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A STUDY ON THE EFFECTIVENESS OF THE HYDROALCOHOLIC EXTRACT OF *Artemisia herba alba* ON BLOOD GLUCOSE, BODY WEIGHT, TESTIS WEIGHT AND TESTICULAR VOLUME VARIATIONS OF TYPE I DIABETIC RATS USING STREPTOZOTOCIN

PARKAMI MR[1*] , KARGAR JAHROMY H [1] , MAHMOUDI TEIMOURABAD S[2], BATHAEE SA[3], HEIDARY Y[1], GHAEDI SH[1] AND FARZAM M[1]

1: Department of Biology, Azad University, Jahrom Branch, Jahrom, Iran.

2: Department of Histology, International branch, Shiraz University, Shiraz, Iran

3: Institution of Supreme Education and Industry of Maragheh, Iran

***Corresponding author: E Mail: r.parkami@gmail.com; Ph.: 09360410378**

ABSTRACT

Artemisia herba alba has always been given attention in traditional medicine due to its therapeutic properties. It has been used to cure diseases such as diabetes. Diabetes causes dysfunction in spermatogenesis, damages testicular tissue and causes infertility. Studying the therapeutic properties of the hydroalcoholic extract of Artemisia Herba Alba on blood glucose, body weight, testis weight and testicular volume variations of type I diabetic rats using streptozotocin. Forty male Wistar rats with the approximate weight of 180-250 gr were randomly selected. Then they were distributed into 5 groups including a control group and 4 groups of 8 diabetic rats who received 55 mg/kg streptozotocin. Therapeutic groups received 200 and 300 mg/kg and streptozotocin group received water and animal feed using gavage. The level of blood glucose, testis weight and testicular volume were analyzed 56 days after developing diabetes in the groups under treatment. Oral treatment of the extract of Artemisia herba alba (300 mg/kg of body weight) for 56 days, significantly decreased the glucose level and significantly increased body weight and improved testicular volume in the groups under treatment. The results of the present research showed that Artemisia herba alba has a hypoglycemic effect on diabetic animals, reduces the side effects of spermatogenesis caused

by diabetes and is effective in preventing the destruction of testicular tissue in rats. So it should be considered for therapeutic purposes.

Keywords: Artemisia herba alba, Hypoglycemic, Spermatogenesis, Rat

INTRODUCTION

Nowadays people are more often inclined towards traditional medicine and prefer to use plant extracts due to higher expenses and side effects of the new medicine and chemicals and synthetic problems **[1]**. Also nowadays diabetes is one of the most frequent diseases of the body's endocrine system which cause dysfunction in the reproductive system and also infertility **[2]**. Sagebrush and wormwood are the Persian names given to a vast majority of artemisa species growing in Iran. These plants are from compositae family and Radiae subgenus. There are different species with different names, most of which have bitter, aromatic leaves and more or less possess the same medicinal properties **[1, 3]**. This genus has 34 herbaceous species of 1 year and a few years which are distributed across Iran. The species exclusively native to Iran are A . Melanolepis and A. Kermanensis. A. Siberia is one of the most important species in terms of animal feed and is among tolerant plants of deserts and semi-deserts of Iran **[4, 5]**. Artemisia Herba Alba includes 1.2% essence based on the weight of dry basis which includes 39% camphor, limonene and 1, 8-cineol (15%), camphene (6%) and alpha-Pinene 5%. Camphor is one of the main ingredients of Artemisia Herba Alba and is antiseptic. After alpha-Pinene, 1, 8-cineol is the most abundant ingredient in essence which has an extensive use in pharmaceutical preparations. When used topically, it has anesthetic and disinfectant effect and is used for the treatment of inflammatory conditions **[5]**. It is used for worm excretion in different regions. Furthermore, it has antiflatulent, cough and headache relieving, anti-worm, antiseptic and insecticidal effect. Its essence has a mild anti-worm effect. Various tests have identified santonin in it even in small doses. The effect of Artemisia herba alba is on candida albicans **[6]**. Due to calcium channels, the extract of Artemisia herba alba has antispasmodic effects and helps dilate the bronchi **[7]**. After entering the respiratory system, Artemisia herba alba is converted to location by available oxygen and is excreted through the respiratory tract and urinary tract. It also prevents fungal growth and inhibits the growth of the bacteria causing unpleasant perspiration odor **[8]**. Secondary metabolites differ from A. Artemisia herba alba are separated. They

are perhaps the most important sesquiterpene lactones which are present with structural diversity in Artemis genus **[9]**. Other studies and surveys are concentrated on flavonoids and essence **[10]**. Sesquiterpene lactones are among the most remarkable natural products which are found in two Artemicia species. These plants are largely important in medicine and this composition can be found in the aerial parts of Artemisia herba alba.

