



Special Issue:

Emerging and Re-Emerging Animal Health Challenges in Low and Middle-Income Countries

Impact of Empagliflozin on the Kidneys of Male Albino Rats

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Abstract | This study aims to investigate the effect of empagliflozin in Albino rat animal model. The drug is previously known to impact the histological structure of the kidneys of male rats, however, mechanistic insights remained unknown. To investigate generic impact of the drug in animals, 15 adult male rats were randomly divided into two groups. The control group consisted of 5 rats, while the treatment group was divided into two subgroups, each consisting of 5 rats. Diabetes condition was induced in all animals of treatment sub-groups with alloxan with 5 mg/kg concentration of empagliflozin, once daily for 30 days- and the animals of the first sub-group were left untreated. A through examinations showed pathological and histological changes in the group of animals with induced diabetes without treatment, as well as in the group with diabetes and treated with empagliflozin. These lesions were characterized by the intra-glomerular haemorrhage and infiltration of inflammatory cells. It was also noted that there was damage to the epithelial lining of some renal tubules, and separation of the cells lining the tubules and their accumulation in the middle of the renal tubule in most sections. In addition, some sections showed glomerular enlargement, while in other sections it shrank, in addition to cell death inside it and the appearance of narrowing of the lumen of some urinary tubules. Accordingly, empagliflozin has clear effects on the histological structure of the kidneys of male rats with induced diabetes. Taken together, our results highlight the importance of using animal model to address wider health issue and propose the consideration of animals in understanding future molecular mechanisms of diseases.

Keywords | Diabetes mellitus, Alloxan, Kidney, Empagliflozin, SGLT2

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INTRODUCTION

Environmental pollution is one of the biggest challenges humanities is currently facing, and the nature of pollutants impact all environments (air, soil, and water). These pollutants belong to either natural sources or resulting from human and industrial activities (Abbas and Abbas, 2013a). Among all type of pollutions, water pollution is considered the most dangerous and has the most severe impact on the environment and human health.

The main sources of water pollution vary between industrial, agricultural, and household waste. Additionally, toxic chemicals and heavy metals reach waterways and affect their quality (Abbas and Abbas, 2013c). Environmental water pollution poses a major threat to public health and the environment and requires urgent and comprehensive measures to control pollution sources and treat polluted water to ensure the sustainability of water resources for future generations (Khaleel et al., 2022). Therefore, it has become necessary to address this complex and serious

problem by removing these pollutants or at least reducing their concentrations to permissible limits to preserve both the environment and health (Maddodi et al., 2020). There are many methods used in treating contaminated water, including ion exchange, sedimentation, coagulation and flocculation, advanced oxidation, biological methods, electrolysis, advanced filtration, reverse osmosis, adsorption, and others (Abbas et al., 2020). Although these methods have proven their worth in purifying water and removing pollutants, they include several obstacles and drawbacks, including high energy consumption, the need for primary treatment, the availability of special equipment, their inefficiency in treating low concentrations, or the requirements of large areas, among others (Rajaa et al., 2023). Among these methods, adsorption technology has emerged as a useful, efficient and economical method, as it does not require large spaces or special equipment, and its energy consumption is considered low compared to other methods, in addition to its ability to deal with many types of pollutants with high efficiency, especially if media with a large surface area are used, such as activated carbon (Alhamd et al., 2024c) or alumina (Ghulam et al., 2020). However, despite high surface area and advanced efficiency of these materials, their high preparation cost, their need for continuous regeneration and their loss of part of their mass with each regeneration process prompted specialists to search for efficient, successful and economical alternatives (Abbas and Alalwan, 2019). Among these materials were agricultural and industrial wastes as promising alternatives in treating pollutants, as they proved their efficiency as adsorbents in treating heavy elements (Abbas and Abbas, 2013b), dyes (Alwan et al., 2021), hardness (Ibrahim et al., 2021), organic acids (Abbas and Abbas, 2014), inorganic toxins (Alalwan et al., 2020), medicines (Ali et al., 2020a), sour components (Abbas and Ibrahim, 2020), medical drugs (Ibrahim et al., 2020) and difficult components of nutritional enrichment (Abbas, 2015), mixed water contaminants (Ali and Abbas, 2020), not only from water but also from soil (Abbas et al., 2019a) and crude oil (Ali et al., 2021). The most important types of agricultural waste that have been used as successful adsorption media are rice husks (Alalwan et al., 2018), banana peels (Abdullah et al., 2023), watermelon rinds (Abbas and Nussrat, 2020), orange peels (Hasan et al., 2021), lemon peels (Al-Hermizy et al., 2022), mandarin peels (Alhamd et al., 2024b), eggshells (Ali et al., 2020a), sunflower seed shells (Abdulkareem et al., 2023), algae (Abbas et al., 2019b), water hyacinth (Hashem et al., 2021), waste tea leaves (Al-Ali et al., 2023), and tree leaves such as buckthorn (Alhamd et al., 2024a), eucalyptus (Ali et al., 2024), and others. The residues of the adsorption process, which are often toxic (Alalwan et al., 2021), have been utilized through the application of the zero residue concept, as these residues have become raw materials for the preparation of useful materials such as acetone (Abbas et al., 2022b), bioethanol (Hamdi et al.,

