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Original Research Article

Effect of quercetin on parenchymatous organ of the alloxan induced diabetes in male rats

Rizgar Khalid Nabi, Mahdi Ali Abdullah*

Department of Pathology, College of Veterinary Medicine, Duhok, Iraq

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***Correspondence:**
Dr. Mahdi Ali Abdullah,
E-mail: mahdi.ali@uod.ac

ABSTRACT

Background: Diabetes is directly involved in oxidative stress production. Therefore, this work was conducted to investigate the histopathological changes which occur in parenchymatous and to evaluate the antioxidant effect of quercetin in alloxan induced diabetes in male albino rats.
Methods: Thirty-six male albino rats were divided into six groups of 6 rats in each group and treated as follows: a control group, quercetin group, diabetic control group, diabetic with quercetin group, diabetic with insulin group, diabetic with quercetin plus insulin group, alloxan was administered as a single dose (140 mg/kg body weight) to induce diabetes.
Results: Result showed histopathological changes which included degenerative to necrotic changes of the liver, kidney and pancreas and this are due to the effect of oxidative stress that occurred from diabetes by alloxan. Conversely, quercetin significantly modulated improved histopathological changes founded on this study with or without of insulin, furthermore, results showed that damaged tissues where improved when groups of rats treated with quercetin and insulin together.
Conclusions: It has been concluded that the quercetin could be promising antioxidants for reducing the risk of oxidation induced by diabetes that lead to nephrotoxicity, hepatotoxicity and pancreatic damage.

Keywords: Quercetin, Insulin, Diabetes, Rats, Alloxan

INTRODUCTION

Diabetes mellitus (DM) is highly concerned with the lifestyle of the people, their economic changes worldwide, according to the World Health Organization (WHO) states. Over the last years the number of diabetic patients worldwide will increase to 200 million and by the year 2025.[1] There are several predisposing factors help in the development of DM. The experimental evidences propose the involvement of free radical/ROS (reactive oxygen species) in the pathogenesis of diabetes and development of diabetic complications.[2,3]

Several researchers have proposed that free radicals take part in the cell damage produced by alloxan. Alloxan, a chemical diabetogen, is reduced in the presence of glutathione via the alloxan radical into dialuric acid. During this redox cycling process, reactive oxygen species are formed that destroy beta-cells in islets of Langerhans.[4] Moreover, it is suggested that transitional metals such as iron, zinc and copper may be involved in alloxan toxicity.[5] Furthermore, it is well known that alloxan administration causes severe necrosis of pancreatic beta-cells.[6]

Recently, natural plant compounds are becoming attractive as therapeutic agents against diabetes because

they have fewer side effects than currently used diabetes drugs. Among them, quercetin is naturally occurring flavonoids that is found in food items such as fruits and vegetables. These compounds have been reported to have many beneficial effects, like it has been proven to be a potent anti-diabetic agent with an antioxidant and anti-inflammatory profile.[7,8] Furthermore, anti-oxidative, antihypertensive, anticancer, antiviral and hepatoprotective activities.[9,10] Also can prevent oxidant injury and cell death by several mechanisms, such as the scavenging of oxygen radicals.[11] Because complication and widespread of diabetes mellitus as well as limited information about plants which used as antioxidant; Therefore, the aim of this study is to evaluate the anti-diabetic activities of quercetin in alloxan induced diabetic rats.

METHODS

Study area

This study was conducted at college of veterinary medicine, department of pathology and microbiology, university of Duhok from September 2019 to April 2020.

Induction of diabetes

The rats were fasted during the night and diabetes was generated by a single subcutaneous (SC) injection of a recently prepared solution of alloxan 140 mg/kg body weight in 0.9% NaCl saline solution (6 ml/kg) into all the rats, according to weight excluding the quercetin and control groups in order to induce diabetes.[12]

72 hours after injection of alloxan, the rats with moderate diabetes, having glucosuria and hyperglycaemia (blood glucose level range above 250 mg/dl) and the urine was examined regularly by URIPATH strips (IVD, PLASMATEC, UK) to confirm the occurrence of diabetes and to determine the presence of glucose in urine.[13]

Animals and experimental protocol

Thirty-six male albino rats, weighting 200-300 gm were used in this study; they were obtained from and maintained in the college of veterinary medicine university of Duhok, rats are under conditions of controlled temperature. Rats were fed commercial pellets and tap water.

