Effect of *Artemesia scoparia* Extract on Kidney Functions and some Antioxidants in Experimental Diabetic Rats

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KEYWORDS

A. scoparia., phenolic, flavonoids, STZ-Induced, Nephron injury

ABSTRACT

One of the factors that cause severe metabolic imbalance and abnormal changes in many tissues, especially in the Kidney, is diabetes mellitus. Therefore, in this study, the therapeutic effects of Artemisia scoparia (A. scoparia) were investigated using a rat model in the control of diabetic infection. Diabetes was induced in the Wistar albino rats by injecting STZ at a dose of 45 mg/kg body. After a two-week acclimatization period, forty male rats were randomly divided into five groups of equal size (n = 8) for a six-week experiment; Group I: non-diabetic untreated rats that were gavaged daily with distilled water for 6 weeks, Group II: STZ-induced diabetic rats that were gavaged daily with distilled water for 6 weeks, Group III: diabetic rats that was injected subcutaneously with the insulin at a dose of 5 IU/kg body weight, Group IV: diabetic rats that were orally administered with the alcoholic extract of A. scoparia at a concentration of 70 mg/kg, Group V: diabetic rats that were orally administered with A. scoparia extract at a concentration of 70 mg/kg. Two hours later, they were injected with insulin subcutaneously at a concentration of 5 IU/kg. During 6 weeks, the levels of blood urea (BUN), creatinine, uric acid, malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were estimated. Kidney samples were also collected for histopathological analysis. The findings indicated that STZ toxicity led to significantly high levels of BUN, creatinine, uric acid, and MDA, along with a significant reduction in SOD, CAT, and GPx. Additionally, STZ caused alterations in kidney histopathology, including kidney damage and tubular necrosis, compared to the diabetic control. However, treatment with A. scoparia significantly enhanced kidney histopathology, reduced the levels of BUN, creatinine, and MDA, and markedly increased the levels of SOD and GPx in the kidneys of STZ-treated rats. It can be concluded that the results of this study indicate that A. scoparia may serve as a natural herbal antioxidant remedy, demonstrating a renal therapeutic effect against STZ-induced nephrotoxicity in rats.

1. Introduction

Herbal medications have received much attention because of their potential to treat mental illnesses (Kang *et al.*, 2023). There has been an increase in their usage in depression therapies because of their high effectiveness, safety, and low cost (Karobari *et al.*, 2022). Recent studies have proposed the use of medicinal plants in treating many diseases. The World Health Organization (WHO) has shown great interest in using plant medicine to avoid many of the side effects of chemical medicines (Umaru *et al.*, 2020). Effective compounds are found in most medicinal plants, among these plants is Artemisia, which belongs to the Asteraceae family, which includes about 300-400 species of herbs and shrubs. It is one of the perennial medicinal plants which spread in many countries of the world. The plant has several types, including what is known as *A. scoparia*. It contains many active and important chemical components, including flavonoids, coumarins, chromones, scoparon and others (Ding *et al.*, 2021). The *A. scoparia* plant is utilized for many uses in medical and other fields. It is widely known for a group of biological effects that are attributed to the presence of volatile oils. It is used to treat infectious diseases such as malaria, asthma, epilepsy, tuberculosis, and other diseases caused by fungal worms and viruses. It is also used to protect against insects, due to its antioxidant and anti-inflammatory properties based on its active components such as flavonoids and phenols. It is also considered an anti-cancer, in addition to the use of its aerial parts in liver and kidney disorders, diabetes, and others (Boudreau *et al.*, 2022).

Diabetes mellitus is one of the most common diseases. It is known as a disorder in the metabolic processes resulting from many pathogens that are characterized by high blood sugar with an imbalance or disorder in the metabolism of carbohydrates, proteins and fats, occurring as a result of a defect in the secretion of the hormone insulin or the action of insulin or both (Singh *et al.*, 2016). According to a 2015 report by the International Diabetes Federation, diabetes is one of the largest medical and economic problems in the world. Nearly 415 million people worldwide suffer from this disease and the number is expected to rise to 642 million by 2040. Moreover, diabetes is the seventh leading cause for deaths in the United States of America (Dwivedi and Pandey, 2020). Previous studies have shown that administering the alcoholic extract of A.*scoparia* to animals orally produced a set of beneficial effects in the metabolic process, including improving the body’s sensitivity to insulin (Rahhal *et al.*, 2022). It also significantly reduced the levels of fatty acids in the blood of rats that were subjected to a high-fat diet that did not cause any changes in the formation of new fats in the liver or adipose tissue, and improved the function of some endocrine glands (Li-ping *et al.*, 2021). Therefore, this study was conducted with the aim of determining the effect of *A. scoparia* on the renal function in diabetic animals.

