THE POTENTIAL THERAPEUTIC ROLE OF GINKGO BILOBA EXTRACTS ON THE PROSTATE IN A RAT MODEL OF STREPTOZOTOCIN-INDUCED DIABETES: A HISTOMORPHOMETRIC STUDY

Hala Taha Shalan

Department of Anatomy and Embryology , Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Corresponding author
Hala Taha Shalan
Mobile: +201001970159
E.mail: halashalan1986@yahoo.com
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ABSTRACT:

Background: *Diabetes mellitus (DM) is a worldwide endocrine and metabolic disease. It is increasing rapidly nowadays due to modern lifestyle habits. Herbal extracts have been applied for a long time in the treatment of several illnesses. Ginkgo biloba extract was a popular herbal treatment for neurological diseases like Alzheimer's and dementia.*

Aim of work: *assess the potential therapeutic role of Ginkgo biloba extracts against diabetes caused by streptozotocin on the prostate gland in adult male albino rats.*

Material and methods: *30 adult male albino rats divided into three groups (10 rats each): Group I (control) divided into two subgroups (five rats each). Subgroup I-a: rats did not undergo any experiments, receiving only food and water. Subgroup I-b: rats received single intraperitoneal (IP) injection of 0.2 ml of 0.1 M sodium citrate. Group II (diabetic group): rats received a single IP injection of 60 mg/kg streptozotocin dissolved in sodium citrate buffer just before injection. Group III (ginkgo biloba group): rats received a single IP injection of 60 mg/kg streptozotocin as discussed in group II. One week after induction of diabetes the rats received ginkgo biloba (100 mg/kg/day) dissolved in 0.4 ml distilled water orally by gastric tube for 4 weeks.*

Results: *In the diabetic group, acinar cells lost their normal structural architecture and revealed few luminal epithelial folds with pale luminal secretions. The stroma shows many congested blood vessels with inflammatory cells and some cells were vacuolated. In ginkgo biloba group there was restoration to the structure of gland. The acini showed few epithelial folds. Dark luminal secretions were observed in some acini*

Conclusion: *Ginkgo biloba extract have a promising therapeutic effect against the structural damaging effects of diabetes caused by streptozotocin on the prostate gland in adult male albino rats.*

Keywords: *Diabetes mellitus, Ginkgo biloba, Prostate, Hyperglycemia.*

INTRODUCTION:

Diabetes mellitus (DM) is a global endocrine and metabolic illness. It increased rapidly nowadays due to the modern lifestyle habits[(1).] Hyperglycemia was the main sign of diabetes, as it enhanced oxidative stress in the association of glucose oxidation in the mitochondria, which acted later as one of the important factors causing macrovascular and microvascular complications[(2&3).] Prostatic complications were commonly reported in patients with DM. DM had an adverse effect

on reproductive organs of male. Spermatogenesis, reduced libido, decreased number of sperm and motility, reduction of semen volume, and serum testosterone had been detected in peoples with diabetes and in induction of diabetes in animals[4&5].

Prostatic fluid played an important role in maintenance of sperm quality. Thirty five percent of patients with diabetes suffered from infertility due to reduced quality of sperms. The prostate shared into diabetic male infertility through reduced volume of prostatic secretion or increased viscosity of semen. The increased viscosity led to impaired semen parameters especially sperm motility. There was an association between diabetes and prostate gland pathology. It was attributed to metabolic disturbance or changes in the level of sex hormone in diabetic patients[6&7]. Function and survival of epithelium of prostate gland were dependent on androgens which were affected by DM[8].

Herbal extracts applied for a long time in the treatment of several illnesses. Ginkgo biloba was one of the most common herbals in the medication of neurological disorder such as Alzheimer, dementia, cognitive impairment, memory loss memory loss, cancer, and cardiovascular sicknesses[9].

Ginkgo biloba extracts had free radical and antioxidant effects. It directly attenuated reactive oxygen species and stabilized cell redox state by upregulating the activity of antioxidant enzymes. Ginkgo biloba extract also enhanced the activity of glutathione reductase and gamma glutamyl cysteine synthetase, which were the main enzymes essential for the synthesis and reduction of glutathione[10&11].

AIM OF THE WORK:

Based on the previous data, this work was conducted to assess the potential therapeutic role of Ginkgo biloba extracts against diabetes caused by streptozotocin on the ventral part of prostate gland in adult male albino rats.

MATERIAL AND METHODS:

Chemicals:

- Streptozotocin: a white powder in a glass bottle (1gm) dissolved in sodium citrate and obtained from Sigma Chemical Co. It is used to induce diabetes mellitus.
- Ginkgo Biloba leaf powder extract (EGb) was obtained in the form of gelatin capsules manufactured by EIMC United Pharmaceuticals (for EMA Pharm Pharmaceuticals).