The rats were divided into 6 groups, each group (6 rats) and treated as follows: Group I (C): Normal control rats were administered standard pellets and water for 30 days, Group II (Q): Quercetin control rats. In which the rats received Q (50 mg/kg in 6 ml distilled water) by oral gavage once daily until last of the experiment, Group III (D): Diabetic control rats. They were induced diabetes with 140 mg/kg S.C. Injection of alloxan with feed and water for 30 days, Group IV: Diabetic with quercetin (DQ): in which diabetes was induced and then treated with quercetin in a daily dose, Group V: Diabetes with Insulin (DI): in which diabetes was induced in the rats and received insulin in a daily dose of 3 IU/rat SC, Group VII: Diabetes with quercetin plus Insulin (DQI):(in which diabetes was induced and treated with both insulin and quercetin with the same above dose. Treatment begun after 48-72 hours of induction of diabetes and confirmation of the occurrence of persistent hyperglycaemia.

Histopathological study

For microscopic evaluation, the samples from the liver, kidneys and pancreas were firstly fixed in neutral phosphate buffered formalin solution (10%). After dehydration by using ascending series of ethanol start from (70, 80, 96, and 100%), then the samples of tissues were cleared by using of xylene and embedded in paraffin at melting point 56^0 C. Tissue sections (5 µm) were cut by microtome and then stained with hematoxylin-eosin (H-E).[14] The tissue section was examined and photographed by using of digital camera.

Ethical consideration

All the experiments were conducted following the approved by the responsible of the college of veterinary Medicine, university of Duhok with highest standard for the human and compassionate use of animals in biomedical research.

RESULTS

The effects of quercetin on alloxan-induced histopathological changes in the liver

The liver section from control rat and quercetin groups showed the normal histological structure of hepatic lobule and portal vein without alterations (Figure1A).

The liver tissues section in diabetic rats showing activation of kupffer cells, severe vacuolation in the cytoplasm of hepatocytes, sinusoidal leukocytosis, and apoptosis of hepatocytes with nuclear changes (Figure1: B), as well as marked dilatation, congestion of central vein, fibrosis and leukocytic infiltration around the central vein (Figure 1C).

However, liver tissues in diabetic rat treated with Q showing slight degenerative changes of hepatocytes, moderate dilatation and congestion of central vein with focal aggregation of mononuclear inflammatory cells and apoptosis (Figure 1E).

While staining section of liver tissues from diabetic rats treated with insulin showed moderate fatty changes of hepatocytes, mild dilatation and leukocytosis of sinusoids, activation of kupffer cells, binucleation of

hepatocytes and slight congestion of central vein (Figure 1F).

Meanwhile, in diabetic rats treated with both Q and insulin, the examined liver sections showed more activation of kupffer cells, limited fibrosis, no necrosis, normal appearance in radiating plates of strands of hepatocytes and slight congestion with slight infiltration of inflammatory cells around the central hepatic vein (Figure 1D).

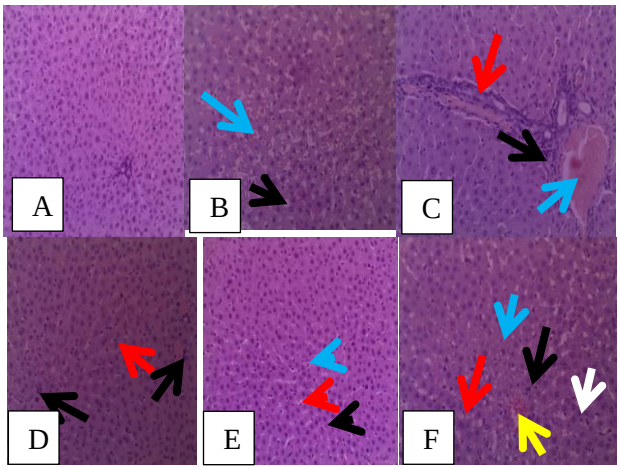

Figure 1: Histopathological changes of liver rats (A-F H and E 20X). (A) Control and quercetin groups of normal hepatic architecture with normal hepatocyte morphology, (B and C) diabetes liver rats with alloxan of sever vacuolation in the cytoplasm of hepatocytes as a fatty degeneration (black arrow) and sever sinusoidal dilatation and hemorrhage (blue arrow) with marked fibrosis (red arrow) and leukocytic infiltration around the central vein (black arrow) with congestion (blue arrow), (D) diabetes liver rats with insulin and quercetin of slight normal appearance in radiating plates of strands of hepatocytes (red arrow) and slight congestion with infiltration of cells around central hepatic vein (black arrow), (E) diabetes rats with quercetin of slight degenerative changes of hepatocytes (red arrow), moderate dilatation and congestion of central vein (black arrow) and apoptosis (blue arrow), (F) diabetes liver rats with insulin of moderate fatty changes of hepatocytes (red arrow), mild dilatation, leukocytosis of sinusoids (black arrow), activation of kupffer cells (white arrow), apoptosis of hepatocytes (blue arrow) and slight congestion of central vein (yellow arrow).

