



EVALUATING THE ANTIDIABETIC POTENTIAL OF BETA-GLUCAN EXTRACTED FROM IRAQI BARLEY: A HISTOPATHOLOGICAL STUDY IN RAT MODELS.

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ABSTRACT

Beta-glucan extracted from Iraqi barley was tested in rats to investigate its anti-diabetic effects in the liver over different time periods. We selected 30 male rats weighing 250-300 g & aged 11-12 weeks to achieve the objectives of the study. Streptozotocin (STZ) 40 mg/kg intraperitoneally induced diabetes in three groups of rats. Three groups were studied: negative control, positive control, and treatment with β -glucan extract. Blood glucose levels were measured before (0 day) & after STZ injection (7, 14, & 21 days). Serum analysis showed an increase in blood glucose levels in diabetic groups, especially after 21 days of injection (598.2 ± 32.67 mg/dL) compared to other groups. The β -glucan extract group showed a significant decrease in blood glucose levels, especially in the last 21 days (249.75 ± 25.30 mg/dL). The diabetic group also showed necrotic liver cells, inflammation & hemorrhagic hepatitis. We found larger Kupffer cells & dilated sinusoids in the β -glucan extract group, which also showed mild sinusoidal congestion and few necrotic liver cells. Beta-glucan extract induced liver cell regeneration and reduced liver lesions. In conclusion, barley β -glucan extract showed significant tissue remodeling & regeneration after diabetes induction, implying potential antidiabetic activity.

Keywords: β -glucan; liver; antidiabetic activity.

تقييم الإمكانيات المضادة لمرض السكر للبيتاغلوكان المستخلص من الشعير العراقي : دراسة نسيجية مرضية في نماذج الجرذان.

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الخلاصة

تم اختبار البيتاكلوكان المستخلص من الشعير العراقي في الجرذان للتحقيق في تأثيراته المضادة لمرض السكري في الكبد خلال فترات زمنية مختلفة. تم اختيار 30 جرذاً ذكراً تزن 250-300 جرام وعمرها 11-12 أسبوعاً لتحقيق أهداف الدراسة. أدى حقن سترپتوزوتوسين (STZ) بجرعة 40 ملغم / كغم داخل الصفاق إلى حدوث مرض السكري في ثلاث مجموعات من الجرذان. تمت دراسة ثلاث مجموعات: السيطرة السالبة والسيطرة الموجبة والعلاج بمستخلص البيتاكلوكان. تم قياس مستويات الكلوكوز في الدم قبل (0 يوم) وبعد حقن سترپتوزوتوسين (7 و 14 و 21 يوماً). أظهر تحليل المصل زيادة في مستويات الكلوكوز في الدم في مجموعات مرضى السكري، وخاصة بعد 21 يوماً من

*This article is taken from the doctoral dissertation of the first researcher.



الحقن (32.67 ± 598.2 ملغم / ديسيلتر) مقارنة بالمجموعات الأخرى. أظهرت مجموعة مستخلص الببتاكلوكان انخفاضاً كبيراً في مستويات كلوكوز الدم، وخاصةً في آخر 21 يوماً (25.30 ± 249.75 ملغم/ديسيلتر). كما أظهرت المجموعة المصابة بمرض السكري خلايا كبدية نخرية والتهاباً كبدياً نزفياً. هناك زيادة في حجم خلايا كوففر وجيوباً أنفية متوسعة في مجموعة مستخلص الببتاكلوكان، والتي أظهرت أيضاً احتقاناً جيبياً خفيفاً وقليلاً من خلايا الكبد النخرية. حفز مستخلص الببتاكلوكان تجديد خلايا الكبد وتقليل أضرار الكبد. وفي الختام ، أظهر مستخلص ببتاكلوكان الشخير إعادة تشكيل وتجديداً كبيراً للأنسجة بعد الإصابة بمرض السكري، مما يشير إلى نشاط مضاد للسكري محتمل.

الكلمات المفتاحية : مرض السكري، الكبد، ببتاكلوكان.