2024), or as catalysts (Abbas et al., 2021), nanomaterials (Alminshid et al., 2021), or additives for concrete used in the construction of x-ray rooms in hospitals and medical facilities (Abbas et al., 2022a).

Despite the unlimited potential of adsorption technology, it is sometimes impossible to treat some wastes, including some types of medicines (Hameed and Abbas, 2024). Drugs released from various human activities, whether from hospitals, pharmaceutical industries, or homes, are one of the biggest environmental and health challenges of the modern era. These drugs, when released into the environment without proper treatment, can cause serious negative impacts on humans and wildlife (Abd Al-Latif et al., 2023). Among these impacts are the pollution of groundwater and surface water, which leads to the entry of harmful chemicals into food chains and harming aquatic organisms. Drugs with biologically active effects can lead to the development of antibiotic resistance in bacteria, posing a serious threat to public health (Abd Ali et al., 2024). In addition, some drugs may cause hormonal disturbances in living organisms, and negatively affect ecosystems. Hence, the importance of developing effective strategies for managing pharmaceutical waste and raising community awareness of the importance of safely disposing of unused drugs, in order to protect human health and preserve the environment (Ibrahim et al., 2020). Therefore, the contribution of pharmaceutical industries in reducing the environmental impact by developing safer and more environmentally friendly drugs, and improving production processes, is a sustainable solution to preserve public health and the environment. In order to achieve this goal, drugs must be produced with special specifications that do not affect non-target organs (Abd Ali et al., 2018). This requires studying the effects of these drugs on different organs of the body to determine their effects in model animals. The current study investigates the potential effects of empagliflozin, one of the drugs widely used in the treatment of type 2 diabetes condition, on the kidneys of rat.

MATERIALS AND METHODS

INDUCTION OF DISEASE CONDITIONS IN ANIMALS

Out of total 15 animals, five *Male Rats* were isolated for the control group (without any treatment), and the remaining 10 rats were injected subcutaneously with Alloxan, which is of Indian origin (Afco). The Alloxan was prepared at the time of injection at a full dose of 120 mg/kg of rat weight, where 1 g of alloxan was dissolved in 10 ml of physiological solution. Before inducing diabetes with alloxan, the animals were starved for 24 h, and after injection they were provided with food and allowed to drink a 5% glucose solution to prevent hypoglycemia (Rashid et al., 2013). After 72 hours, the blood sugar level was checked using a German-made Company diabetes device (Accu-Chek) to

confirm the induction of diabetes.

DIVISION AND DISTRIBUTION OF ANIMALS

In this study, a total of 15 white male rats were used, which were housed inside cages in the animal house at the University of Diyala, Department of Biology Sciences, College of Education for Pure Sciences. They were 3-4 months old, and their weight ranged between 167-200 grams of body weight. All animals were then divided into three groups. The first group was the control group, which was given a physiological solution throughout the experiment. As for the second group, it was divided into two secondary groups that were injected with alloxan to induce diabetes. The first secondary group had induced diabetes, while the second secondary group had diabetes and was treated with the drug empagliflozin at a concentration of 5 mg/kg of animal weight, which continued for 30 days, and the amount of the drug that was dosed to the rat used was calculated. according to the Equation 1 (Abd Al-Latif et al., 2023).

$$\frac{x}{D} = \frac{W_{rat}}{1000} \dots (1)$$

x : represents the amount of drug to be injected into experimental animals, measured in mg/kg of body weight, D : The specified dose of the drug is (5) mg/kg body weight, and W_{rat} : Weight of the rat used in the experiment.