MATERIALS AND METHODS

Chemicals

Streptozotocin (STZ) was purchased from (MP Biomedicals, LLC, USA), ethanol and acetone were obtained from (Solarbio CHEMIE PVT.LTD, China).

Plant Collection and Extract Preparation

A.scoparia was collected, in collaboration with the Desert Studies Center – University of Anbar, from the west of Ramadi city - Anbar Governorate. After collecting the plant, it was cleaned and washed well with water to ensure that it was clean and free of dust or impurities. After that, it was left to dry at room temperature. Then, dried leaves were collected and grinded using an electric grinder to obtain powder, which was stored in sterile glass jars until use (Boakye *et al.*, 2017). Using the Soxhlet extraction in the laboratories of the Department of Biology at the College of Education for Pure Sciences – University of Anbar, 50 grams of the powder of the plant material were weighed and soaked in 500 milliliter of crude methanol. Then, filtrate was obtained and evaporated under reduced pressure and stored at 4ºC for future use (Boudreau *et al.*, 2018).

Animals

This study used 40 male Swiss white rats (Sprague Dawely), whose weights ranged between 170-210 grams and were placed in plastic cages measuring 30 x 50 cm with metal covers. The animals were subjected to ideal conditions of a light cycle that was divided into 11 hours of light and 13 hours in the dark, and the temperature was fixed at 22±2°C. Food and water were given continuously and in sufficient quantities throughout the study period.

Experimental design

Induction of diabetes mellitus

Streptozotocin was used at dose of 45 mg/kg body weight dissolved in 0.1 M citrate buffer (pH 4.5) in a volume of 1mL/kg body weight that was freshly prepared and injected within 5 minutes by intraperitoneal (IP) route. Fasting blood sugar (FBS) was measured by reagent strips (Accu-Chek®, Roche, Germany) after three days to ensure the existence of diabetes. Rats with blood glucoserange 300mg/dL were considered diabetic. Following a two-week acclimatization period, forty male rats were randomly divided to five groups of equal-size (8 per group) for a six-week experiment. Group I: non-diabetic untreated rats that were gavaged daily with distilled water for six weeks, Group II: STZ-induced diabetic rats that were gavaged daily with distilled water for six weeks, Group III: diabetic rats that were injected subcutaneously with the hormone insulin at a dose of 5 IU/kg body weight, Group IV: diabetic rats that were orally administered with alcoholic extract of the *A.scoparia* at a concentration of 70 mg/kg, and Group V: diabetic rats that were orally administered with *A. scoparia* extract at a concentration of 70 mg/kg, two hours later they were injected with insulin subcutaneously at a concentration of 5 IU/kg.

Blood samples

At the end of the experiment, which lasted for 6 weeks, the animals were starved for 24 hours, and the next day the animals were anesthetized using chloroform. Blood samples were collected from the heart of eight rats of each group at the end the experimental period in small dry tubes and centrifuged at 3000 rpm for 15 minutes. Then, serum were separated and stored at – 20 ºC until biochemical analysis.

Serum Markers

The level of glucose in blood serum was measured using a glucose test kit imported from the Spanish Company Linear according to the method (Dingeon *et al.*, 1975), while Creatinine, Urea and Uric acid in serum were measured by colorimetric assay kit (Linear, SPAIN) according to the producer's instructions.

Estimating Antioxidants and Lipid Peroxidation

Serum catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) activities were measured according to the methods of (Luck and Bergmeyer., 1974), (Kakkar *et al.*, 1984) and (Reddy *et al.*, 1985), respectively. The level of malondialdehyde (MDA) in blood serum was estimated using a ready-made test kit prepared by the American Company Elabscience, using a colorimetric method on a spectrophotometer (Kei, 1978).

Histopathological studies

Small pieces of the kidneys were fixed in 10% neutral buffered formalin, embedded in paraffin wax, sectioned at (5 µm) thickness and stained with hematoxylin and eosin (H and E) for light microscopic examination (Gharban et al., 2019).

Statistical analysis:

Data were expressed as Mean ± S.E.M., with a value of (P≤0.05) which was considered statistically significant. Statistical evaluation was performed by ANOVA followed by the Student's t-test. All analysis was made with the statistical software Microcal Origin. All statistical analyses were performed using GraphPad® software (Hussen et al., 2024).