INTRODUCTION

Diabetes is a chronic disease caused by genetic and environmental factors & is characterized by high blood sugar levels due to a lack of insulin secreted by the pancreas (Khudaier & Radhi, 2024). Suffering from diabetes due to weight loss & nutrition; As the liver is unable to produce a sufficient amount of foods rich in sugar & starches, which leads to survival in the blood, which requires type 2 diabetes (Paramasivam *et al.*, 2023). Most cells in the body need insulin to allow glucose to enter the cells from the blood. If the food intake is rich in sugar & starches (Amjeed, & AL-Rubaye, 2024), the liver and pancreas are unable to produce enough insulin to bring sugar into the cells, & some of the sugar remains in the blood, which is type 2 diabetes (Al-Hamdani *et al.*, 2019 & Ali & Abd, 2017). Persistent high blood sugar levels are considered an abnormal condition and this is due to two reasons: either the pancreas. It begins to secrete less insulin, or the body's cells lose or weaken their response to insulin, and over time a state of high blood sugar (blood sugar) occurs, (Mikhael *et al.*, 2020; Choudhury *et al.*, 2020; Nasser & Dawood, 2021). According to (AbdulSaid *et al.*, 2023). Barley ranks fourth among cereals in the world economically & is considered an important crop. However, it is rarely used in human food, but nowadays it has gained wide popularity because it contains biologically active compounds such as β -glucan (Abadi & Naser, 2019). Barley is also considered a functional cereal (Goudar *et al.*, 2020; Ahamed & Hamdia, 2023). Barley contains dietary fiber, vitamins and minerals. Such as β -glucan in large quantities, it helps improve cholesterol levels and regulate blood sugar levels (Taheri *et al.*, 2022; Nashmi & Naser, 2023). Moreover, β -glucan can enhance the effectiveness of cellular immunity (Córdova-Martínez *et al.*, 2021). Barley grains are believed to have a good content of soluble and insoluble fibers such as beta-glucan (Dufková *et al.*, 2023) and phenols (Mejía *et al.*, 2020). Including dietary fiber such as β -glucan in the human diet is beneficial for health as it reduces plasma lipid levels & provides good control of insulin & blood sugar levels in diabetics (Karim & Sabir, 2021). Many phenols have been shown to have anti-inflammatory & antioxidant properties, making them essential for human health. Eating them as part of a diet rich in fruits & vegetables helps promote overall health & avoid chronic diseases (AL-Sahib & AlSaadi, 2020). According to (Jasim & Nasir, 2020). Some phenols are powerful antioxidants that can donate electrons or hydrogen atoms to neutralize free radicals. (Rahaman *et al.*, 2023). Research & investigations have increased to extract antioxidants from various medicinal plants (Al-Fahdawi & Mustafa, 2024; Al-Samarrai, 2011). The process of converting materials into nanocomposites is a pioneering development in the world of medicine (Alshaikhly & Al-khafaji, 2023). Compounds that are reduced to the nano level have better



absorption & distribution within the body, which increases the effectiveness of treatment. In addition, this strategy allows for more precise targeting of the affected individuals (**Torabian *et al.*, 2022**). Delivering the active pharmaceutical ingredient to the intestinal lymphatic system has the potential to significantly reduce the risks of primary metabolism, P-glycoprotein (P-gp) efflux, & permeability problems. This can be achieved using lipid-based nanofabrication (**Tiwari *et al.*, 2023**). Silver nanoparticles are a novel approach to address the issues associated with increasing antibiotic resistance, & recent studies have proven their superiority in managing & eliminating a variety of microbes (**Hussain *et al.*, 2023**) .

The aim of the study is to investigate the molecular changes in body tissues resulting from diabetes and analyze the effects of barley beta-glucan in vivo through the gene expression profile of liver tissues.

MATERIALS AND METHODS

In-Vitro Study:

Preparation Of Raw Barley

The barley variety "Abai99" was obtained from the Agricultural Research Center of the Iraqi Ministry of Trade, harvested in 2022 from the Al-Azizia region in Wasit Governorate. Initially, the barley grains were pearled to remove 20% (w/w) of the original grain weight, which corresponds to the outer layers as described in (**Abadi& Naser, 2019**) The remaining 80% (w/w) of the grains were collected and sieving was performed using a sieve with a mesh size 250 microns. All of the samples had a moisture level of less than 10%.

