 0.05). In addition, the testosterone levels of the Diabetes + *Diplotaenia turcica* (100 and 200 mg/kg) groups were significantly higher than the diabetes group (p <0.001). Testosterone levels of *Diplotaenia turcica* (100 and 200 mg/kg) groups were quite high compared to diabetes and diabetes + *Diplotaenia turcica* groups (p <0.001).

Table 1. Effect of *Diplotaenia turcica* root extract administrate on reproductive hormone values in health and STZ induced diabetic rats.

Groups	FSH (mIU/L)	LH (mIU/L)	Testosterone (nmol/L)
Control	0.41±0.04	0.43±0.03	2.93±0.31
Diabetic	0.33±0.02 *	0.33±0.02*	0.28±0.07*
Diplotaenia turcica root extract 100	0.41±0.04$^{\Phi}$	0.42±0.03$^{\Phi}$	3.13±0.36$^{*,\neq}$
Diplotaenia turcica root extract 200	0.31±0.02*	0.37±0.02 *	2.01±0.15$^{*,\neq}$
Diabetic+ *Diplotaenia turcica* root extract 100	0.32±0.02 *	0.37±0.03*	0.68±0.09$^{*,\#}$
Diabetic+ *Diplotaenia turcica* root extract 200	0.28±0.03 *	0.35±0.02 *	0.61±0.05$^{*,\#}$
P values	**0.001**	**0.012**	**0.001**

***p:** Significant compared to the Control Group (p <0.05). $^{\Phi}$**p:** Significant compared to the Diabetes Group (p <0.05). $^{\neq}$**p:** Significant compared to the Diabetes and Diabetes+ *Diplotaenia turcica* root extract Groups (p<0.05), $^{\#}$**p:** Significant compared to the Diabetes Group (p<0.05). **FSH:** Follicle stimulating hormone, LH: Luteinizing hormone.

The motility, density, and abnormal sperm ratios of all groups are presented in detail in Table 2. The motility and density values of the diabetes group were extremely low compared to the control and *Diplotaenia turcica* root extract groups (p < 0.001). In the *Diplotaenia turcica* root extract (100 mg/kg) group, sperm density and sperm motility were increased compared to the control group, however this increase was not statistically significant (p > 0.05). In the *Diplotaenia turcica* root extract (200 mg/kg) group, sperm density and sperm motility were decreased compared to the control group (p < 0.001). It was determined that *Diplotaenia turcica*, which was added to the diabetes group at a dose of 100 mg/kg, made an improvement in sperm motility and density values towards the control group values. However, it was found that *Diplotaenia turcica* given to the Diabetes group at a dose of 200 mg/kg did not perform the improvement provided by the dose of 100 mg/kg.

Table 2. Effect of *Diplotaenia turcica* root extract administrate on sperm parameters in health and STZ induced diabetic rats.

Groups	Motility Rate (%)	Density (x10^6)	Abnormal Sperm Rate (%)		
			Head	Tail	Total
Control (n=7)	76.42±2.43^{a}	115.14±3.53^{a}	3.28±0.48^{e}	6.42±0.78^{e}	9.42±0.53^{e}
Diabetic (n=7)	27.85±2.67^{e}	45.00±3.31^{e}	16.85±0.37^{a}	22.14±0.69^{a}	39.14±0.89^{a}
Diplotaenia turcica root extract 100 (n=7)	77.14±2.67^{a}	119.28±3.63^{a}	2.85±0.37^{e}	5.42±0.53^{f}	8.14±0.69^{f}
Diplotaenia turcica root extract 200 (n=7)	60.71±1.88^{b}	105.14±3.53^{b}	6.14±0.69^{d}	9.14±0.37^{d}	15.14±0.69^{d}
Diabetic+ *Diplotaenia turcica* root extract 100 (n=7)	48.57±2.43^{c}	85.14±3.62^{c}	9.28±0.48^{c}	12.14±0.37^{c}	21.57±0.53^{c}
Diabetic+ *Diplotaenia turcica* root extract 200 (n=7)	40.71±3.45^{d}	67.71±4.46^{d}	12.57±0.78^{b}	17.14±0.37^{b}	29.28±0.75^{b}
Significance	**(p <0.001)**	**(p <0.001)**	**(p <0.001)**	**(p <0.001)**	**(p <0.001)**

Note: The different subscript letters (a, b, c, d, e) in the same column indicate significant differences between groups (p <0.001).

When the abnormal sperm ratios are analyzed, it was found that the values in the diabetes group were very high compared to the control and other groups. It was determined that 100 mg/kg *Diplotaenia turcica* given in addition to the diabetes group caused a significant decrease in abnormal sperm rates, but the healing effect of *Diplotaenia turcica* given at 200 mg/kg dose was not up to 100 mg/kg (p <0.001).