After the end of the experiment, all animals were dissected, the organ under study was removed carefully from them, and preparations were made to make histological sections. Formalin solution of 10% was used to preserve the samples for 24 hours, after that they were washed by tap water and finally transferred to a concentration of 70% alcohol to preserve the sample. All steps required to make histological slides were carried out as described in (Suvarna et al., 2013). To stain the slides, Haematoxylin and Eosin stain was used, and samples were examined and photographed using an optical microscope equipped with a digital camera.

RESULTS AND DISCUSSION

The results of the current study showed that in the kidneys of male white rats with alloxan-induced diabetes during the experimental period of 30 days, there were histopathological changes in the kidneys, including congestion of the urinary tubules, the occurrence of severe bleeding between the renal tubules, and the disappearance of the cells lining some of the urinary tubules, which leads to the expansion of the lumen of the urinary tubule. Additionally, oedema was observed in the treated animals (Figure 1).

The results of the study also showed that the kidneys of male white rats with alloxan-induced diabetes suffered from pathological changes, including infiltration of

inflammatory cells. We also notice in the cortex area congestion of blood vessels and an increase in the thickness of the kidney vessel wall (Figure 2).

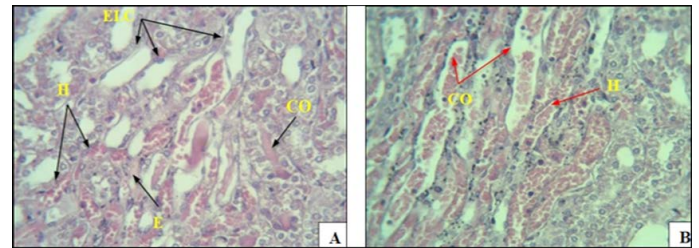


Figure 1: (A) Histopathological section of the kidneys of male rats with alloxan-induced diabetes for 30 days, showing congestion of the urinary tubules CO, hemorrhage H, loss of tubule lining epithelial cells ELC, and edema E. (B) showing congestion of the urinary tubules CO, hemorrhage H (H & E 40x).

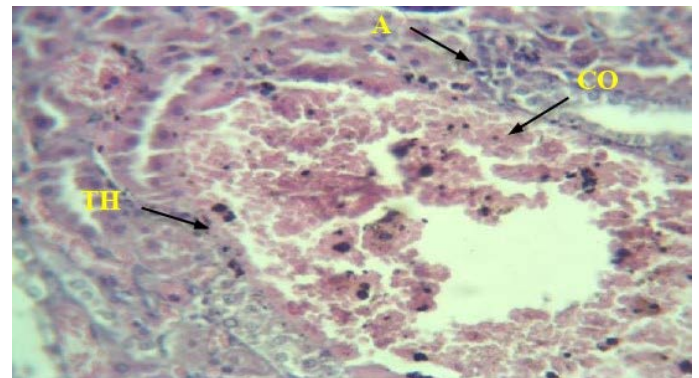


Figure 2: Histological section of the kidneys of male rats in the group suffering from induced diabetes shows vascular congestion. Blood CO, inflammatory cell infiltration A, increased vessel wall thickness in the cortical area TH (H & E 40x).

As the results showed, by making sections and examining them under a light microscope, the occurrence of cellular degenerative damage in the kidneys of male rats with induced diabetes, represented by a narrowing of the lumen of the urinary tubules, especially the proximal tubule, due to the enlargement of the lining epithelial cells, and the appearance of bleeding between the tubules. We also notice the separation of epithelial cells in some tubules and their aggregation. In the middle, necrosis of the lining epithelial cells occurred, and Bowman's area was reduced as a result of the enlargement of the glomerulus and the occurrence of bleeding inside it and the death of some of its cells. Necrosis was observed between the cells of the glomerulus as shown in (Figures 3 and 4).

The results of the current study also showed that the experimental group with diabetes and treated with the empagliflozin drug at a concentration of 5 mg/kg of rat weight for 30 days, pathological histological changes occurred in the kidneys of the rats, represented by

bleeding between the urinary tubules, rupture and necrosis between the epithelial cells lining the urinary tubules, as was observed in most of the tubules. Epithelial cells are grouped in the center of the urinary tubule, (Figure 5).