Streptozotocin is an antibiotic which is used to develop experimental diabetes in rats. Diabetes is one of the most common endocrine disorders which is usually characterized by insulin deficiency, impaired tissue function and reduced tissue sensitivity to insulin and is associated with the disorder in the normal metabolism of carbohydrates, fats and proteins **[11]**.

Recent advances in understanding etiology and pathogenesis have resulted in the revision of diabetes classification. These modifications are indicative of attempts to classify diabetes based on pathogenic processes causing hyperglycemia. The age of the patient, starting age and the type of treatment is not involved in the classification. Although this classification does not have clearly defied boundaries; it is possible that symptoms of a certain type of diabetes are present in the patient, but the diseases be classified in other groups **[12]**. In some cases especially in the non-insulin dependent form, the disease is recognized too late and as a result, patients show signs of insulin-dependent diabetes and the patient cannot be classified in a certain type of diabetes according to the causes, mechanisms and symptoms **[13]**.

There are a lot of medicinal herbs effective in lowering blood glucose but few have been investigated. For example alcoholic extract of cinnamon has anti-diabetic effect in the form of increased tissue sensitivity to glucose mechanism or bitter melon lowers blood glucose levels in diabetic rats **[14]**. Also onion and garlic extract lower blood glucose levels and improve the performance of the reproductive system **[15]**. So we decided to investigate the effect of Artemisia herba alba on diabetes.

MATERIALS AND METHODS

This study is purely empirical and all moral principals take into consideration. Forty male Wistar rats with the approximate age of 10 weeks and approximate weight of 180-200 gr were used in this research. They were kept in the animal house of Azad University of Jahrom for a week to adapt to the environment. Environment temperature was 25±0 ˚C and dark-light period was 12 hours of darkness and 12 hours of light and

the rats were randomly divided into 5 groups with 8 members.

1) Control group
2) Diabetic group: One streptozotocin injection (intraperitoneal method)
3) The diabetic group receiving metformin (APO Canada Inc.) (using gavage method for 56 consecutive days)
4) The diabetic group receiving 200 mg/kg of body weight Artemisia Herba Alba extract (using the garbage method for 56 consecutive days)
5) The diabetic group receiving 300 mg/kg of body weight Artemisia Herba Alba extract (using the garbage method for 56 consecutive days)

The method of diabetes induction in the rats: a single dose of 50 mg/kg streptozotocin (Sigma Inc.) was administered to rats using intraperitoneal method. The solvent of this drug is NaCl 9% and 100 mM sodium citrate and its PH is 4.5. It should be noted that 5 to 7 days are required for the induction of streptozotocin effect. That is why metformin administration started one week after streptozotocin injection.

Method of *Artemisia Herba Alba* Preparation

The stems and leaves of Artemisia Herba Alba are grounded and 100 gr of powdered Artemisia Herba Alba are poured into peculator with 1000 ml 70% ethanol and are kept in it for 72 hours. Then the extraction was performed using the percolation method. In order to dry the extract, the solution is poured into a desiccator so that water, alcohol and other additional substances are evaporated by vacuum pump. In order to prepare an extract with 200 and 300 mg doses the powder is solved in 1 ml of distilled water solvent.

Blood Glucose Measurement Method

The amounts of blood glucose of the rats were measured using glucometer before streptozotocin injection and 7 days after it. It should be noted that the rats didn't receive any food for 12 hours before the blood samples were taken.

Stereological Study and Cavalieri Method

cross over network will be used to calculate the slab level which will be randomly placed on the sample. In this network the surface or area of each point is specified and is obtained by simple counting intersects on the sample surface using a microscope projector. The volume is calculated by the corresponding formula.

The data regarding body weight, they weight of the rats, testis weight, testicular volume, blood glucose level and numbers

obtained by counting the number of seminiferous tubes in different groups and numbers from plasma hormone levels were analyzed separately and compared for each test using SPSS software with two-way ANOVA method and DUNCAN test and t-test. The graphs were plotted based on the information obtained from analyzing the numbers with two-way ANOVA using Excel. The values used are the average ± standard error of the mean (SEM) and the significant level of P is less than % 5.

RESULTS

The results suggest that streptozotocin reduces body weight significantly and other groups experience an insignificant reduction of body weight compared to control group. The results suggest that streptozotocin reduces the weight and volume of left and right testis significantly but metformin 300 significantly increases these parameters. Artemisia Herba Alba 200 has no significant effect on them. The results of blood glucose variation after the test showed a significant increase in all groups.