Results

Biochemical analysis

The results of the current study showed a significant increase (P≤0.05) in glucose concentration in the second unhealthy group treated with STZ, while a significant decrease was observed for the same indicator above in the third, fourth, and fifth groups (Fig. 1). Also, the results showed a significant increase (P≤0.05) in the concentration of urea, creatinine, and uric acid in the second group with diabetes (STZ group), while a significant decrease (P≤0.05) in the level of creatinine was observed in the third, fourth, and fifth groups when compared with the second group with diabetes, while no significant differences appearing when compared with the healthy control group (Fig. 2,3,4).The results also indicated a significant decrease (P≤0.05) in urea concentration in the third, fourth, and fifth groups when compared with the second unhealthy group, while they indicated a significant decrease (P≤0.05) in the uric acid concentration in the third and fifth groups only when compared with the infected group. The best results were given in the fifth group.

Moreover, the results showed a significant increase (P≤0.05) in the level of MDA in the second group with diabetes when compared with the healthy control group, while there was a non-significant decrease (P≤0.05) in the third and fourth groups. However, the results of the study showed a significant decrease in the above indicator in the fifth group when compared with the infected group (Fig. 5), while it was observed that there was a significant decrease (P≤0.05) in the level of Antioxidant enzymes, GPX, CAT, and SOD in the diabetic group treated with STZ, while the results recorded a significant increase in the level of these enzymes in the third group. The results also showed a significant increase (P≥ 0.05) in the level of these antioxidants in the two. fourth and fifth groups compared to the second unhealthy group (Figure 6,7,8).

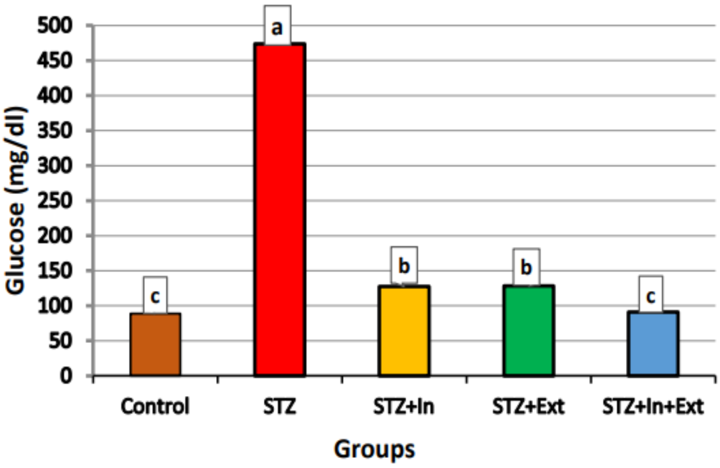

Figure (1): The effect of the alcoholic extract of the *A.scoparia* on the glucose concentration in animals treated with STZ

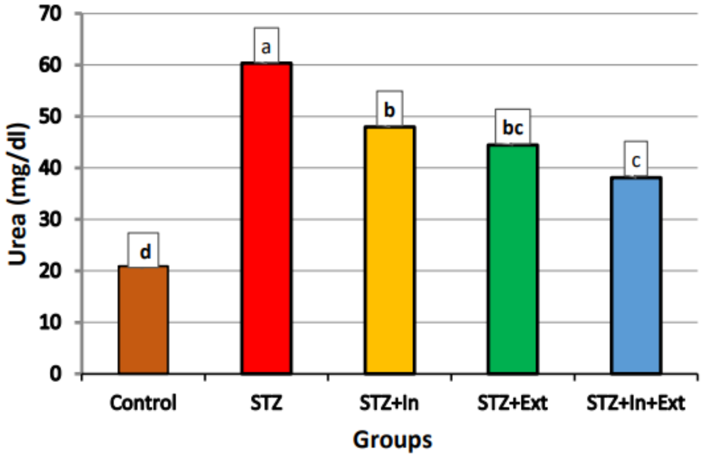

Figure (2): The effect of the alcoholic extract of the *A.scoparia* on the Urea concentration in

