**Investigating the Effect of Hydroalcoholic Extract of Sesame and Ziziphora clinopodioides phora Clinopodioides in Treatment of Testicle Damages Resulted from Streptozotocin-Induced Diabetes in Vistar Rats**

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**Abstract**

**Background:** Diabetes plays an important role in creating metabolic damage because of generating oxidative stress and it appears that sesame and ziziphora clinopodioides phora clinopodioides encompass in treatment of diabetes-induced testicular injuries because of their antioxidant properties.

**Materials and Methods:** In this study 48 male vistar rats with weight range of 200 to 220gr were selected and divided into control, diabetic and experimental groups of 1, 2, 3 and 4. Diabetic group that became diabetic by intraperitoneal injection of 55mg/kg, first experimental group (diabetic + 100mg/kg sesame) and second experimental group (diabetic 150 mg/kg), third experimental group (diabetic 100mg/kg) and fourth experimental group (diabetic 150mg/kg) who became diabetic after two months, were administered sesame and ziziphora clinopodioides phora clinopodioides extract for five weeks. At the beginning of fifth week blood sample were taken from subjects and biochemical factors and blood hormones as well as testicle dimensions were evaluated macroscopically and histologically.

**Results:** Reduced amount spermatogonia and sertoli cells, decreased spermatogenesis process, number of sperms and their activity was observed among diabetic groups and sesame has shown better activity in fixing defects compared to ziziphora clinopodioides in experimental groups.

**Conclusion:** Sesame plays a therapeutic role in improving diabetes-induced testicular injuries by the ability to prevent and improve oxidative stresses.

**Keywords:** Diabetes; Sesame; Ziziphora clinopodioides; Sertoli Cells; Testicular Injury.

**Introduction:**

Currently, diabetes is a major factor in disability and hospitalization of patients and imposes significant expenditures to the society in such a way that in India, about 92 million dollars is spent each year for treatment of diabetic patients with erectile dysfunction. Since erectile dysfunction overshadows survival of generations, by alleviating its problems with herbal medicine approved by all parties, is very important [1]. Four to 5 million people in Iran suffer from diabetes [1]. Methods currently used to treat non-insulin dependent diabetes including diet change and oral hypoglycemic factors have their own limitations. Using herbal medicine in treatment of diabetes mellitus is very common in middle Asian countries. The World Health Organization have provided recommendations for these countries about using these herbal medicines [2].

Many plant species are being used in traditional medicine of various nations for their hypoglycemic properties to treat diabetes mellitus [3].

Sesame, a species of gamopetalous dicotyledones, is typically used as a food and in pharmacological industry, it is used as a solvent in intramuscular injection solutions. It is also being used topically on various organs of the body. Sesame oil is also used as antidote to poisons. In addition, it can be used for treatment of burn scar on skin. Continuous consumption of sesame can affect the memory improvement. Studies being conducted suggest that enriched antioxidants and unsaturated fat in sesame oil can assist controlling of hypertension. It is the most popular oil in Asia and is regarded as a major oil product. Because of manual harvesting restrictions, in order to extract oil, today modern methods are used to produce it.

Anti-inflammatory effect of sesame is comparable to anti-inflammatory effect of steroid and non-steroid medicines with phenylbutazone. This medicine manifests its anti-inflammatory effect by inhibiting synthesis of inflammatory prostaglandins. Flavonoid, terpenoid, saponin, alkaloid, tannin, polysaccharide and monosaccharide including arabinose, mannose and glucuronic acid derivatives are identified (12). Cycle of flavonoid compounds is purified from stem extract of this plant. Since flavonoids can reduce level of free radicals in cells as antioxidant, they can be employed to reduce destructive effects of diabetes and increase the activity of pancreatic β-cells.

Ziziphora clinopodioides is a plant, which belongs to Lamiaceae family, ziziphora species the aerial parts of which are used as spice. This plant grows in most areas of Iran and encompasses 9 native subspecies in Iran. Because of having antioxidant properties, it can remove destructive effects of diabetes in the body [4].

All parts of this plant can be used according to traditional medicine. Many herbal species are used for treatment of diabetes mellitus in traditional medicine of various nations for their hypoglycemic properties [5].

In a study under the title of *«The Effect of Hydroalcoholic Extract of Ziziphora Clinopodioides on the Number of Pancreatic Β-Cells in Streptozocin-Induced Type I Diabetic Suri Rats»*, the antioxidant and hypoglycemic role of it are mentioned [6]. Therefore, the aim of this study was to investigate the effect of hydroalcoholic extract of sesame on treatment of testicular injures resulted from stroptozotocin-induced diabetes in rats and to investigate the effect of various dosages of this extract on the level of serum insulin and glucose as well as to investigate the amount of testosterone hormone. It is hoped to observe increased spermatogenesis and testosterone hormone as well as decrease in blood glucose considering antioxidant property of sesame and ziziphora clinopodioides .