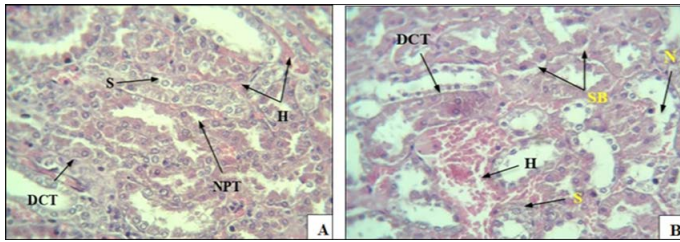


Figure 3: (A): A cross-section of kidney tissue in rats with induced diabetes, showing severe bleeding between the urinary tubules (H), especially the proximal tubule (NPT), swelling (S). (B): Section showing necrosis (N) of the cells of some urinary tubules, swelling (S), separation of cells from the basement membrane (SB), narrowing of the lumen of some tubules collection of separated epithelial cells in the middle DCT tubule, swelling (S), H bleeding (H & E 40x).

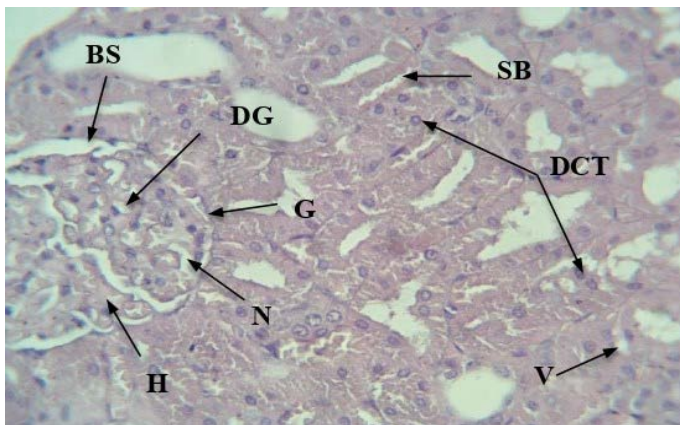


Figure 4: A section of the kidneys of male rats of the experimental group with induced diabetes showing the appearance of histological changes such as glomerular enlargement, intraglomerular haemorrhage (H), narrowing of Bowman's space (NBS), detachment of some epithelial cells (SB), necrosis (intra-glomerulus) (N), death of some glomerular cells (DGC), and accumulation of detached epithelial cells Middle tubule DCT (H & E 40x).

The current results of the study showed that the kidneys of diabetic male rats treated with empagliflozin suffered from negative degenerative changes, including infiltration of inflammatory cells and shrinkage of the glomerulus in some tissue sections, leading to an increase in the Bowman area (Figure 6). An increase in the thickness of some epithelial cell nuclei was observed, in addition to Bowman's capsule wall thickens, bleeding occurs within the glomerulus, rupture occurs between the epithelial cells and necrosis occurs between the glomerular cells, in addition to congestion and bleeding between the urinary tubules, as well as necrosis of the epithelial cells, as shown in.

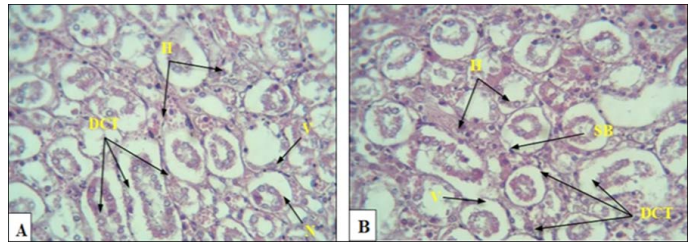


Figure 5: (A): A section showing the changes in the urinary tubules in the cortex area of male rats with induced diabetes and treated with empagliflozin, which are represented by the accumulation of epithelial cells separated from the basement membrane in most of the urinary tubules in the middle of the DCT, N necrosis, H bleeding, V vacule. (B) showing separation of the epithelial cells lining the tubules from the basement membrane SB, H bleeding, V vacule, (H & E 40x).