Extraction Of B-Glucans:

Beta-glucan was extracted from barley flour (*Hordeum Vulgare* L.) variety "Aba 99" was obtained from the Agricultural Research Center of the Iraqi Ministry of Trade, harvested in 2022 from the Aziziyah region in Wasit Governorate. as a method of **Al-Maadidi (2021)** using the following method: Weighed 50 g of flour and added 500 ml of distilled water, then the pH was adjusted to 7 using sodium carbonate. The mixture was exposed to heat at 55°C for 30 minutes, then centrifuged at $15,000 \times g$ for 15 minutes, and the clear solution was taken. After adjusting the pH to 4.5 using HCl to precipitate proteins, the proteins were centrifuged again at $12,000 \times g$ for 30 min. Concentrated ethyl alcohol was added 1:1 to the solution and left for 12 hours at 4°C, then centrifuged at $3,000 \times g$ for 15 minutes. The precipitate was dried using a freeze-dryer at -50°C for 4 hours, and the precipitate was ground and weighed to calculate the beta-glucan percentage. The powder was stored at refrigeration temperature.

Invivo Study:

Preparation of Materials and Animals Used in the Study:

The standard rodent chow diet was obtained from Purina LabDiet(®), Inc. (Prolab(®) RMH 3000). A 50 mM sodium citrate buffer with a pH of 4.5 was prepared by Fisher. Streptozotocin (STZ) was prepared by Sigma, along with a 10% (w/v) sucrose solution as needed. The rats were housed in specialized cages with precise control over temperature, humidity, and lighting conditions. 1.5 ml tubes, 1 ml syringes, 25-G needles, and several other equipment were used. The study included a sample of 30 male rats, with weights ranging from



250 to 300 grams and ages between 11 to 12 weeks. Each treatment group consisted of ten animals. Five male rats were housed in each cage at $24^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and $55\% \pm 5\%$ humidity for 14 days prior to the experiment. Lighting was provided from 8:00 AM to 8:00 PM.

Experimental Animal Groups:

G1: Control Negative Group: Healthy rats receiving daily doses of saline solution ($n = 10$ rats).

G2: Control Positive Group: Untreated diabetic rats ($n = 10$ rats).

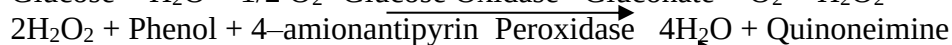
G3: Beta-Glucan Extract Group: Diabetic rats treated exclusively with a beta-glucan solution, administered orally at a dose of 200 mg/kg body weight per day for 21 days ($n = 10$ rats).

Treat Animals With Stz:

This study weighed and placed 4 mg of STZ in a 1.5-ml aluminum foil-lined microcentrifuge tube for every three rats. In a 50-mM sodium citrate buffer at pH 4.5, we dissolved STZ to 4 mg/mL before injection. Since STZ deteriorated quickly (15–20 minutes after dissolving in citrate buffer), we prepared and injected the solution within 5 minutes. STZ solution was given intraperitoneally (IP) to experimental group mice using 1-ml syringes and 25-G needles (Luna *et al.*, 1968) at 40 mg per kilogram. The control group received the same intraperitoneal citrate buffered saline with a pH of 4.5. We put the rats back in their cages. For five days, we gave them ordinary food and 10% sucrose water. The sixth trial day saw us transition from 10% sucrose to regular water.

Estimation of Serum Glucose Level:

Blood samples were taken from the tail artery after fasting laboratory animals for 8 consecutive hours to examine blood sugar levels using the ELISA method with a diagnostic kit from Rat GLUT4 (Glucose Transporter 4) ELISA Kit (Catalog No: E-EL-R0430). The method followed was based on (Titeiz *et al.*, 1982), where glucose is oxidized to gluconic acid and hydrogen peroxide in the presence of the enzyme peroxidase and a hydrogen donor. This reaction interacts with phenol and 4-aminoantipyrin, resulting in a red dye that absorbs at a wavelength of 450 nm, which correlates with the glucose concentration in serum according to the following equations:



the normal range for glucose in human serum is between 80-120 mg/dL.

Period Of Study:

On experimental day 0, all animals fasted for 8 hours before receiving the STZ injection, followed by days 7, 14, and 21. Tail-vein blood samples from the STZ group were tested for higher blood sugar levels using the Enzyme-Linked Immunosorbent Assay (ELISA) method GLUT4 (Glucose Transporter 4) ELISA Kit (Catalog No. E-EL-R0430) (Chong *et al.*, 2012).

Treatment Of The Experimental Animals With β -Glucan Extract:

As advised by (Recordati *et al.*, 2021), the dosage of β -glucan extract was found to be 200 mg per kilogram of body weight. Over the course of 21 days, these daily doses were administered directly through a feeding tube, or stomach tube.