**Materials and Methods:**

Sesame and ziziphora clinopodioides were harvested from Abr Village in Shahrood in 2015 and dried in 3oC oven or furnace after being cleaned in the shadow. Then, dried leaves were powered (about 80 grams) and put in soxhlet apparatus for 72 hours along with 400ml ethanol (80%). Then, the extract was filtered and dried using rotary apparatus.

This article is the result of the design of 3465 of Shahid Sadoughi University of Medical Sciences in Yazd.. In this study, 32 male vistar rats with weight range of 200 to 220gr weight were selected and divided into 4 groups of control, diabetic, first experimental and second experimental groups. Control group received intraperitoneal citrate buffer according to their weight along with other groups becoming diabetic to maintain the body balance. Diabetic group that became diabetic by intraperitoneal injection of 55mg/kg streptozotocin (made by Sigma Co. with product code of S0130), first (diabetic+ sesame 100mg/kg ) and second (diabetic 150mg/kg) experimental groups received sesame extract for 5 weeks through gavage after two months of being diabetic. Animals were kept in clean cages with temperature of 22-24oC, light cycle of 12:12 light/dark and relative humidity of 40-60% in laboratory. At the beginning of fifth week, samples were taken directly from the heart after anesthesia (using ketamine and xylazine) and biochemical factors and blood hormones as well as macroscopic observations (including age, diameter, length, and volume of testicles) were evaluated and testicular sections were saved in 10% formalin to conduct histologic experiments and to be transferred to the laboratory.

**Macroscopic Investigation:**

To investigate testicle weight, a scale with an accuracy of 0.001g was used. Length and diameter of testicle was measured by caliper and testicular volume was measured using calibrated cylinder.

**Measuring Diameter of Seminiferous Tubule:**

Diameter of seminiferous tubule was measured using Singh method. Twenty five tubules were randomly selected in each section of testicle and average diameter of tubule was calculated by measuring small and large diameter of each tubule using a calibrated micrometer connected to the eyepiece of microscope.

**Sertoli Cell Count:**

Twenty five tubules were selected in each field and each cross section of testicle and then sertoli cell count was conducted under microscope. Mean of this value was calculated for each group.

**Study of Spermatogenesis:**

After microscopic observations of seminiferous tubule, Table 1 was presented where the number of 2 and 1 spermatocytes, spermatids, the number of luminal sperm bundles, thickness of basement membrane as well as weight, length, diameter and volume of testicles, diameter of seminiferous tubule and average number of sertoli cells were investigated in 25 different tubules.

**Method of Testosterone Analysis:**

Serum testosterone with plasma is measured using Gamma-B testosterone kit. The basis of this kit is RIA method with double antibody. In this kit, respectively specified values of sample, marked testosterone (1251-T) and testosterone anti-serum were added together.

After incubation in normal temperature, the sample is incubated and then centrifuged to separate deposits. The number of occupied locations of anti-serum by marked testosterone is inversely related to the concentration of sample testosterone. Testosterone concentration is specified by counting gamma nodes and comparing results with standard serums.

**Insulin Analysis Method:**

After separating blood serum from blood contents by biochemical kit, blood insulin was investigated.

**Blood Glucose Analysis Method:**

After separating blood serum from blood contents by Pars Azmoon kit, blood glucose was investigated.

**Statistical Analysis:**

Statistical calculations were conducted using SPSS 21 and to compare the mean of groups, one-way ANOVA was employed. In cases where a significant response was observed, Tukey posttest was used to find the place of disputes. P<0.05 was considered statistically significant and values were expressed as mean±SD. (P<0.00\*, P<0.05\*\* and P<0.01\*\*\* were defined) (mean±SD).

**Results:**

Diabetic rats suffered from many diabetes-induced complications including bulimia, polydipsia and diarrhea.

**Tissue structures:** In control group, testicular tissue was covered with albuginée layer and seminiferous tubule cell collections were observed. Tissue structures in diabetics group were destructed and a significant decrease was observed in cell collections and tissue structures in treatment group showed significant improvement by administrating 150mg/kg ziziphora clinopodioides (Table 1). The number of spermatogenic cells decreased significantly in diabetic group compared to control group and the number of spermatogenic cells in 1st and 2nd experimental groups increased significantly compared to diabetic group (Figure 1).

Table 1: Tissue comparison was conducted using one-way ANOVA in different groups.