Table1: Min of Body Weight (Pri Test & Post Test)

Group		Control	Estreptozosin	Metformin	Estreptozosin + Artemisia 200	Estreptozosin + Artemisia 300
Body weight	peri test	± 5/35 244/8	246 ± 5/76	265/5 ± 8/75	258/25 11/84	261 ± 3/32
	post test	± 2/91 322/25	171/4± 15/34*	229/8 ± 8/06	22/4 ± 8/69	228 ± 2/69
FBS	peri test	96 ± 2/35	386 ± 6/76	375 ± 3/75	365 ± 1/84	322/4 ± 8/69
	post test	94 ± 2/91	394 ± 3/34*	195 ± 2/06*	275 ± 3/75*	195 ± 2/06*

Table2: Min of Weight & Voluome (Peri Test & Post Test)

Group	Control	Estreptozosin	Metformin	Estreptozosin + Artemisia 200	Estreptozosin + Artemisia 300
Volume right testis	0/82 ± 0/035	0/52 ± 0/03*	0/97 ± 0/032	0/82 ±0/035	1/05 ± 0/076
Volume Left testis	0/89 ± 0/032	0/050 ± 0/04*	0/96 ± 0/030	0/83 ± 0/031	1/06 ±0/079
Weight right testis	1/43 ± 0/035	1/13 ± 0/076*	1/53 ± 0/075	1/38 ± 0/084	1/607 ±0/032
Weight Left testis	1/45 ± 0/037	1/14 ± 0/071*	1/52 ± 0/071	1/37 ± 0/082	1/609 ±0/029

DISCUSSION AND CONCLUSION

Since the usage of herbal drugs is increasing in the world, the status of herbal medicinal products has been approved in modern medicine. Due to the development of competitive effects with endogenous

estrogens (inside the body), Artemisia Herba Alba keeps adverse reactions resulting from changes in female and male hormone levels balanced before and after puberty by occupying peripheral receptors. Therefore with regard to hormonal changes and partially due to the consumption of estrogenic drugs, controlling the complications and preserving the health are among the priorities of pharmaceutical companies. Recommending auxiliary consumption and providing these herbal estrogens not only preserves health, but also generates income and has a good market.

In this research the effect of Artemisia Herba Alba with the doses of 200 mg and 300 mg on histological and stereological changes of the testis has been studied.

The studied parameters after the administration of the *Artemisia herba alba* extract include: body and testis weight variations, testicular volume variations, blood glucose variations.

The Effect of Streptozotocin on Blood Glucose Level in Male Rats

This substance was extracted from a species of streptomycin in 1956 as antibiotics. It has a broad antimicrobial spectrum and its diabetogenic, analytic and oncogenic effect were determined later.

Considering the results in the table and the comparison chart of body glucose before and after the test, it is concluded that like the studies of Holman *et al*., the blood glucose of rats receiving STZ increases. Also in similar studies the same doses of STZ had a very positive effect for developing diabetes in rats. It also has a direct effect on pancreatic tissue and the destruction of B cells and causes dysfunction in insulin-production **[16]**.

The effects of Artemisia Herba Alba on Blood Glucose

Considering the results, comparison of blood glucose before and after the administration of the extract with different doses shows that the blood glucose of the rats in which diabetes was developed using STZ, significantly decreased after 56 days of administration of Artemisia herba alba abstract. This result suggests that, with regard to the investigated studies, because at the moment one of the available non-insulin pharmaceutical methods for diabetes mellitus is modifying their own diets, herbal medicine can be useful for solving the problems of diabetes in the future **[17]**.

STZ is an anti-cancer agent and an antibiotic and is used for the degeneration and necrosis of pancreatic beta cells to develop diabetes in a variety of animals **[18]**.

There are few researches about the hypolipidemic effect of Chenopodium

leaves **[19]** but it has not been reported to date.

In another study intracellular stores of calcium were investigated for the vasodilating effect of Artemisia Herba Alba which results in a decrease in the blood glucose of diabetes rats and the improvement of their disease. Other similar studies have approved that Artemisia Herba Alba lowers blood glucose and increases gastric acid secretion due to its specific compounds **[20]**. Also phenolic compounds in Artemisia Herba Alba lower blood glucose. They include two types named hispidulin and cirsilined which have a tendency to stick to GABA receptors.

Oral treatment of the aqueous extract of Artemisia Herba Alba significantly lowers serum glucose and blood glucose of rats in which diabetes was developed using streptozotocin compared to healthy rats. Aqueous extract of the aerial parts of Artemisia Herba Alba with the dose of 200-300 mg/kg of body weight ($p< 0.05$) increases the insulin level of the rats in which diabetes is developed significantly. There are few reports available about the hypoglycemic effects of the aerial parts the plans with Artemisia Herba Alba genus **[21]**.