The effects of quercetin on alloxan-induced pathological changes in the pancreas

Section from pancreas of diabetic rats treated with alloxan showed irregular outline structure of islet of pancreas with prominent hyper plastic islet, shrunken and atrophy of islets of langerhan's of pancreas with degenerative and necrotic changes especially in the center as well as cystic dilatation of pancreatic duct with dilatation of interlobular duct beside proliferation of fibrous connective tissue around the dilated irregularly rounded interlobular pancreatic duct. In other hand, in diabetic rat's results observed more than one islet and more than one dilated interlobular duct were frequently present within a single pancreatic lobule. (Figure 2A and B).

While sections of pancreas from diabetic rats treated with Q, results showed reduction in vacuolation and lesions, and an expansion of pancreatic islets as well as identifiable pancreatic islets were clearly observed beside that, there was no evidence of inflammatory cell infiltration or fibrosis. In other hand result observed an improvement of pancreatic structure with both portion exocrine and endocrine, beside normal islet of pancreas and the border between exocrine and endocrine portions became distinct (Figure 2C).

The histopathological observation from pancreas of diabetic rats treated with insulin, results showed an improved of pathological changes which are represented by an irregular outline structure of islet of pancreas with moderate degenerative, necrotic changes of cell composed especially in the center and congestion blood vessels beside moderate fibrosis of pancreatic duct, further more results showed that most of acinar cells appears as normal after (Figure 2D).

The clear improved of pathological changes founded from section of diabetes pancreatic rats when rats received both of Q and insulin together represented by an increase in the cellular density along with a reduction in the inflammatory cells infiltration inside the islet as well as there were more activation of beta cells, some ducts were noticed near islets with some cellular connection observed nearly regular outline and normal cell morphology of pancreatic tissue with mild fibrosis of pancreatic duct with dilatation compared to control groups respectively (Figure 2E and F).

The effects of quercetin on alloxan-induced pathological changes in the kidney

The normal kidney tissue section of the control rats demonstrated normal structure of glomerulus surrounded by the Bowman's capsule, distal convoluted tubules and proximal without any inflammatory alterations while the group of rats was treated with Q alone demonstrated slight normal structure of renal tissues with mild degeneration and congestion of renal tubules without fibrosis (Figure 3F).

As shown in (Figure 3A and B) the diabetic kidney rats sections showed severe pathological changes characterized by present of degenerated glomeruli with infiltrated of inflammatory cells and a thickening of its basement membrane. The proximal convoluted tubule exhibited oedematous changes with deposition of hyaline

substances. Furthermore, mesangial expansion, glomerular hypertrophy and severe cell swelling of most of renal tubules with narrowing of its lumen as well as congestion of renal veins and capillaries between renal tubules with infiltration of mononuclear inflammatory cells.