L: Length (Large Diameter)

B: Breadth (Small Diameter)

Table 1. *A comparison of tissue changes in control, diabetic, 1st and 2nd experimental groups*.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PV | Control | Diabetic | 1st experimental | 2nd experimental | 3rd experimental | 4th experimental |
| spermatogonium | 78.16±6.22 | 58.83±1.6$ | 67.34±4.24$ | 71.24±4.01$ | 65.34±2.24$ | 69.34±4.01$ |
| spermatocyte | 63.33±3.81 | 48.33±3.2$ | 52.83±1.9$ | 57.60±4$ | 54.83±3.9$ | 55.63±4$ |
| spermatid | 125.8±5.1 | 78.33±6.83\* | 96.33±2.92\* | 114.12±3$ | 100.33±3.92\* | 109.83±3$ |
| Sertoli cells | 17.33±2.1 | 5.5±1.25\* | 11±1.87# | 18±1.7$ | 15±1.87# | 17±1.7$ |
| Thickness of basement membrane | 1.58±0.11 | 2.57±0.17\* | 1.3±0.11\* | 2.5±0.1$ | 1.3±0.11\* | 2±0.1$ |
| Seminiferous tubule (diameter) | 267.6±11.21 | 196.3±5.32\* | 236.1±11.64# | 251.93±12.2$ | 236.1±11.64# | 241.93±12.2$ |

An increase in thickness of basement membrane was observed in diabetic group compared to control group. In addition, considering conducted investigations, it was specified that atrophy of seminiferous tubule in diabetic rats was increased significantly but these injuries are reduced by administering sesame. Furthermore, a significant decrease was observed in testicular weight (p<0.01), diameter (p<0.01), length (p<0.01) and volume (p<0.01) in diabetic group compared to control group. A significant increase was also observed in testicular weight (p<0.01), diameter (p<0.01), length (p<0.05) and volume (p<0.01) in first and second experimental groups compared to diabetic groups.

Table 1. Morphologic changes of testicle texture in various groups were investigated using one-way ANOVA that is defined in ranges p<0.001, P<0.05 and p<0.01 (mean±SD).

Table 2. *A comparison of testicular volume, length, diameter and weight between control group and experimental groups*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PV | Control | Diabetic | 1st experimental | 2nd experimental | 3rd experimental | 4th experimental |
| Testicular weight (grams) | 1.52±0.048 | 1.18±0.048$ | 1.38±0.037$ | 2.1±0.051$ | 1.28±0.037$ | 1.4±0.051$ |
| Testicular diameter (mm) | 1.18±0.037 | 0.98±0.073$ | 1±0.057$ | 1.4±0.06$ | 1.02±0.057$ | 1.2±0.06$ |
| Testicular length (mm) | 2.04±0.050 | 1.4±0.07$ | 2±0.04# | 2.91±0.04# | 1.74±0.04# | 1.89±0.04# |
| Testicular volume (mm3) | 2.054±0.15 | 1.046±0.046$ | 1.1±0.014$ | 1.5±0.015$ | 1.2±0.014$ | 1.5±0.015$ |

Table 3. *A comparison of mean±SD of insulin and testosterone and blood glucose among control and experimental groups*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PV | Control | Diabetic | 1st experimental | 2nd experimental | 3rd experimental | 4th experimental |
| Testosterone | 4.1±0.509 | 0.34±0.05$ | 1.42±0.06$ | 2.0±0.02$ | 1.60±0.02$ | 1.70±0.02$ |
| Insulin | 4.66±0.54 | 0.1±0.073$ | 2.66±0.66$ | 3.1±0.36$ | 2.7±0.36$ | 2.8±0.36$ |
| Glucose | 85.42±5.06 | 300.42±9.56$ | 220.36±5.12$ | 190.74±4.98$ | 240.74±4.98$ | 230.74±9$ |



**Figure 1. A, B, C, and D show seminiferous tubules. A-shows seminiferous tubules and sertoli cells in control group; B-shows wrinkling of seminiferous tubules, increased interstitial space and reduction of germ cells and sertoli cells in diabetic group; C, D, E, F- show increase in diameter of seminiferous tubules and increase in sertoli cells as well as significant decrease in interstitial space relative to diabetic group in 1st and second experimental groups.**

**Discussion:**

Results of immunohistochemical tests demonstrated that long-term treatment by hydroalcoholic extract of sesame (80%) for diabetic rats have resulted in improvement of diabetes-induced testicular injuries including macroscopic and microscopic investigations (Tables 1 and 2) compared to diabetic rats + ziziphora clinopodioides.

Complied with current results, Ghaffari et al. in 2000 demonstrated that treatment by hydroalcoholic extract (50%) of sesame reduces serum glucose in rats treated by alloxan [7, 8]. This study reports the effect of anti-hyperglysemic effect of sesame extract which is a Greece medicine used by Greek physicians to treat diabetes [7].