animals treated with STZ

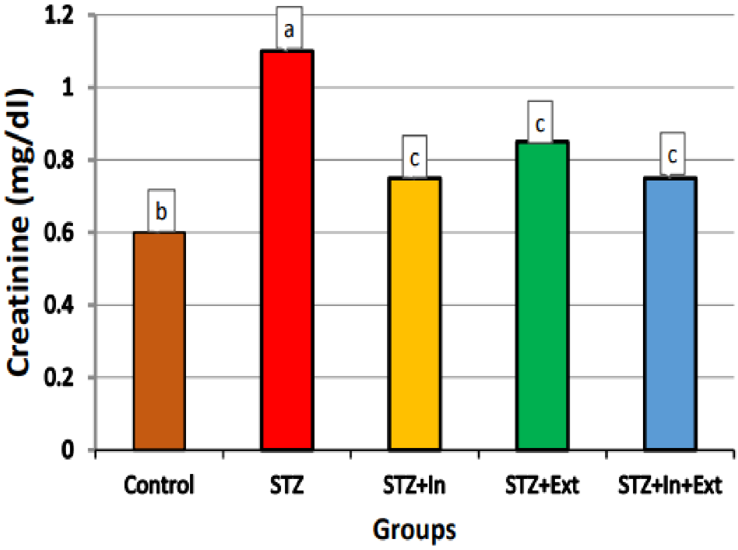

Figure (3): The effect of the alcoholic extract of the *A.scoparia* on the Creatinine concentration in animals treated with STZ

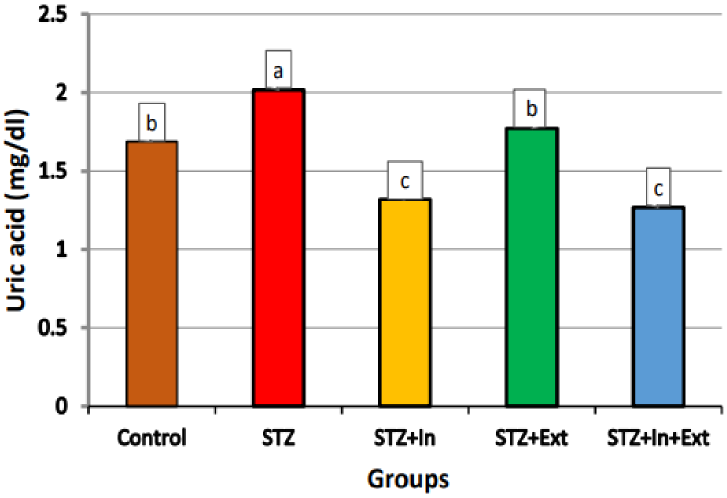

Figure (4): The effect of the alcoholic extract of the *A.scoparia* on the Uric acid concentration in animals treated with STZ

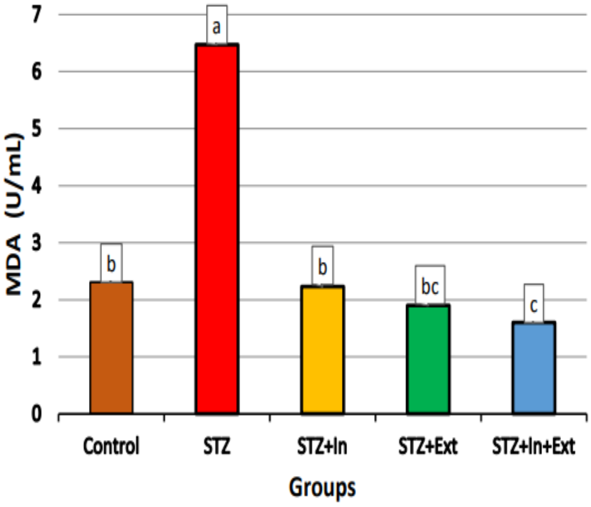

Figure (5): The effect of the alcoholic extract of the *A.scoparia* on the MDA level in animals treated with STZ

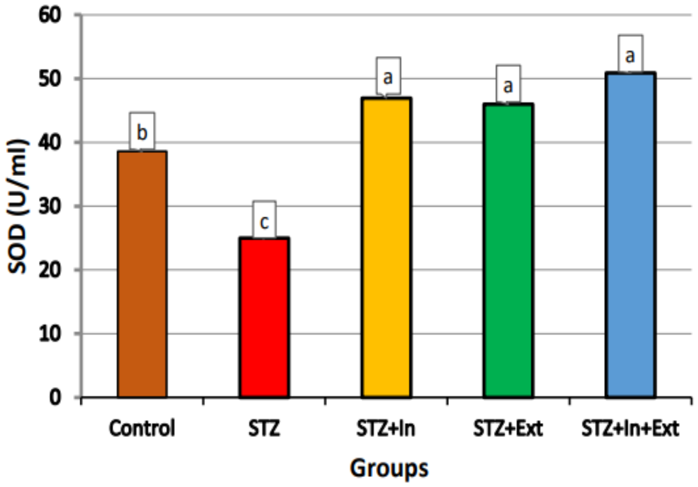

Figure (6): The effect of the alcoholic extract of the *A.scoparia* on the SOD level in animals treated with STZ