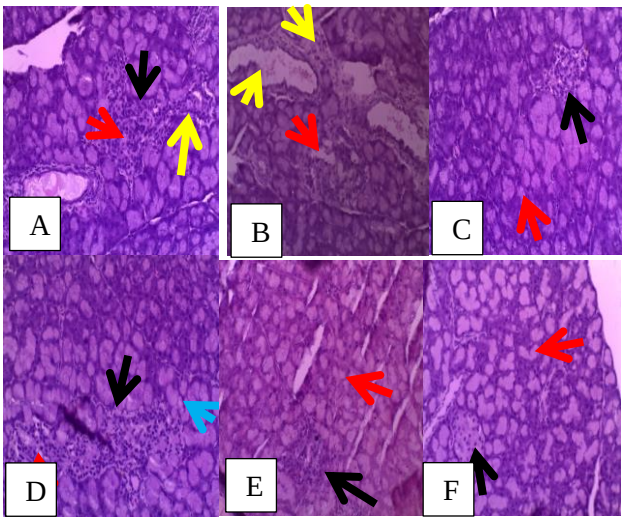

Figure 2: Sections of pancreatic rats (A-F H and E 20X). (A) Diabetes pancreatic rats with alloxan of irregular outline structure of islet of pancreas with prominent hyperplastic islet (black arrow) with degenerative and necrotic changes of cell composed especially in the center (red arrow) and sprouting of a new islet from a preexisting one (yellow arrow), (B) prominent degenerative changes as clears as vacuolation (red arrow), dilatation of pancreatic duct with fibrosis (yellow arrow), (C) diabetes pancreatic rats with quercetin of normal islet of pancreas (black arrow) with normal exocrine portion of pancreas (red arrow), (D) diabetes pancreatic rats with insulin of the irregular outlining of the islet of pancreas (black arrow) with moderate cytoplasmic degenerative changes in islet cells especially in center of the islet (red arrow) and normal acinar cells appears (blue arrow), (E) diabetes pancreatic rats with insulin and quercetin of normal islet of pancreas (black arrow) with normal cell that embedded in exocrine portion of pancreas (red arrow), (F) control and quercetin groups of pancreatic rats of normal islet of pancreas (black arrow) with normal exocrine portion of pancreas (red arrow).

On examining of sections of diabetes kidney rats with Q results showed there was some of glomeruli appears normal, while some others range from enlargement to shrinking as well as moderate degenerative changes of renal tubules with slight infiltration of mononuclear inflammatory cells (Figure 3: C).

The analysis of renal tissue section from diabetes rats received insulin; the changes observed are moderate dilated renal capillaries, hyaline deposits in mesangial area and tubular degenerative changes as well as congesting of renal capillaries (Figure 3D).

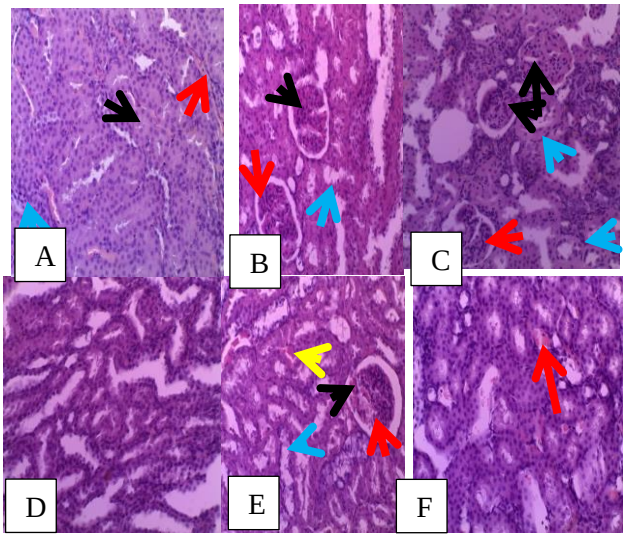

Figure 3: Sections of kidney rats (A-F H and E 20X). (A) Diabetes kidney rats with alloxan of severe cell swelling of most of renal tubules with narrowing of its lumen (black arrow), congestion of renal capillaries (red arrow) and infiltration of inflammatory cells (blue arrow), (B) glomerular hypertrophy with thickening of its basement membrane and mesangial expansion (red arrow), deposition of hyaline substances (black arrow) beside degeneration renal tubules with desquamation and edematous changes (blue arrow), (C) diabetes kidney rats with quercetin of some glomeruli appears normal (red arrow) some others ranges from enlargement to shrinking (black arrow) and moderate degenerative changes of renal tubules (blue arrow), (D) diabetes kidney rat with insulin of moderate glomerular shrinking (red arrow) with accumulation of hyaline substance in mesangial area (black arrow) and tubular degenerative changes (blue arrow) beside congesting or renal capillaries (yellow arrow), (E) diabetes kidney rats with insulin and quercetin of slight normal changes of most of renal tubule, (F) section of control kidney rats and quercetin of normal structure of renal tissues with mild congestion of renal tubules (red arrow).

However, the pathological reactions where enhanced when the rats treated with both of Q and insulin together as shown in (Figure 3: E), decrease of abnormalities represented decreased of expansion of the glomeruli and mesangial matrix as well as decreased the thickening of the basement membrane with more arrangement of the glomeruli and no obvious of inflammation.