Animals:

Thirty adult male albino rats were used, aged from 6-8 months, and weighing from 200 -250 gm, Ras were obtained and housed at the animal house of the Medical Ain Shams Research Institute (MASRI), Faculty of medicine, Ain-Shams University. They were retained in medium-sized metal cages at room temperature with good ventilation and regular dark/light cycles. Access to food and water was freely allowed. All rats have taken place under the same circumstances all the experiment. The experiment followed the guidelines of Ain Shams University Ethics Committee.

Rats were divided randomly into three groups (10 rats each):

Group I (control group): divided into two groups (five rats each):

Subgroup I-a (negative control): five rats did not undergo any experiments, receiving only food and water.

Subgroup I-b (positive control): five rats received single intraperitoneal (IP) injection of 0.2 ml of 0.1 M sodium citrate buffer.

Group II (diabetic group): received a single IP injection of 60 mg/kg streptozotocin dissolved in sodium citrate buffer just before injection. The blood glucose levels were

measured three days after the streptozotocin injection by a blood glucose meter (Accu-Check Advantage, Roche, Germany). Animals with blood glucose level of (≥250 mg/dl) were considered diabetic[12].

Group III (ginkgo biloba group): received a single IP injection of 60 mg/kg streptozotocin as discussed in group II. One week after diabetes induction the rats received ginkgo biloba (100 mg/kg/day) dissolved in 0.4 ml distilled water orally by gastric tube for 4 weeks [13].

Before start in the experiment blood glucose levels were measured by a blood glucose meter (Accu-Check Advantage, Roche, Germany) to exclude diabetes from the beginning.

At the end of experiment, the animals were sacrificed, and the ventral lobe of prostate was obtained. The samples were taken and divided into two parts.

Preparation of paraffin blocks and staining methods:

Prostatic specimens were fixed in formaldehyde solution 10% neutral buffered for 48 h and then after being washed briefly in water the specimens were dehydrated by using ascending grades of ethyl alcohol (70, 80, 90, 95, and 100%), then the samples were cleared and fixed in paraffin blocks. dissected at 5 μm cut; then the sections were stained with hematoxylin and eosin for general morphological and structural study and Masson's trichrome stain for collagen fibers detection[14&15].

Preparation of epon blocks for semithin sections and staining method:

The obtained tissues were fixed in fresh 3% glutaraldehyde for 4 h. Then 1 mm specimens were cut and washed in 0.15 mol/l phosphate buffer, pH 7.4, for 2 h (two changes), and then postfixed in 1% osmium tetroxide for 1 h. The specimens were dehydrated and embedded in epoxy resin. One-millimeter-thick sections were stained with toluidine blue (1%) for examination by light microscopy [16].

Morphometric analysis:

Morphometric analysis was achieved by using Image-J software on a computer connected to an Olympus microscope connected with a digital camera (BX3M series, Olympus, Tokyo, Japan). Ten randomly chosen non-overlapping fields in ten different sections from ten rats of the same group were examined to measure the mean height of the prostatic epithelium (μm) (on H&E-stained sections X400) and the mean area % of collagen fibers (%) (on Masson's trichrome stained sections). The magnification used was x100 with an objective lens of x10. Pixels were calibrated for actual measurements using a stage micrometer.

Statistical analysis:

Data analysis was performed by PSPP freeware (Version 20, IBM Corp., Armonk, NY, USA). One-way ANOVA and Bonferroni Post Hoc test were used to compare the differences between every two groups. Data were offered as the mean value ± standard deviation (SD). Results were considered highly significant when P-value ≤ 0.001, significant when P-value ≤ 0.05 and nonsignificant, when P-value > 0.05.

RESULTS

General histological picture:

Groups I (control group)

Light microscopic examination of Hx. & E.- stained sections of ventral prostate showed that, no significant differences were detected between the subgroups of group I, therefore the results of two subgroups will be discussed together. The gland was consisted of acini of regular shape and variable sizes. These acini were lined with columnar epithelium and had luminal secretions of variable densities. The acini showed many luminal epithelial folds **(Fig. 1)**. The acinar epithelium consisted of simple columnar epithelium having basophilic cytoplasm and

basally located rounded vesicular nuclei. The lumen showed few acidophilic secretions with regular basement membrane **(Fig. 2).**

Masson's trichrome-stained sections showed scanty collagen fibers in between the stroma of prostatic acini **(Fig. 3)**.

In semithin stained sections, the prostatic acinar epithelium of control rats appeared columnar with rounded vesicular nuclei with prominent nucleoli and regular basement membrane **(Fig. 4).**

Group II (diabetic group):

Light microscopic examination of Hx. & E.-stained sections of the ventral prostate of diabetic rats revealed some acini with few luminal epithelial folds and apparently decreased luminal secretions. **(Fig. 5).** Widening of the stroma with cellular infiltration and dilated congested blood vessels was seen **(Fig. 6).** Some of the epithelial cells showed vacuolation with deeply stained degenerated pyknotic nuclei. The apical cells are destructed **(Fig. 7).**

Masson's trichrome-stained sections showed abundant collagen fibers in between the stroma of prostatic acini **(Fig. 8)**.