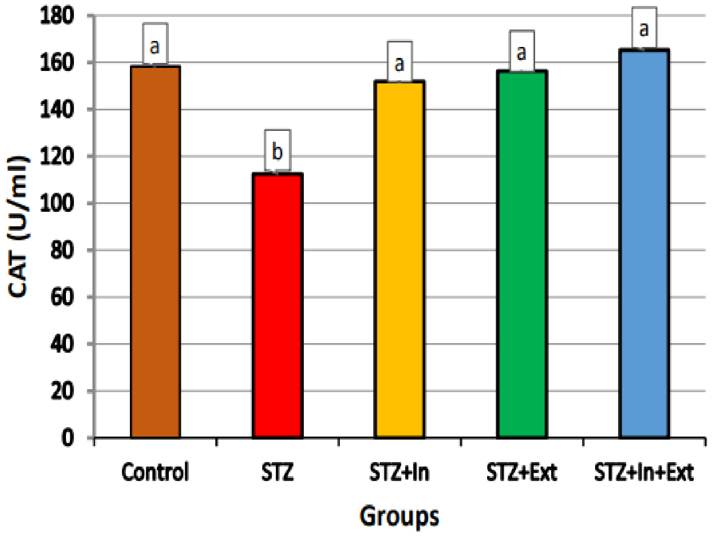

Figure (7): The effect of the alcoholic extract of the *A.scoparia* on the CAT level in animals treated with STZ

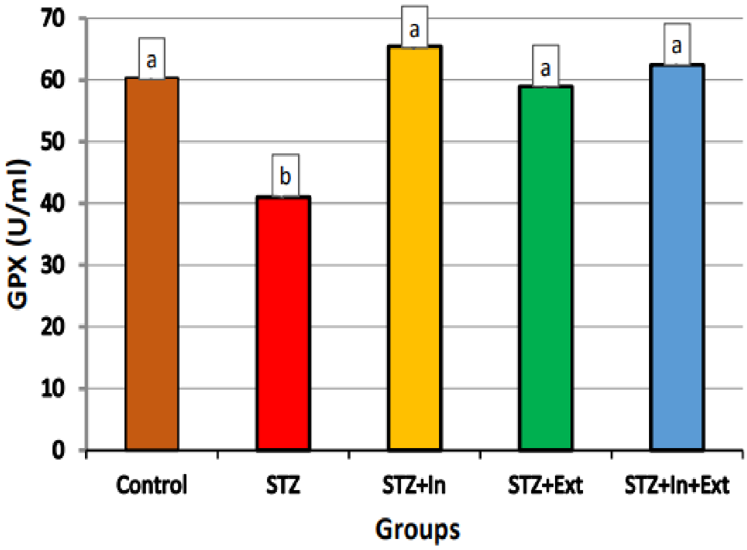

Figure (8): The effect of the alcoholic extract of the *A.scoparia* on the GPX level in animals treated with STZ

Histopathological analysis

Histological parts of the kidneys from the healthy control group exhibited a normal histological pattern, displaying the typical shape of the glomerulus (G) along with its standard size, encased by Bowman's capsule (BC), and featuring the expected appearance of Bowman's space (BS), as well as the proximal convoluted tubule (P) and the distal convoluted tubule (D) (Fig.9). However, in the second group treated and afflicted with diabetes, there were histological changes represented by the presence of dilatation of blood vessels and the presence of a state of blood congestion. In addition, atrophy was observed in a number of glomeruli, with the presence of severe swelling of some lining epithelial cells (Fig.10).

The histological changes in the third group showed the presence of degeneration of some lining epithelial cells, as well as necrosis of a number of these cells. In addition, an increase in the number of mesangial cells, as well as the presence of atrophy of some glomeruli was also noted as well as the presence of inflammatory cell infiltration of white blood cells (Fig.11). Concerning the changes occurring in the fourth group treated with the extract only, it was observed that there was atrophy of some glomeruli with bleeding in the renal interstitial tissue (Fig.12), while the results of the histological examination of the fifth group showed that the kidney tissue appeared almost similar to the healthy control group (Fig.13).