Discussion and Conclusion

Diabetes causes problems in the male reproductive system by damaging the hypothalamic-pituitary-gonadal axis, disrupting spermatogenesis, creating problems in ejaculation, creating undesirable effects in all of the listed conditions (Sexton ve Jarow, 1997). In addition, diabetes is known to progress with hyperglycemia. Reactive oxygen species, which occur in large amounts in hyperglycemia, cause damage to the mitochondria of germ and leydig cells and cause disruption of spermatogenesis (Li et al., 2013; Long et al., 2015).

Sperm count, motility and morphology are very important markers for testicular functions. Based on the data in Table 1, sperm morphology, epididimal sperm count, and motility are seen to be

adversely affected in diabetic rats compared to the control group, which is in agreement with the results of study showing deterioration in spermatogenesis under hyperglycemia (Artimani et al., 2018; Bal et al., 2011; Nelli et al., 2013; Rashid et al., 2015; Soliman et al., 2018). These negativities detected in sperm parameters can be explained by inhibition of spermatogenesis due to diabetes (Dawson et al., 1992). In this study, *Diplotaenia turcica* (100 mg / kg) supplementation resulted in remarkable recovery in diabetic male rats, epididimal sperm count, sperm motility, and sperm morphology. These findings clearly show us the spermatogenic activity of the extract and support the use of the *Diplotaenia turcica* plant by the local people.

Serum testosterone levels and gonadotropin levels were significantly lower in the diabetic group compared to the control group ($p < 0.012$ and $p < 0.001$, respectively). This outcome was consistent with previous reports on the changes in reproductive hormone parameters in diabetic rats (Ballester et al., 2004; Fedail et al., 2016). Based on the data in Table 1, after a 100 mg/kg dose of *Diplotaenia turcica* root extract the testosterone level increased compared to the control and diabetes groups, however a higher dose decreased the testosterone levels compared to the control group. This could be due to the androgen release activity of a 100 mg/kg *Diplotaenia turcica* root extract dose.

Sexual dysfunction occupies an important place among the complications of diabetes in men (Isidro, 2012). Looking at the testosterone values in Table 1, it is seen that there is a significant decrease ($p <0.001$) in the diabetes group. This may have been due to a decrease in the number or impairment of the Leydig cells, where testosterone is secreted. As a matter of fact, leydig cells both decrease in number due to diabetes and decrease their testosterone synthesis, which is their main function (Ballester et al., 2004). Testosterone is a very important hormone for the structural and functional development of male reproductive organs (O'Hara & Smith, 2015). Our findings related to the decrease of testosterone, which has a very positive effect especially on libido, in diabetic situations are in line with the previous study results (Artimani et al., 2018; Bal et al., 2011; Nelli et al., 2013; Rashid et al., 2015; Soliman al., 2018). As a matter of fact, serum testosterone concentration has been reported to show a negative correlation with blood sugar level (Kim et al., 2014). Testosterone values of the *Diplotaenia turcica* root extract (100 and 200 mg/kg) groups were significantly higher than those of the diabetes and diabetes + *Diplotaenia turcica* root extract groups ($p < 0.001$). This outcome presented parallels with studies indicating an increase in testosterone levels in diabetic groups due to the administration of a number of extracts such as Mucuna pruriens, Cocculus hirsutus, and Kaempferia parviflora, which were acknowledged as antidiabetics (Lert-Amornpat et al., 2017; Patil et al., 2014; Suresh and Prakash, 2012). The results of this study suggest this supplement could provide an androgenic effect, as *Diplotaenia turcica* root extract particularly and significantly increases serum testosterone levels in STZ-induced diabetic rats.The literature review did not indicate a similar study that focuses on the use of *Diplotaenia turcica* root extract in diabetic rats. The present study is the first to indicate the application of *Diplotaenia turcica* root extract with diabetic rats results in significant recovery rates on testicular dysfunction and impaired spermatogenesis. In conclusion, it is possible to assert the *Diplotaenia turcica* root extract is spermatogenic and androgenic in STZ-induced diabetic rats. It is essential that further studies focus on assessing the effects of *Diplotaenia turcica* root extract on reproductive function and other complications related to diabetes and the effects of different doses.

In the literature review, no similar study was found on the use of *Diplotaenia turcica* on sperm parameters and reproductive hormones in diabetic rats. With this study, it was demonstrated that the application of *Diplotaenia turcica* to diabetic rats for the first time restores testicular dysfunction and impaired spermatogenesis. As a result, we can say that the root extract of *Diplotaenia turcica* has spermatogenic and androgenic effects in STZ-induced diabetic rats. It is our recommendation to undertake additional studies to evaluate the effects of the root extract of *Diplotaenia turcica* on the reproductive function and other complications related to diabetes, and to determine what effects different doses will have.

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