Semithin stained sections showed, the acinar cells were detached from irregular basement membrane. The cells of the acini have irregular nuclei **(Fig. 9).**

Group III (ginkgo biloba therapeutic group):

Light microscopic examination of Hx. & E.- stained sections of the ventral prostate, showed that, the gland was formed of acini of regular shapes and variable sizes. The acinar epithelial folds were numerous. Dark luminal secretions were observed in some acini **(Fig. 10).** The epithelial cells were high columnar with basophilic cytoplasm and the nuclei appeared rounded and vesicular. The epithelium was resting on a regular basement membrane **(Fig. 11).**

Masson's trichrome-stained sections showed minimal collagen fibers in between the stroma of prostatic acini **(Fig. 12)**.

Semithin stained sections showed the lining epithelium was intact and formed of columnar cells that had vesicular rounded nuclei with prominent nucleoli **(Fig. 13).**

Morphometric results and statistical analysis:

Morphometric measures for the mean height of the prostatic epithelium (µm) on H&E-stained sections and the mean area % of collagen fibers (%) on Masson's trichrome stained sections were summarized in diagram and Table mentioned below.

The mean height of the prostatic epithelium in the diabetic group (group II) showed a statistically significant decrease as compared to the control, while the diabetic-Gingko biloba group (group III) showed a statistically significant increase as compared to the diabetic group and a non- statistically significant decrease compared to the control. The mean area percentage of collagen fibers content in the diabetic group (group II) showed a significant increase compared to the control group, while the diabetic-gingko biloba group (group III) showed a statistically significant decrease as compared to the diabetic group and a non-significant increase compared to control group.

Groups / Parameters	Group (I) control group	Group (II) diabetic group	Group (III) ginkgo biloba group
Epithelial height (µm)	12.908 ± 0.569	7.143 ± 0.476 *	11.904 ± 0.814
Area percentage of collagen fibers (%)	7.825 ± 0.580	14.986 ± 0.842 *	8.696 ± 0.659

Table: Summarizes the epithelial height, the area percentage of collagen fibers [Mean ± standard deviation] in different rat groups. $P < 0.05$ is significant versus control (Group I) (*)

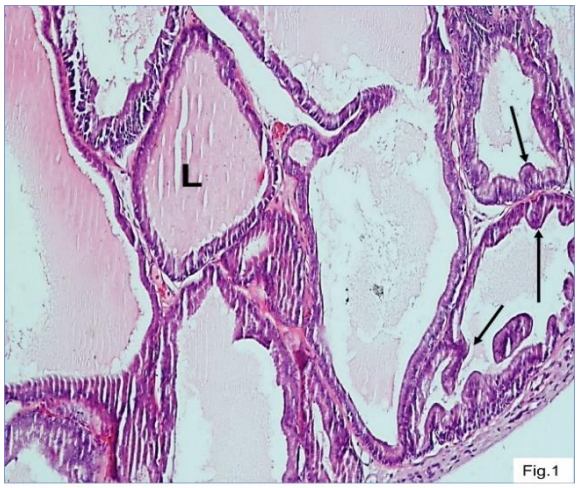

Fig (1): A photomicrograph of a section in the ventral prostate of albino rats control group, showing different sizes acini with luminal secretions (L) of variable densities. The acinar epithelial folds are numerous (arrow).
Hematoxylin and eosin, ×200

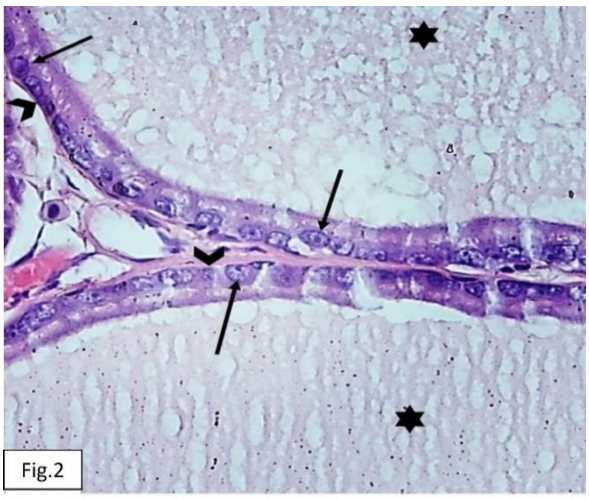

Fig. (2): A photomicrograph of a section in the ventral prostate of albino rats control group, showing parts of the lining epithelium of some acini. It is formed of columnar cells resting on a regular basement membrane (arrowhead); they have basophilic cytoplasm and basally located rounded vesicular nuclei (arrow). The lumina show acidophilic secretions (star).
Hematoxylin and eosin, ×400