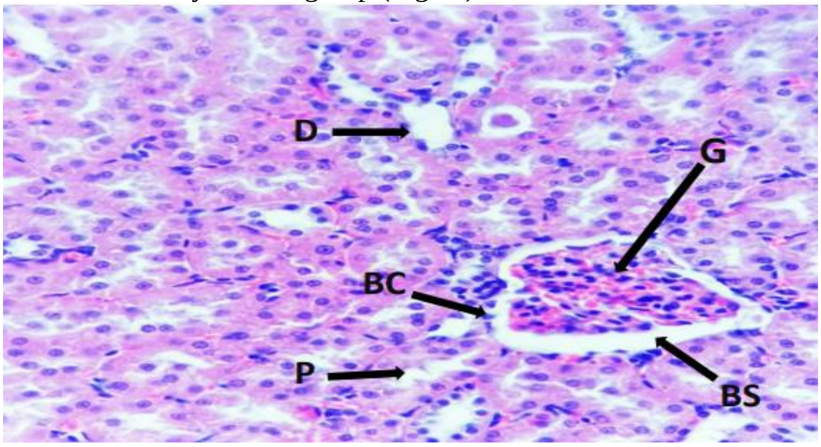

Figure 9: section of kidney of the control group showing normal histological appearance, displaying the normal shape of the glomerulus (G), surrounded by Bowman's capsule (BC), Bowman's space (BS), proximal convoluted tubule (P), and distal convoluted tubule (D) H and E, BX400

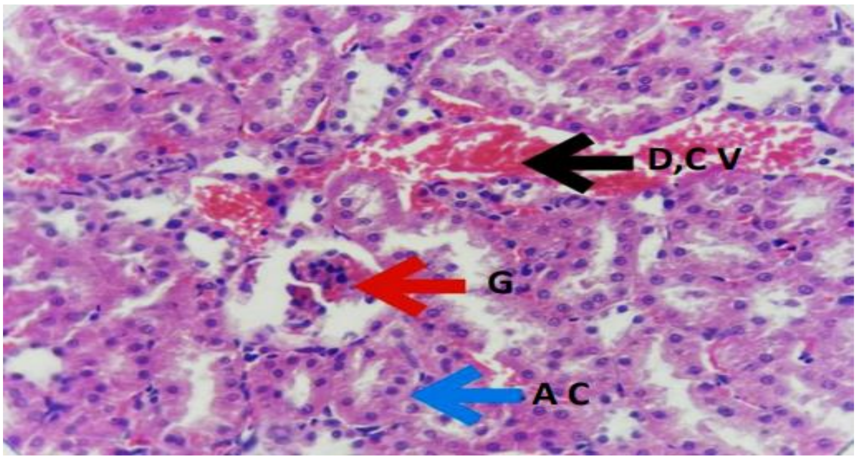

Figure 10: section of the kidney of the diabetic group showing blood vessels dilations with congestion (black arrow), glomerular atrophy (red arrow) and acute epithelial cell swelling (blue arrow)H and E, BX400

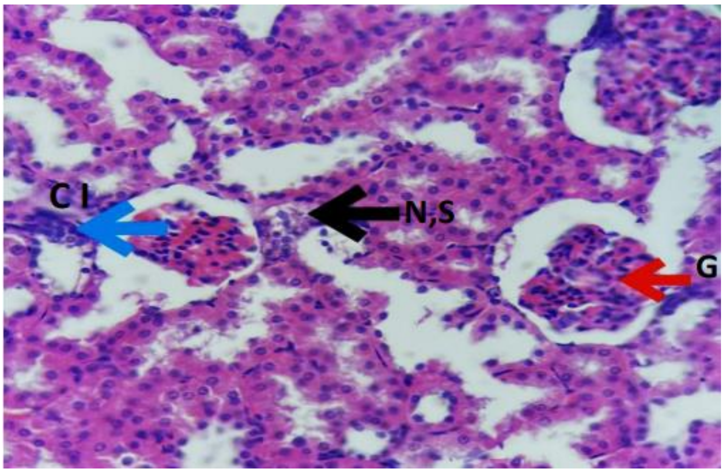

Figure 11: section of the kidney of insulin group showing tubular epithelial degeneration with necrosis (black arrow), Mesangial cell hyperplasia with glomerular atrophy (red arrow) and inflammatory cell infiltration (blue arrow). H and E, BX400.