Preparation Of Tissue Samples:

Five rats from each group were sacrificed at the end of the experimental (21 days) of injection of STZ drug. Tissue samples from liver was fixed in 10% buffered formalin, embedded in paraffin, and sliced at 5 μ m. Hematoxylin and eosin. Light microscopy investigated tetroxide (Luna, 1968; Chong *et al.*, 2012; Layton, 2018). Fix tissues immediately after acquisition. A tissue fixative should inhibit evaporation, enzyme autolysis, swelling, shrinking, and bacterial or mold attack. It should also change tissue components to preserve their shape after embedding, sectioning, and staining. Fixed-tissue specimens are fragile to segment. After infiltrating a supportive media, embed the specimen in a block of the same medium, and attach it to the specimen holder of the microtome for cutting thin slices. Most embedding media are paraffin and celloidin (Layton *et al.*, 2018). After slices are cut and placed on glass slides, the supporting media is removed and tissues are dyed.

Statistical Analysis:

The statistical analysis was conducted using SPSS software version 21. For calculating descriptive analysis including mean $\pm$ SD. ANOVA analysis was used for comparing multiple groups.

RESULTS

Serum glucose levels:

Figure 1 depicted the concentrations of serum glucose in different groups across various periods of the current investigation. The study found no significant differences in serum glucose levels before the streptozotocin injection in the negative control group, positive control group, and beta-glucan extract group (154.2 ± 16.88 , 146.8 ± 24.70 , and 138.6 ± 20.96) at period zero. Seven days after diabetes induction, serum glucose levels significantly increased for the aforementioned groups (167.7 ± 17.84 , 517.5 ± 28.50 , and 487.7 ± 49.06). After 14 days, the positive control (diabetic) group had higher serum glucose concentrations (571.5 ± 20.87) compared to the other treated groups (beta-glucan), which had lower levels (365.63 ± 26.40) compared to the previous period and the positive control group. However, these levels remained greater than normal when compared to the negative control group. After 21 days, the negative control group remained at normal levels (158.4 ± 23.83). In comparison, the positive control group (diabetic) showed considerably higher levels (598.2 ± 32.67). β -glucan extract groups had lower levels than the previous period (249.75 ± 25.30). A slight decrease in serum glucose levels was observed in the groups that consumed the barley flour mixture. The results indicate that beta-glucan contributed to lowering glucose levels in diabetic mice, although the levels remained higher compared to the negative control group.

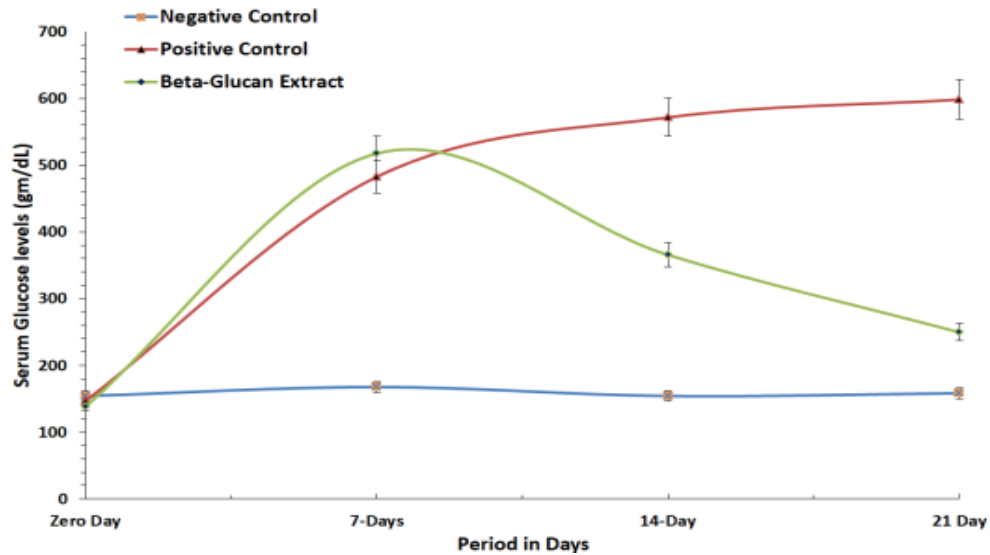


Figure (1): Serum glucose levels before and after STZ injection in different groups across various periods.