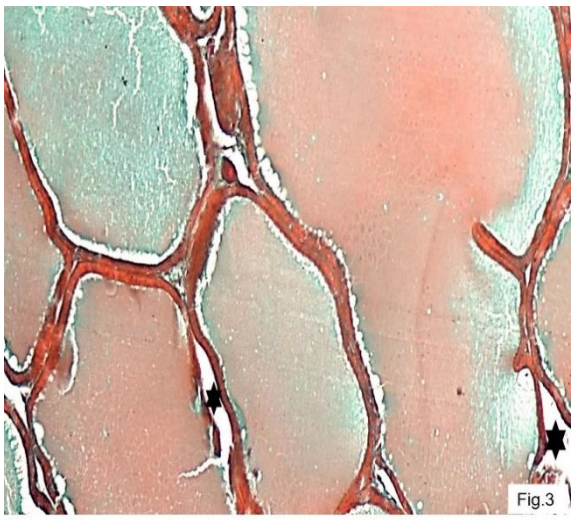

Fig (3): A photomicrograph of a section in the ventral prostate of albino rats control group, showing scanty collagen fibers (star) in the stroma between the prostatic acini.
Masson's trichrome, X400

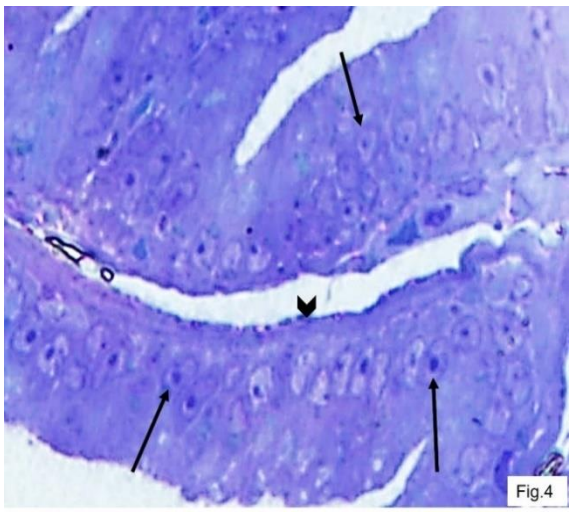

Fig (4): A photomicrograph of a semithin section in the ventral prostate of albino rats control group, showing the lining epithelium of two acini. It is formed of columnar cells; the nuclei were rounded and vesicular with prominent nucleoli (black arrow) with regular basement membrane (arrowhead).
Toluidine blue, ×1000

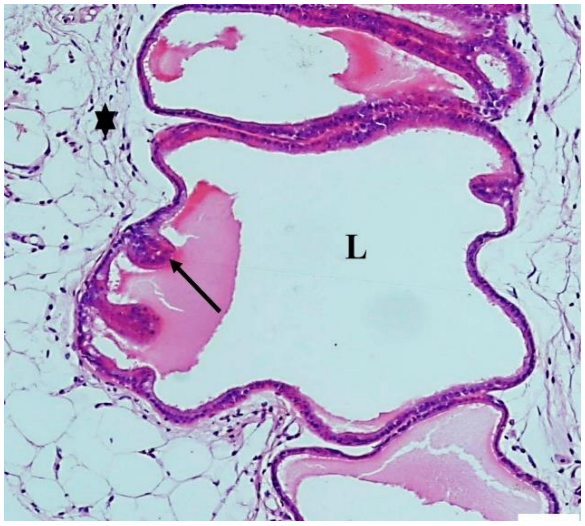

Fig. (5): A photomicrograph of a section in the ventral prostate of albino rats of the diabetic group showing acini of variable sizes and shapes. A few epithelial folds are noticed (arrow) and apparently decreased luminal secretions (L) are seen. The inter acinar area shows many collagen bundles (star).
Hematoxylin and eosin, ×200

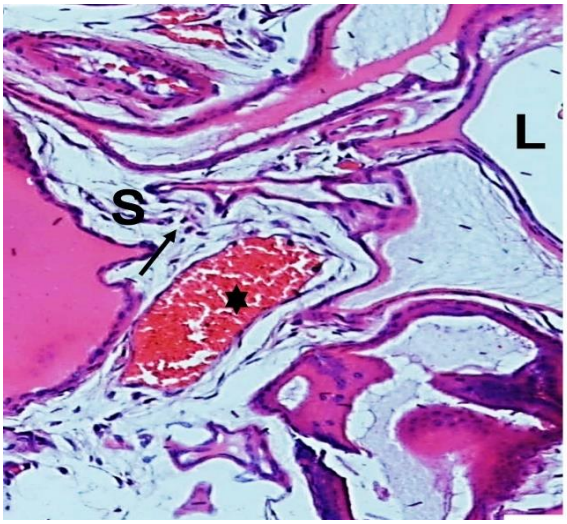

Fig. (6): A photomicrograph of a section in the ventral prostate of albino rats of the diabetic group showing widening of the stroma (S) with cellular infiltration (black arrow) and dilated congested blood vessels (black star).
Hematoxylin and eosin, ×200