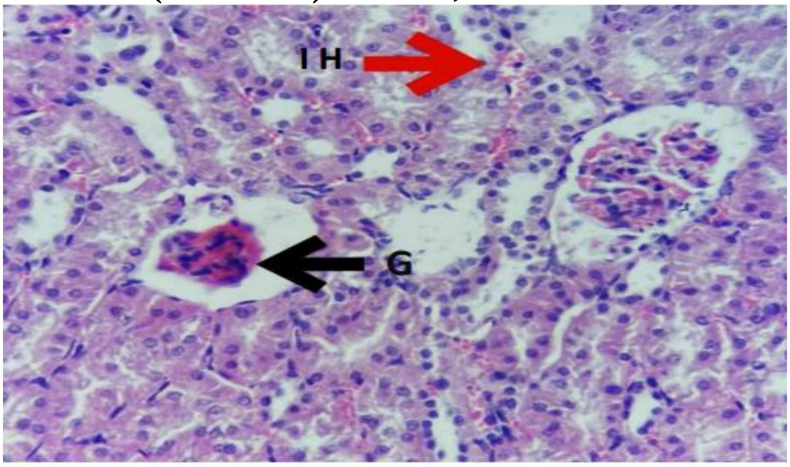

Figure 12: section of the kidney of *A. scoparia* group showing glomerular atrophy (black arrow) and interstitial hemorrhage (red arrow). H and E, BX400.

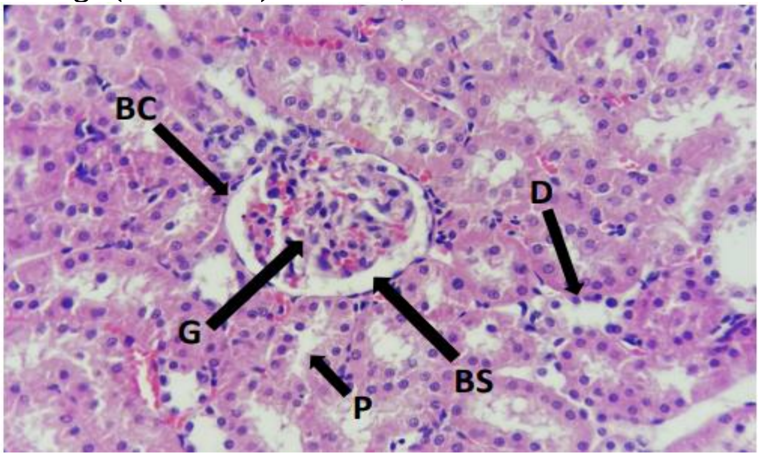

Figure 13: section of the kidney of extract+ insulin group showing normal histology architecture. H and E, BX400

Discussion

The increase in the level of glucose as a result of injections with streptozotocin (STZ) led to the development of diabetes and the destruction of the pancreatic beta cells that produce insulin. This has led to a decrease in the secretion of the insulin and the inability to introduce glucose into the cells of the body to benefit from it (Goyal *et al.*, 2016), thus increasing the level of glucose in the blood and increasing the index of insulin resistance, which is also considered one of the distinctive signs of type 2 diabetes, or there may be a defect in the function of insulin receptors, which reduces their ability to transmit the insulin signal into the cell (Skovsø, 2014).

The *A. scoparia* extract also contains components of essential oils such as Camphor, Artemisia ketone, Germacrene and others, which also has enhanced the role of insulin in reducing glucose levels and, thus, lowering the values of the insulin resistance index and improving insulin sensitivity (Ding *et al.*, 2021). It was also observed that the level of glucose decreased in the fifth group. The reason behind this may have been attributed to the result of the synergistic effect of the alcoholic extract of the *A. scoparia* with insulin injections, meaning that the presence of this alcoholic extract enhanced the effectiveness of the insulin, which would bind to the glucose to bind to the insulin receptors located on the surfaces of the cell membranes and thus reduce the levels of glucose in the blood (Sharafati-Chaleshtori *et al.*, 2021).

The rise in the levels of urea, creatinine, and uric acid in the second infected group may be due to the damage in the kidneys as a result of streptozotocin-induced diabetes, as well as enlargement of the glomeruli with a loss of glomerular spaces and deformation of the inner lining of the kidneys as a result of diabetes. The kidneys are known for their role in filtering the blood (Xie *et al.*, 2017), and getting rid of waste products (urea, creatinine, uric acid). However, due to diabetes, they are destroyed and fail to perform their function properly. This leads to the collection of these substances in the blood and thus an imbalance in kidney function and the occurrence of diabetic complications, including diabetic nephropathy, which is considered one of the main causes of deaths around the world (Alaofi, 2020).