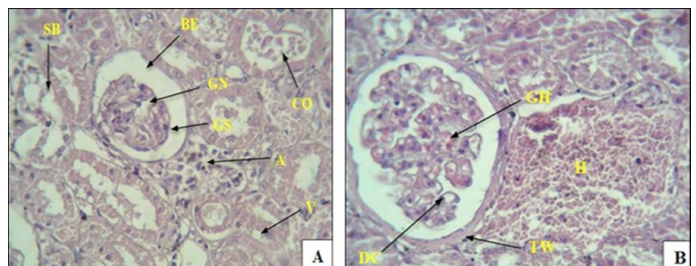


Figure 6: (A): A section of the kidneys of diabetic rats treated with Empagliflozin showing the occurrence of pathological changes in the cortex area, including shrinkage of the glomerulus (GS), widening of Bowman's space (BE). While (B) showing increased capsular wall thickness (TW), glomerular necrosis (GN), intraglomerular hemorrhage (GH), death of some glomerular cells (DC), and infiltration. Inflammatory cells A, rupture V, epithelial cell detachment SB, severe bleeding H, congestion of some renal tubules CO (H & E 40x).

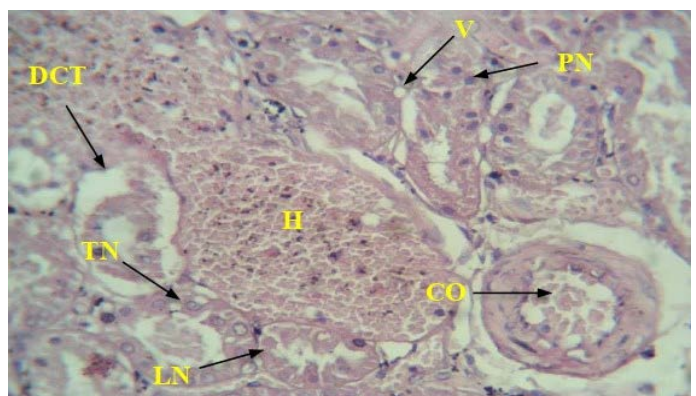


Figure 7: A section showing the kidneys of diabetic rats treated with empagliflozin: CO congestion, severe bleeding (H), loss of nuclei of some cells of the urinary tubules (LN), while thickening of the nuclei occurs in other tubules (PN), in addition to the thickness of the nuclei of some of the epithelial cells lining the urinary tubules (TN), swelling V, Collection of epithelial cells separated from the basement membrane in the tubule lumen DCT (H & E 40x).

The results of the study also showed that there is congestion of blood vessels, severe bleeding, and separation of epithelial cells from the basement membrane. There is also a loss of cell nuclei in some tubules, while in other tubules there is an increase in thickness, and in others we notice their thickening, [Figure 7](#).

Diabetes affects all types of kidney cells, including tubular interstitial cells, foot cells, endothelial cells, and glomerular mesangial cells ([Maezawa et al., 2015](#)). Chronic diabetic patients suffer from poor control or lack of control of the level of glucose in the blood, which leads to a worsening of the disease condition, which results in structural changes in the kidneys. The most common pathological changes are glomerular dilatation, thickening of the basement membrane, fibrosis, and others ([Tang et al., 2021](#)), and these are consistent. With the findings of the current study, diabetes has affected kidney tissue. The concept of diabetes is incurable based on the results of global studies and research, although it can be managed with the help of selected medicines, including traditional and modern medicine ([Alam et al., 2018](#)). The SGLT2 inhibitors are one of the main targets nowadays. These inhibitors-(proteins) responsible for 80% to 90% of glucose reabsorption in the kidney, are used to treat type 2 diabetes and diabetes-related complications such as diabetic kidney disease ([Cai et al., 2021](#)). Empagliflozin is a new class of drugs that has many effects in addition to its hypoglycemic effect. It has been found that this drug shows kidney protective capabilities in diabetic nephropathy, and this depends in part on the inhibition of epithelial-mesenchymal transition (EMT) and abnormal breakdown of sugar in tubular cells. ([Abd Ali et al., 2024](#)). This drug shows antioxidant and anti-inflammatory properties in the kidneys in diabetic rats, as well as the prevention of cardiovascular diseases ([Ibrahim et al., 2020](#)). Since there is an interconnection between the tissues of both the kidneys and the heart, it occurs when taking the drug empagliflozin meets metabolic requirements by improving cardiac capacity and thus leads to improvement of kidney tissue via the neurohormonal system ([Abd Ali et al., 2024](#)). [Ojima et al. \(2015\)](#) have indicated through *in vivo* experimentation that Empagliflozin reduced renal inflammation and oxidative stress and thus works to reduce damage to renal tubular cells. In addition, they found that the drug EMPA has the ability to improve inflammation in patients who suffer from diabetes due to enhanced antioxidant response of leukocytes. Empagliflozin works to inhibit SGLT2, as these inhibitors exert anti-inflammatory methods by inhibiting inflammasome activity, as well as anti-fibrotic effects by stimulating macrophages and inhibiting fibroblast differentiation ([Palmiero et al., 2021](#)) and improve endothelial dysfunction. Empagliflozin works to inhibit SGLT2 and SGLT2 helps protect and strengthen the kidney. This is attributed through glomerular tubular