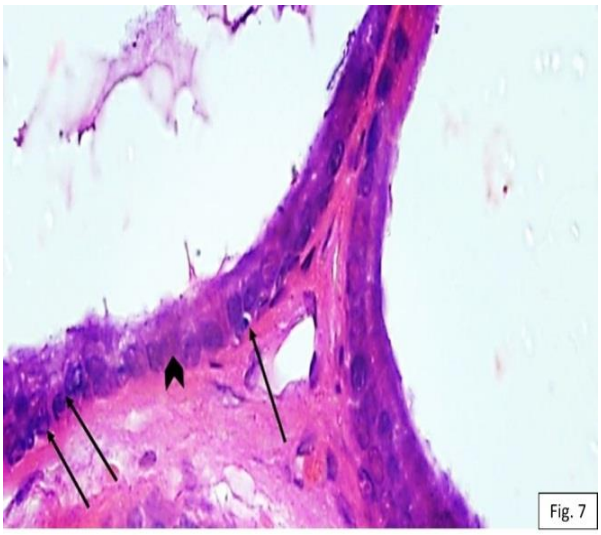

Fig (7): A photomicrograph of a section in the ventral prostate of albino rats of the diabetic group showing that, some epithelial cells appear with vacuolated cytoplasm and pyknotic nuclei (black arrow), other cells seem pale and degenerated (arrowhead). Hematoxylin and eosin, ×400.

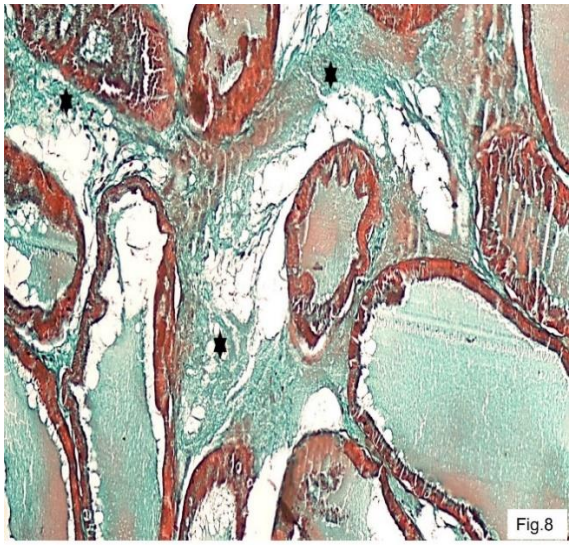

Fig (8): A photomicrograph of a section in the ventral prostate of albino rats of the diabetic group showing abundant collagen fibers (star) deposition in the stroma between the prostatic acini. **Masson's trichrome**, X400

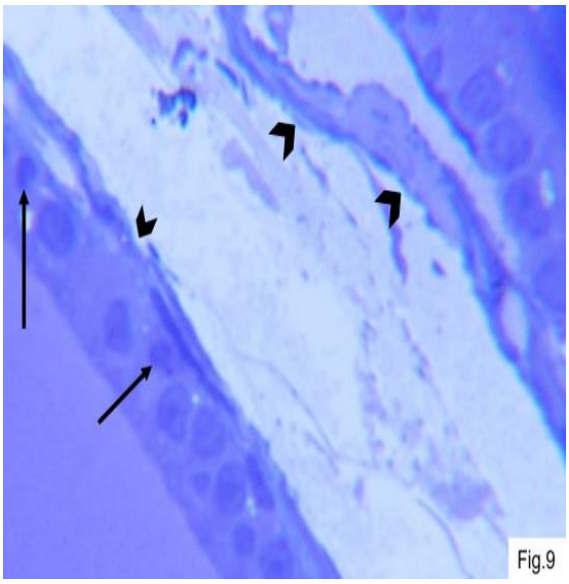

Fig (9): A photomicrograph of a semithin section in the ventral prostate of albino rats of the diabetic group showing a part of the lining epithelium the acini. The basement membrane appears partly detached and irregular (arrowhead). Some epithelial cells appear with irregular nuclei (black arrow).
Toluidine blue, ×1000