In 2011, Mahdavi et al. reported that intraperitoneal treatment of sesame extract for 4 weeks increases activity of anti-oxidant liver and kidney enzymes in streptozotocin-induced diabetic rats. This extract significantly increases malone dihydrate which is a lipid marker in diabetic rats along with total anti-oxidant capacity in non-concentration-dependent plan [4]. Therefore, as Mahdavi et al. stated, sesame extract has protective role against oxidative injuries in streptozotocin-induced diabetic rats [8].

In 2009, Konyalιoglu et al. demonstrated that treatment with aqua extract of ziziphora clinopodioides for 21 days has dose-dependent anti-hyperglysemic effect in streptozotocin-induced diabetic rats. Their results showed positive effects of ziziphora clinopodioides on rats that suffered from disorders in lipoprotein profile, antioxidant status and glucose tolerance resulted from streptozotocin. Therefore, possibly, aqua extract of ziziphora clinopodioides is useful in controlling diabetes, disorders in lipid profiles and oxidative stress by activating pancreatic anti-oxidant enzymes that complies with results of present study in reducing glucose (Table 3) [6, 9].

In general, results of this study showed that alcoholic extract of sesame treats destructive effects of diabetes better compared to ziziphora clinopodioides. Possibly, sesame is of anti-diabetic performance by activating peroxisome proliferator-activated receptor (PPAR)-γ. The major and effective component of this plant is gallic acid in this part of the plant [3, 10]. Sperm cells of mammals contain a high amount of non-saturated fatty acids, plasmalogens and sphingomyelin that are regarded as important substrates in oxidation [11]. In natural conditions, there are antioxidant mechanisms in reproductive tissues that prevent oxidative injuries in mature gonadal and spermatozoa cells. Antioxidants available in sesame have removed destructive effects of diabetes and tissue and macroscopic improvement of testicle is observed in experimental groups [12].

In general, diabetes results in oxidation of lipids, proteins and DNA by creating free radicals and oxidative stress that consequently produces extensive injuries in testicles. Diabetes mellitus have created testicular tissue changes by producing apoptosis, atrophy of seminiferous tubules, reducing tubules diameter and reducing collections of spermatogenic cells [13, 14]. Therefore, atrophy of seminiferous tubules and decreased number of spermatogenic cells are regarded as morphologic signs of disorder in spermatogenesis and the aim of this study was to reduce diabetes-induced testicular injuries by administering various doses of sesame [15, 16].

In another study, main effects of sesame were pointed out through which significant changes occur in I and II seminiferous tubules and inhibition of spermatogenesis in spermatocyte stages of small tubules in diabetic rats. And in our results decreased diameter of seminiferous tubules and increased diameter of basement membrane in diabetic groups verifies it which complies with results of this study. In addition, in treated diabetic groups it appears that using various following mechanisms, sesame results in increased tubular diameter, decreased basement membrane and improvement in spermatogenic cells. (Table 3) [17].

Diabetes increases oxidative stress and creates activated oxygen that result in cell damage by peroxidation of lipids and oxidative destruction of proteins and DNA [18].

Thickness of basement membrane of seminiferous tubules plays an important role in spermatogenesis [19]. During diabetes, thickness of basement membrane of seminiferous tubules increases and this increase results in decreased spermatogenesis and consequently decreased diameter of seminiferous tubules. On the other hand, there is a positive relation between diameter of tubules and spermatogenesis activity [20].

In this study, the amount of testosterone and insulin hormones was evaluated and a significant increase was observed in testosterone and insulin hormones that may be the result of antioxidant activity of sesame [9].

Considering other studies [7], in this study the hypoglycemic effects were verifies once more.

**Conclusion**:

In general, optical microscopic studies resulted from this project showed that in testicles of diabetic rates, diabetes-induced increase in thickness of basement membrane seminiferous tubules decreases significantly by treatment with sesame for 5 weeks.

In addition, with regard to the results obtained from this study, reduction of sertoli cells results in reduction of spermatogenic (since it is responsible to feed seminiferous cells). Sertoli cells play a vital role in spermatogenesis by providing physical and nutritional support as well as hormone signals required for successful spermatogenesis.

Therefore, as sertoli cells decrease, the number of generative cells decreases significantly. In this study, diabetes has resulted in reduction of sertoli cells and consequently decreased number of generative cells.

In this study, it was specified that in male vistar rats, diabetes results in malfunction of testicles and sesame therapy has improved this function by protecting seminiferous tubules and spermatogenic cells. In general, all diabetes-induced injuries in second experimental group (diabetic+150mg/kg sesame) has been better compared to 1st, 3rd and 4th experimental groups and therefore diabetic males with erectile dysfunction are recommended to take 100mg/kg hydroalcoholic extract of sesame despite antioxidant properties of ziziphora clinopodioides. It is hoped that this study could be a turning point to the treatment of erectile dysfunction in diabetic men.

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