feedback. These inhibitors, in turn, increase the passage of sodium along the nephron. This increase is sensed by the macula cells to narrow the glomerular afferent arterioles. This results in the reduction of blood flow and thus protects the glomeruli by reducing intraglomerular pressure. The pharmacological effects of SGLT2 inhibitors depend greatly on their pharmacokinetics, especially their distribution and retention in the target organ, which is the kidney.

Empagliflozin was considered to have a moderate effect, based on its pharmacokinetics, pharmacodynamics, and pharmacological results. The results of the current study demonstrated through histological sections obtained from the kidneys of male rats suffering from induced diabetes after dosing them with the drug empagliflozin during the experiment period of thirty days. Many changes occurred in the kidney tissue, as these changes were represented in the tubular and glomerular cells. The reason for this may be due to the accumulation of the drug and its accumulation in the kidneys. The substance alloxan, which induced diabetes in rats, led to severe damage and disruption of kidney function, and this indicates that diabetes. It affects the kidneys directly, which affects the kidney tissues. Since the function of the kidneys is to remove and dispose of medications, minerals, and wastes, the secretion may harm the tissues, tubes, and vessels when these substances pass through them, thus leading to their damage ([Salvatore et al., 2021](#)). It was also observed in the cortex area of the kidneys of diabetic rats treated with empagliflozin, congestion of blood vessels and swelling of their walls. This may be due to the fact that Empagliflozin has a low activity to remove and suppress oxidative stress through suppressing the generation and synthesis of free radicals (ROS) generated by alloxan, which leads to kidney poisoning, and this is what was found in the study, when free radicals interact with cellular materials such as fats, proteins, and nucleic acids, it causes cell damage. It is possible that this actually occurred in our current study, or that the accumulation of the drug may have led to an increase in blood flow to these vessels. This resulted in an inflammatory response in the area of damage and also led to damage to epithelial cells in the renal tubules and glomeruli when compared with the control group ([Pourghasem et al., 2014](#)).

Empagliflozin is also attributed to effect on blood pressure, body mass index, uric acid levels, albuminuria, and hemodynamics within the kidneys. Therefore, the effect of these drugs on blood vessel pressure leads to congestion as a result of the change in pressure, as it was observed in the experimental group with induced diabetes mellitus treated with empagliflozin at a concentration of 2 mg/kg that changes occurred in the form of infiltration of inflammatory cells, which are the result of inflammation or accumulation of drugs. In addition, the drugs may cause

systemic immune reactions, leading to kidney inflammation and injury. It is possible that fibrosis which results from kidney injury may be responsible for attracting immune cells to the kidneys (Kumar et al., 2022). The results also showed the occurrence of bleeding between the renal tubules and edema. It was observed that the epithelial cells lining the renal tubules sloughed off and gathered in the middle of the lumen. An expansion of the glomerular space (Bowman's space) also appeared. This occurs as a result of shrinkage of the glomerulus due to its being affected by diabetes or as a result of drug accumulation or is due to the death of some of its cells, as happened. Necrosis of cells in some renal glomeruli and some renal tubule cells, and this is consistent with the result reported earlier (Kumar et al., 2022), where it was shown that the occurrence of these changes correlated to the inhibitory effect of SGLT2 on the kidneys.

CONCLUSIONS AND RECOMMENDATIONS

Treatment of male rats with induced diabetes conditions using the drug Empagliflozin, ameliorate oxidative stress and inflammation and improve a small part of the kidney dysfunctions and functions caused by diabetes. It is considered one of the SGLT2 inhibitors, which works to balance and reabsorption of glucose. In the kidneys as well as improving insulin sensitivity in rats. Our results highlight the importance of using animal model to address wider public health issue and propose the application in understanding molecular mechanisms in future.

AUTHOR'S CONTRIBUTION

All authors contributed equally.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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