The reason for the decrease in the levels of urea, creatinine, and uric acid is the synergistic effect between the alcoholic extract of the *A. scoparia* plant and insulin (Sajid *et al.*, 2016). The alcoholic extract of *A. scoparia* contributes to improving kidney functions damaged by diabetes, which helps them to better get rid of urea, creatinine, and uric acid, as well as reduce pressure on the kidneys (Ding *et al.*, 2021) by stimulating insulin to reduce the level of glucose in the blood and improving insulin sensitivity, which slows the progression of diabetic nephropathy. The decrease in the levels of urea, creatinine, and uric acid is due to the active role in the rest of the groups of the alcoholic extract of the *A. scoparia* plant and insulin separately in reducing kidney function indicators (Paes *et al.*, 2023). The alcoholic extract of the plant is characterized by the presence of some active compounds such as alkaloids, phenols, and terpenoids that contributed to reducing kidney damage caused by diabetes and reducing the toxic effects of free radicals (Liang *et al.*, 2022).

The MDA level increased as a result of injections with STZ, which led to the induction of diabetes in rats. Diabetes caused an increase in the rate of lipid peroxidation, loss of membrane integrity, and an increase in the production of free radicals, thus increasing the MDA index (Sheweita *et al.*, 2016). Therefore, the concentration of MDA is a good indicator of the occurrence of the process of lipid peroxidation, as the oxidation products of the lipids of the cellular membrane of the cells work to increase the level of fluidity of the beta cell membrane in the pancreas, as the membranes lose their permeability property and disrupt the enzyme receptors. This leads to the disintegration or death of the beta cells (Al-Khatawi *et al.*, 2025). The decrease in the MDA index is due to a synergistic effect of the alcoholic extract of the *A. scoparia* plant with insulin, as they played an effective role in reducing the effects of diabetes by increasing the levels of antioxidants. Also, alcoholic extract is very rich in antioxidant compounds, thus it helps reduce glucose levels in the blood and contribute to reducing the effectiveness of oxidative stress and neutralizing free radicals (Sajid *et al.*, 2016). in addition, alcoholic extract of the *A. scoparia* plant works to inhibit the process of oxidation of lipids in cell membranes as a result of oxidative stress that leads to programmed cell death (Ding *et al.*, 2021).

The decrease in the levels of GSH, SOD and CAT in the second group with diabetes may result from giving STZ that leads to the production of types of free radicals, and then an increase in the level of oxidation and oxidation of fats, proteins, and DNA, as well as a decrease in the level of glutathione reductase (GSH) in the blood plasma, which is the main reason (Idris *et al.*, 2020) of the decrease in the effectiveness of SOD and CAT. Also, STZ has the ability to destroy biomolecules and cause damage, which causes harm and damage to the enzyme superoxide dismutase and catalase by depleting the raw materials involved in building the enzyme, which leads to a decrease in their effectiveness (Nwakuilite *et al.*, 2020), while an increase in antioxidant enzymes was observed in the group treated with the *A. scoparia* extract. This can be explained by the fact that the plant contains biologically active compounds such as phenols and flavonoids that work to build internal antioxidants in the body, including catalase, superoxide dismutase and glutathione, thus they protect cells from oxidative stress by destroying free radicals and inhibiting lipid peroxidation (Waris *et al.*, 2018).

The second group with diabetes showed the presence of histological changes in the kidneys. This may be due to the high levels of glucose in the blood (hyperglycemia), which caused damage to the small blood vessels in the kidneys, leading to their hardening and narrowing, or perhaps to the direct toxic effects of STZ, which caused diabetes and affected the functional and histological structure of the kidneys (Madić *et al.*, 2021). In addition, the high levels of glucose in the blood led to an increase in the formation of advanced glycation end-products (AGEs) that accumulate in the walls of blood vessels and renal tissue, causing damage to the renal tissue and bleeding between cells, perhaps due to the toxic effect of free radicals resulting from STZ. This affects its function and causes the size of the glomeruli to shrink (Qi *et al.*, 2020).

Concerning the group that was treated with the natural extract and insulin, there were slight changes. These changes are attributed to the mutual effect between the alcoholic extract of the *A. scoparia* plant and insulin. This might be explained by the fact that alcoholic extracts contain high concentrations of active compounds such as flavonoids, terpenoids, polyphenols, and others, which possess antioxidant properties and scavenge free radicals, and may have side effects when used (Rahhal *et al.*, 2022). Also, the alcoholic extract of the *A. scoparia* plant contains many biologically active compounds that caused a decrease in the oxidation of lipids in the renal cell membranes and an increase in antioxidants in rats, which contributed to strengthening and improving the structure of the renal tissue (Ding *et al.*, 2021).

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