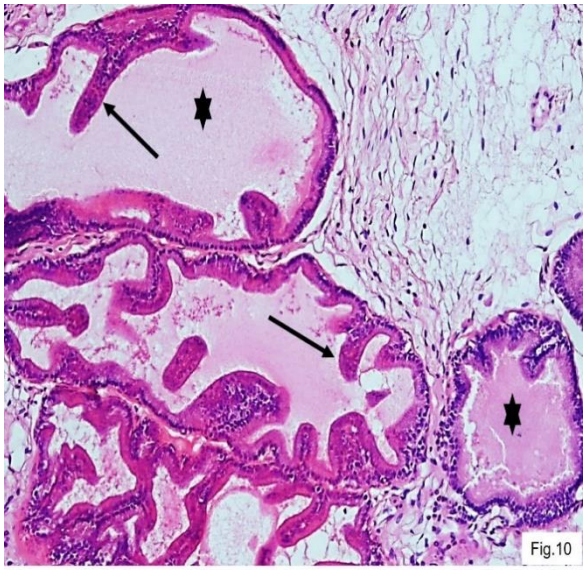

Fig (10): A photomicrograph of a section in the ventral prostate of albino rats of the protective group showing acini of regular shapes and variable sizes. The acinar epithelial folds are numerous (arrow). Dark luminal secretions are observed in some acini (star).
Hematoxylin and eosin, ×200

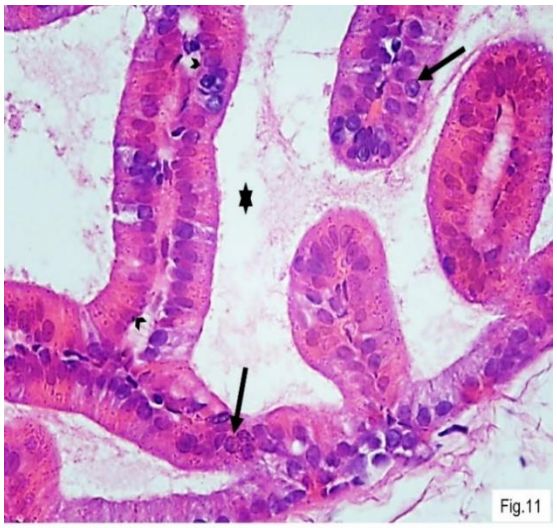

Fig (11): A photomicrograph of a section in the ventral prostate of a rat from the protective group showing parts of the lining epithelium of the acini which have regular basement membrane (arrowhead). The cells of one acinus are tall with basophilic cytoplasm and rounded vesicular nuclei (black arrow). Notice the minimal collagen fibers (star) in the stroma. ematoxylin and eosin, ×400

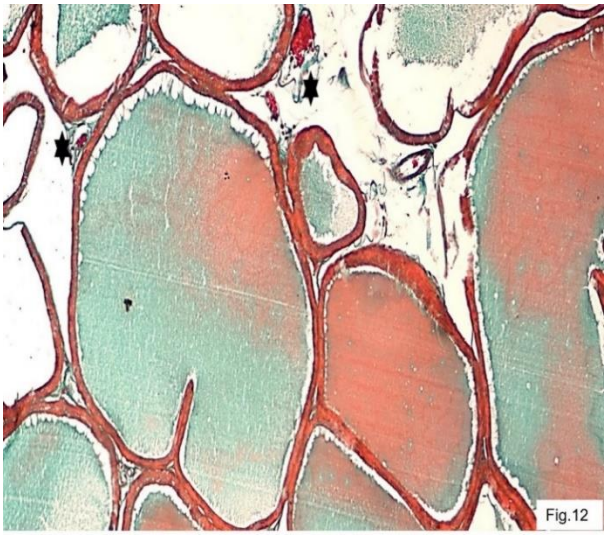

Fig (12): A photomicrograph of a section in the ventral prostate of a rat from the protective group showing minimal collagen fibers (star) in the stroma between the prostatic acini.
Masson's trichrome, X400

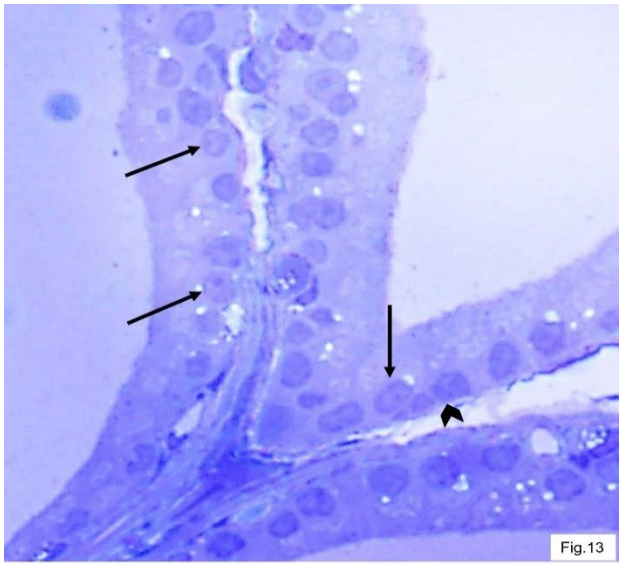

Fig (13): A photomicrograph of a section in the ventral prostate of a rat from the protective group showing lining epithelium of the acini. Acini lined by columnar cells; the nuclei were rounded and vesicular with prominent nucleoli (black arrow) with regular basement membrane (arrowhead). Toluidine blue, ×1000