Histopathological Changes:

Histopathological examination of liver tissues showed distinct changes between the treatment groups. The control group (Fig. 2) showed healthy liver tissue, while the diabetic group (Figs. 3 and 4) showed severe pathological changes such as necrotic hepatocytes, inflammation, and hemorrhagic hepatitis due to the high glucose levels, which negatively affect the liver of the rats. β -glucan extract-treated group (Figs. 5 and 6) showed mild sinusoidal congestion and few dead hepatocytes. Moreover, the infiltration of enlarged Kupffer cells and dilated sinusoids were obvious. The beta-glucan extract-treated group showed features suggestive of improvement, such as mild sinusoidal congestion and few dead hepatocytes compared with the diabetic group.

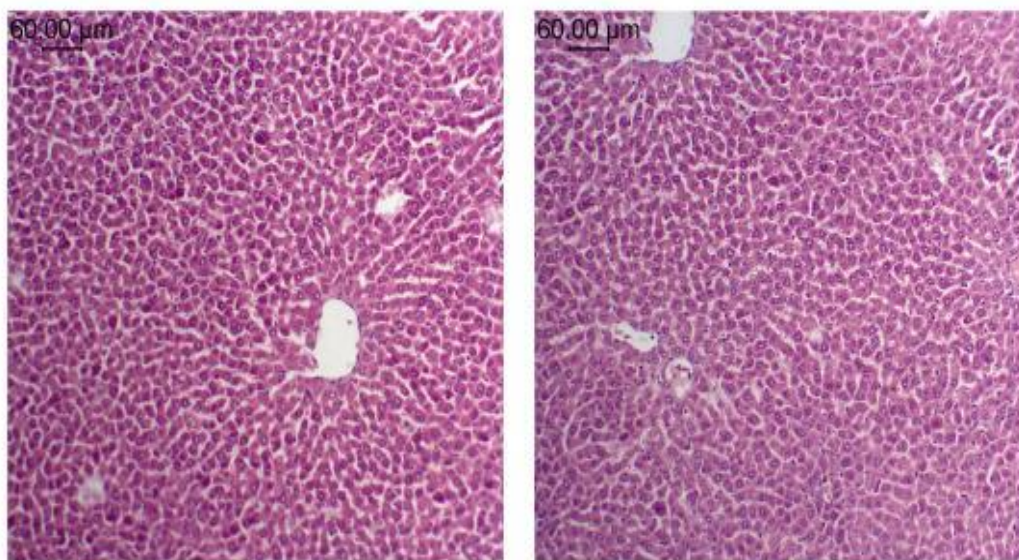


Figure (2): Section of liver of rat of the control group showed normal liver texture. H&E, 100X.

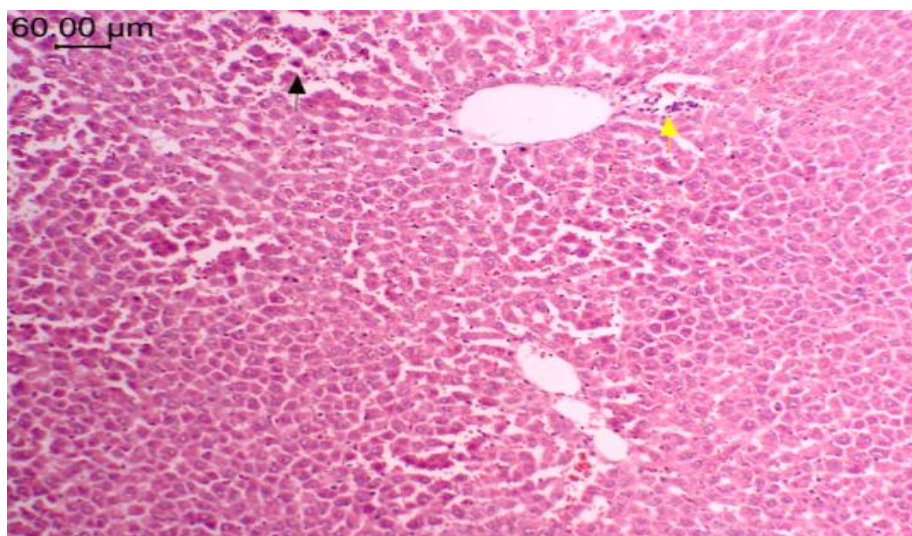


Figure (3): The untreated type 1 diabetic group showed severe necrotic hepatocytes (black arrow), the hepatocytes loss their normal striation, infiltration of inflammatory cells (yellow arrow), and dilated sinusoids were also evident. H&E, 100X.