Some reports suggest that extracts of Artemisia Herba Alba genus are useful for curing diabetes. The decoction of Artemisia Herba Alba is used for curing diabetes in Iraq and to date there has been no report of side effects from its use **[22]**.

In other researches about Artemis conducted by a number of researchers in the Netherlands, it was suggested that it lowers blood glucose in diabetic rats **[23]**. Artemisia santonicum is used to cure diabetes in Turkey and its capability to lower blood glucose in diabetic rabbits has been reported **[24]**.

The data of the present research showed that Artemisia herba alba lowers blood glucose and increases the serum level of animals in which diabetes is developed using streptozotocin.

Therefore Artemisia herba alba can be suggested as a blood glucose lowering drug because serum insulin in the rats in which diabetes is developed using streptozotocin increased compared to healthy rats.

It can also be suggested that the hypoglycemic effect of *Artemisia Herba Alba* is due to the existence of flavonoid compounds **[25]**.

Interpretation of testis weight results

With regard to the results, weight variations between the groups receiArtemisiamHerbahAlba alba with 200-300 mg doses and also rats receiving metformin in male rats have no significant

difference with control group but a significant difference was observed between the diabetic group on which no treatment was administered and control group; testis weight decreased. One of the reasons for that is a reduction in testosterone concentration which is involved in divisions of spermatogonia. With the increase in testosterone release, spermatogenesis increases and the increased sperm count increase testis weight. It is reported that by removing pituitary, spermatogenesis effect reduces testis weight considerably **[26]**.

Testosterone is essential for the division and growth of germinal cells **[27]**. In similar researches the diameter of seminiferous tubules was reported to be another parameter determining testis weight.

Interpretation of the Effect of *Artemisia Herba alba* Extracts on Testicular Volume

In the results of statistical analysis of comparison between the average testicular volumes in the groups under treatment after 56 days it was observed that there is a significant difference between the control group and all other groups. A significant increase was observed in the three diabetic groups which received metformin and Artemisia Herba Alba extract with 200 and 300 mg/kg doses for 56 days compared to control group. This increase was observed in the diabetic groups receiving distilled water for 56 days. A significant decrease was observed ($P< 0.05$) and according to the researches the effect of garlic extract on the testicular tissue in diabetic rats due to the antioxidant properties of garlic decreases diabetes and prevents a sharp decrease in the diameter of seminiferous tubule, the number of Sertoli cells and prevents the decrease in diameter, length and volume of testis **[28]**. Also in other researches melatonin was detected as a strong antioxidant for preventing the atrophy of tubule embonpoint ferrous and degeneration of reproductive cells and increasing the wall thickness **[28]** of seminiferous which increases testicular volume. With regard to extensive researches in this field, due to flavonoid properties and particular compositions, the extract of Artemisia Herba Alba decreases diabetes and has an interactive effect on germinal cells in testicular tissue and prevents the destruction of testicular tissue. It increases the amount of hormones in serum level and increases Sertoli-Leydig cells and correspondingly increase spermatogenesis and germinal diameter of epithelium. The extract of Artemisia Herba Alba increases testicular volume in diabetic groups. It was also reported in 2008 that the extract of the ethanol rhizome with the scientific name of

curculigo orenioides increases spermatogenesis in albino rats which increases testicular volume in diabetic rats due to antioxidant and flavonoid properties. These findings are similar to those of other researches **[29]**.

CONCLUSIONS

Artemisia herba alba is a family of composite and includes compounds such as flavonoids, sesquiterpenes and antioxidants with antidiabetic, analgesic and phytoestrogenic properties. Other studies have been conducted about antioxidants to date and their positive effects have been proven; especially because the beneficial effects of Artemisia Herba Alba in reducing diabetes complications in diabetic individuals and physiological changes have been proven **[6, 29]**.

The studies show that the beneficial effects of Artemisia herba alba in diabetic individuals can be in flavonoids andsesquiterpenes extracted from the compounds in Artemisia herba alba **[30]**.

With regard to this issue it can be said that Artemisia Herba Alba can be useful in lowering blood glucose and controlling diabetes and also the effect of diabetes on other tissues and can decrease the complications in spermatogenesis process and male infertility. The information obtained in this research show that the administration of the extract of Artemisia herba alba with 200 and 300 mg/kg doses has a favorable effect on testicular tissues of diabetic rats during 56 days of continuous administration and lowers blood glucose, improves weight variations and testicular volume and body weight in the groups under treatment.

The present studies showed that the extract of Artemisia Herba Alba with higher doses show better results during the test and shows the highest effect on different parameters in the test to a significant level.

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