DISCUSSION

Diabetes mellitus is the most important and famous heterogeneous metabolic syndrome disease involving the endocrine pancreas. Diabetes mellitus present throughout the world and has been projected to become one of the

world's major disablers and killers within next some years.[15]

Liver of diabetic groups observed sever pathological changes which is varies between groups of study as well as compared to control and quercetin groups, which is similar to the effects observed in previous diabetic animal models.[16] The unorganized hepatocytes, micro vesicular vacuolization, granular degeneration, and necrosis are marked changes observed in the diabetic liver.[17] Moreover, our study clearly similar to other study reported that liver sections of untreated diabetic rats showed degenerative changes in the hepatocytes represented by disorganization of the hepatic cords, congestion of the central veins with mild hepatocellular necrosis and the sinusoids were infiltrated by mild nonspecific inflammatory cells, and the hepatocytes showed pyknosis, karyorrehexis, chromatolysis and cytoplasmic vacuolization.[18] The effective damage of alloxan of the tissues could be attributed to alloxan stimulates H_2O_2 generation, which cause DNA fragmentation and increase oxidative stress in liver and pancreas cells.[19,20]

The improved damage of liver was founded in this study in diabetic rats treated with quercetin and insulin separately which showed slight pathological changes of liver compared to diabetic rats and this are in agreement with previous histological studies have shown that quercetin rescued the liver damage of diabetic rats by increasing the activity of antioxidant enzymes and by scavenging hydroxyl, superoxide, alkoxyl, and peroxyl radicals.[21] Consistent with our findings, the severity of hepatic injuries were clearly decreased with combined treatment of both insulin and quercetin, the result founded no considerable hepatic changes were observed, indicating the protective effect of quercetin against the hepatic complications of diabetes and may be due to decreased the effect of oxidation in liver that occurred by sugar and this are accordance with who showed that insulin has anti-apoptotic action, at least in part, through XIAP induction in rat liver as well as observed that insulin treatment damages the high production of percentage OH generated by the diabetic state in the rat liver.[21-23] The histopathological changes that observed in alloxan- induced diabetic rats presented sever pancreatic tissue damage which this are consistent with the findings obtained by who demonstrated, the pancreas tissues of diabetic rats revealed a reduction in the number of islets, degeneration of beta cells, hydropic degeneration, clumping of beta cells, pyknosis, and necrosis, which caused a change in the morphology of the cells due to the alloxan-induced partial damage of some beta cells.[16,24] In the present study, the islet cells were restored by quercetin, which recovered the degenerated cells as well as recommended that any change to the structure, size, and role of pancreatic islets indicates metabolic changes related to insulin secretion, insulin sensitivity, and loss of glycaemic control.[25]

The moderate degenerative and necrotic changes of pancreatic tissues was founded with rats when treated with insulin and this are agreement with [26] who showed insulin plays a role in the immovability of blood glucose levels and in inhibiting apoptosis. However, our studies observed that when combined administration of quercetin with insulin, causes more functional cells compared with the individual treatment groups, this finding may explain the higher level of insulin that was found.[27] In addition, the quercetin with insulin treatments restore the pancreas histology by alleviating oxidative stress.[28]

One of the major complications associated with diabetes is diabetic nephropathy (DN), which results from the expansion of mesangial cells, a hallmark of diabetic rats, In the current study, the diabetic group showed acute swelling of cells, hydropic degeneration of tubules, widening of Bowman's space, glomerular atrophy, congestion of capillaries, and tubular necrosis.[29] The severe pathological changes due to alloxan reagent compared to control and Q group this results are in accordance with who revealed that the accumulation of extracellular matrix protein, the thickening of the glomerular and tubular basement membranes, tubule interstitial fibrosis, glomerulosclerosis, renal endothelial dysfunction, albuminuria, proteinuria, and a reduction in the glomerular filtration rate occurred in diabetic group. Furthermore, they reported that diabetic group showed severe tubular and glomerular alterations.[30,31] Cellular swelling, tubular changes including tubular basal membrane thickening, peritubular infiltration, epithelial desquamation, mesangial matrix expansion within glomerulus and capillary and intracytoplasmic vacuolization were obvious.

The degree of expansion, degeneration and glomerular and tubular changes was reduced in each groups of rats which received of quercetin and insulin compared to diabetic group which is consistent with the results obtained by each of who showed insulin plays a role in the immovability of blood glucose levels and in inhibiting apoptosis and also suggested that tubular and glomerular changes were reduced in quercetin administered groups.[26,32,33] Furthermore, the diabetic rats treated with quercetin demonstrated a recovery of the normal structure of kidney with intact tubules and glomerular epithelial cells.[34,35]

CONCLUSION

It has been concluded that the quercetin could be promising antioxidants for reducing the risk of oxidation induced by diabetes that lead to nephrotoxicity, hepatotoxicity and pancreatic damage**.**

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Ethical approval: The study was approved by the Institutional Ethics Committee

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