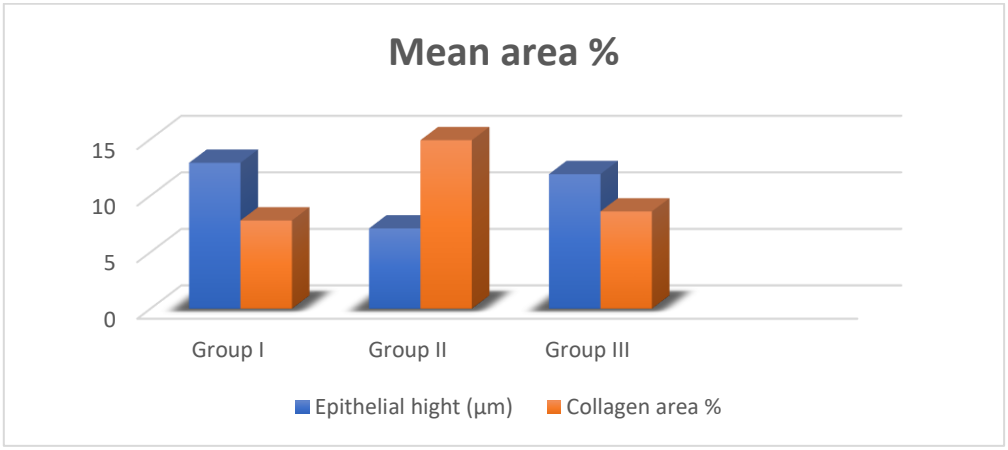

Diagram: Demonstrating the morphometric comparison between the experimental groups regarding the mean epithelial height (µm) and collagen area %.

DISCUSSION:

Fertility dysfunction is considered the biggest diabetic complication due to the dangerous impact of diabetes on the reproductive system of male. These complications are generally not preventable; therefore, doctors must be aware of the potential fertility complications caused by diabetes mellitus[17]. Many clinical trials have reported the benefits of herbal extracts and their effective role in controlling level of blood glucose in patients with diabetes[18].

In current work, prostatic acini of diabetic rats showed wide structural variations. Most of them were wide with few luminal projections. Few acini showed cellular detachment and apoptosis. The basement membrane was irregular. Cells had irregular nuclei. These results synchronized with previous studies which indicating that

Streptozotocin-induced DM suppressed the reproductive activity due to structural alterations in the testes and hyperglycemia-induced oxidative stress[19-23].

Diabetes mellitus stimulates apoptosis in many organs of body including the prostate gland. Apoptosis and atrophy of prostatic epithelium in diabetes was like atrophy of the gland after castration, which was caused by the loss of androgen-dependent acinar cells. These actions could be commuted by the establishment of androgens which demonstrated anabolic effect of testosterone on the acinar epithelial growth and proliferation [24, 25]. Hussein, 2009 [26] detected that, changes in secretory epithelium of diabetic rats affected mainly organelles concerned in secretory process, and the extracellular matrix.

In diabetes, exhaustion of insulin caused decrease in production of testosterone as insulin had a stimulating effect on androgen production by affecting the hypothalamic–hypophyseal–testis axis. It also had a local effect through insulin receptors. Rats affected with diabetes administered treatment with insulin and testosterone demonstrated a highly elevation in expression of androgen receptor [27, 28]. Vikran et al.[29] detected that suppressing release of insulin during sexual maturation delayed the growth of prostatic gland. *Popoola et al.*[30] supposed that low levels of LH in diabetic rats, changes in the prostatic fluid phosphorus, and zinc accumulation may cause marked inhibition of cell growth and proliferation and increased prostatic acinar apoptosis.

Many researchers stated that diabetes may depress the activity of Leydig cells leading to low testosterone levels. Diminishes testosterone production may inhibit the development of sexual glands of males, including the prostate gland [31,32]. Disruption between oxidation and antioxidant state had a major role in appearance of diabetic complications in different body organs. Increased oxidative stress condition with decreased levels of the antioxidant enzymes in diabetic patient caused destruction to the DNA which leaded to apoptosis[33,34].

In the present study, there was deposition and infiltration of collagen fibers in the stroma by inflammatory cells. There was marked thickening of the fibromuscular stroma which showed a significant increase in collagen area percentage. Similar results were also recorded in previously made studies[35]. It was higher incidence of benign, enlarged prostate in diabetic men than in those without diabetes. The high blood glucose can disturb the correct normal function of immunological cells and causes cellular inflammation and destruction to the nuclear structure by cytokine production, oxidative stress and stimulation of growth factors[36,37].