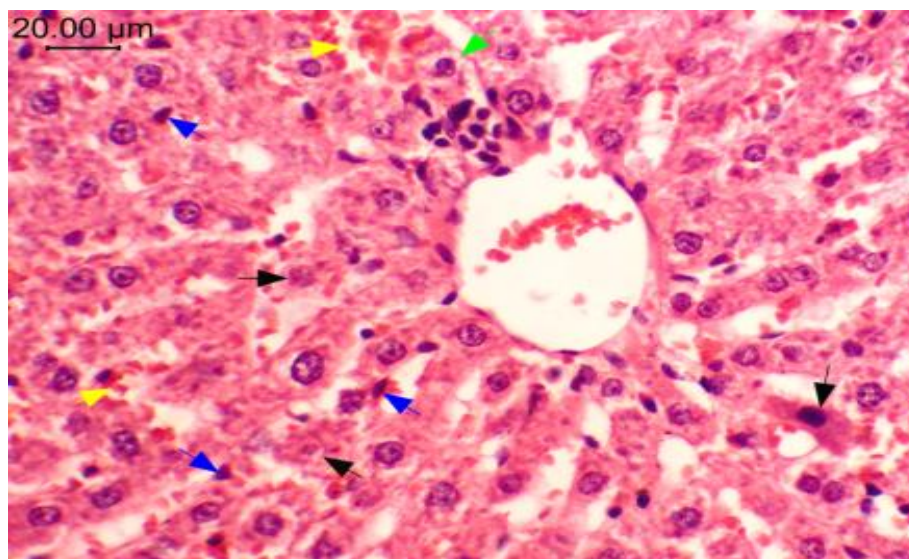


Figure (4): The untreated type 1 diabetic group showed severe hemorrhagic hepatitis. Some hepatocytes showed hydropic degeneration (green arrow) and other are necrotic (black arrows), severe extravassated RBCs (yellow arrows), and heavy infiltration of Kupffer cells. H&E, 400X.

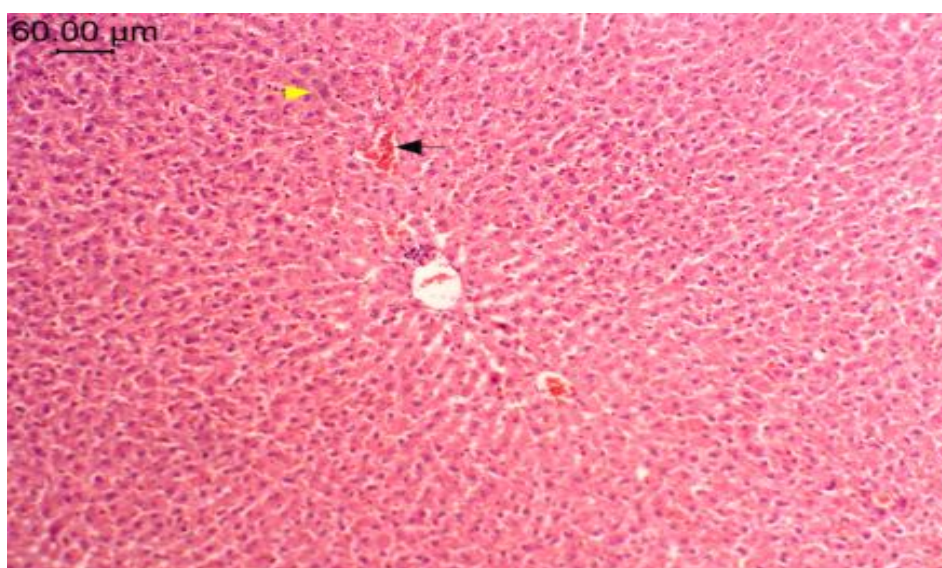


Figure (5): section of liver of Beta-Glucan extract treated group showed presence of extravassated RBCs (black arrow) between hepatocytes, congested sinusoids, some necrotic hepatocytes (yellow arrow), and infiltration of inflammatory cells. H&E, 100X.