In diabetic rats treated with Ginkgo biloba, the prostate gland nearly restored its normal structure. Acini consisted of one layer of tall columnar cells with basal nuclei. The basement membrane was regular. The acini had luminal acidophilic secretions and many papillary projections.

Ginkgo Biloba extract was considered one of the most common botanical compounds globally. It was consumed as protective and therapeutic against variety of diseases such as neurological diseases, insufficiency of the peripheral blood flow, vertigo, and tinnitus. Ginkgo Biloba extract had also antioxidant and cytoprotective properties. Ginkgo biloba was shown to be highly effective regarding the suppression of intracellular production of procollagen and subsequently deposition of collagen in the interstitial tissues[38,39].

Ginkgo biloba was a complex mixture of components which had perfect wide pharmacological activities. It could act through many mechanisms including reactive oxygen species scavenger and stimulating antioxidant ability. Antioxidants had shown to improve diabetes by improving the

function of β-cells in experimental animal models and detected that stimulating pancreatic islets with their antioxidant defense mechanisms might be a useful therapeutic approach in therapy of diabetes and its complications [40,41]. Rhee et al. and Peng et al.[42&43] found that administration of Ginkgo biloba minimized the levels of the pro-inflammatory cytokine's and in the pancreas of streptozotocin induced mice alleviating the pancreatic inflammation and enhancing the β-cell function. Ginkgo biloba could also improve the age-related prostatic hyperplasia and deformed acinar shape by improving the difference between estrogen and androgen levels, minimize epithelial and stromal growth factors which increased due to chronic inflammation, and that because Ginkgo has blood flowing, anti-inflammatory, and free radical eliminating effects.

Conclusion:

Based on the above discussion, it could be concluded that Ginkgo biloba extract have promising therapeutic effect against the structural damaging effects of diabetes caused by streptozotocin on the ventral prostate gland in adult male albino rats.

Conflict of interest:

No conflict of interest.

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الدور العلاجي المحتمل لمستخلصات الجنكة بيلوبا على البروستاتا في نموذج الفئران لمرض السكري الناجم عن الستربتوزوتوسين: دراسة نسيجية مورفومترية

هاله طه عبد الرحمن شعلان

قسم التشريح والاجنه كليه طب جامعه عين شمي

المقدمة: يعد داء السكري مرضا من أمراض الغدد الصماء والتمثيل الغذائي في جميع أنحاء العالم. وقد زاد بسرعة في الوقت الحاضر بسبب عادات نمط الحياة الحديثة. تشكل المستخلصات العشبية المطبقة تشكل استخداما طويلا في علاج العديد من الأمراض. و يستخدم مستخلص الجنكة بيلوبا عشبيا يستخدم على نطاق واسع في علاج الأمراض العصبية مثل مرض الزهايمر والخرف.

الهدف من العمل : تقييم الدور العلاجي المحتمل لمستخلصات الجنكة بيلوبا ضد مرض السكري الناجم عن الستربتوزوتوسين في الجزء البطني من غدة البروستاتا في ذكور الفئران البيضاء البالغه.

المواد والطرق: تم استخدام ثلاثون من ذكور الفئران البيضاء البالغة مقسمة إلى ثلاث مجموعات (عشر فئران لكل منها): المجموعة الأولى (المجموعه الضابطه) لم تتلق أي علاج. المجموعة الثانية (مجموعة تم اصابتها بمرض السكري)تم اعطاء كل فار 60 ملغم/كغ حقنه من الستربتوزوتوسين داخل البريتون, تم اذابه الدواء في مخزن سترات الصوديوم العازل (0.1 مول/لتر) قبل الحقن مباشرة. المجموعة الثالثة (مجموعة الجنكة بيلوبا): تلقت حقنة واحدة من 60 مغ/كغ من الستربتوزوتوسين على النحو الذي نوقش في المجموعة الثانية. بعد أسبوع واحد من احداث مرض السكري ، تلقت الفئران الجنكة بيلوبا (100 ملغ / كغ / يوم) مذابة في 0.4 مل من الماء المقطر عن طريق الفم عن طريق أنبوب المعدة لمدة 4 أسابيع.

النتائج: فقدت الخلايا الأسينارية بنيتها الهيكلية الطبيعية. كشفوا عن عدد قليل من الطيات الظهارية المضيئة مع إفرازات لمعان شاحبة. تظهر السدى العديد من الأوعية الدموية المزدحمة بالخلايا الالتهابية وبعض الخلايا كانت فارغة. في مجموعة الجنكة كان هناك استعادة لهيكل الغدة. أظهر الأسيني القليل من الطيات الظهارية. لوحظت إفرازات لمعان داكنة في بعض الأسيني

الخلاصه: مستخلص الجنكة بيلوبا له تأثير علاجي ضد الآثار الضارة الهيكلية لمرض السكري الناجم عن الستربتوزوتوسين على غدة البروستاتا البطنية في ذكور الفئران البيضاء البالغة.