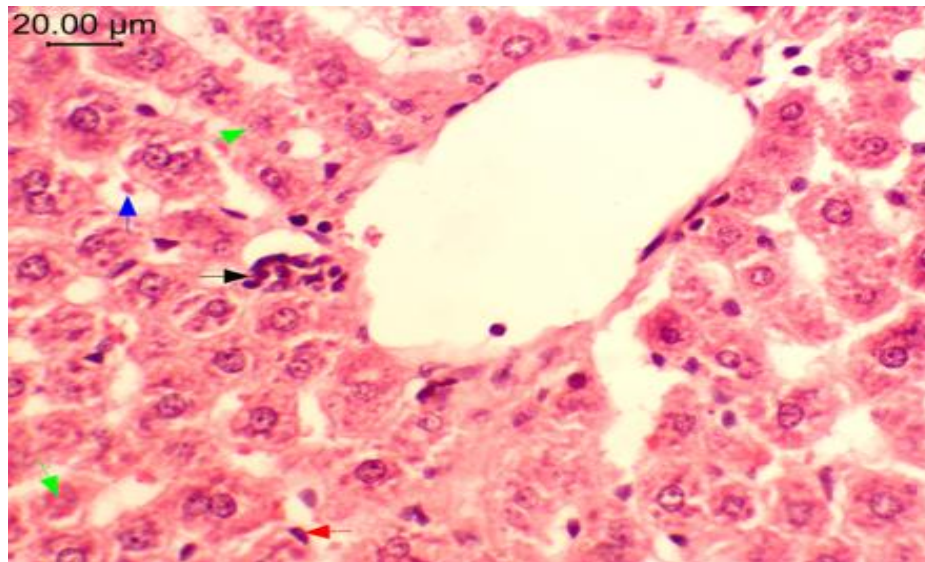


Figure (6): section of liver of Beta-Glucan extract treated group showed congested sinusoids (blue arrow), some necrotic hepatocytes (green arrows), and infiltration of inflammatory cells (black arrow). H&E, 400X.

DISCUSSION

The histological abnormalities that occur in the liver as a result of diabetes treatment can be linked to several reasons, including the effect of drugs used to treat diabetes (**Vincent et al., 2011**). The diabetic group showed molecular layer abnormalities, with gaps and cell loss in the CA3 region, which are diagnostic signs of diabetic neuropathy. According to (**Oberdörster et al., 2005**), chronic high blood sugar in diabetic patients leads to oxidative stress, neuroinflammation, and neuronal cell death, which contribute to the altered histological characteristics. Research (**Jayachandran et al., 2018**) suggests that taking β -glucan therapy may help alleviate the neurological changes associated with diabetes due to its neuroprotective and neuroprotective properties. (**Tangvarasittichai, 2015**). This effect is attributed to the antioxidant and anti-inflammatory properties of beta-glucan. It may take more time for barley flour to positively affect the healing of liver tissues (**Al-Hamdani et al., 2019**).

Research (**Zhao et al., 2023**) suggests that metabolic disorders, insulin resistance, and oxidative stress are the causes of diabetic liver problems, leading to hepatocyte death, inflammation, and hemorrhagic hepatitis. According to a study by (**Ferdous & Nemmar, 2020**), beta-glucan extract can treat liver diseases by reducing oxidative stress and inflammation, and increasing liver function through immunomodulation (**Chen et al., 2020**). Studies by (**Awasthi et al., 2022; Al-Karagoly, 2012**) also suggest that beta-glucan treatment has the potential to alleviate diabetes problems due to its antioxidant, anti-inflammatory, and immunomodulatory properties. The results also confirmed the ability of barley flour to reduce and regulate glucose levels due to its fiber content, helping alleviate diabetes symptoms and prevent high blood sugar. Additionally, barley is a rich source of magnesium, which enhances



the activity of enzymes involved in glucose utilization and insulin secretion (**Al-Hamdani et al.,2019**).

CONCLUSION

During histopathological examination, the response to treatment against diabetes varied among different tissue groups. In liver tissue, the group treated with beta-glucan extract showed signs of improvement, such as mild congested sinusoids and fewer dead hepatocytes. The efficacy of beta-glucan showed more favorable effects across liver tissues. Further comparative studies will be needed to determine the superior efficacy of beta-glucan against diabetes.

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