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Sitagliptin Mitigated Cyclosporine-Induced Renal Oxidative Stress, Apoptosis and Histopathological Alterations

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Abstract

Aim: Cyclosporine A (CsA)-induced nephrotoxicity remains an important issue in modern immunosuppressive treatment. Sitagliptin, an established diabetic treatment, has shown promise due to its antioxidant, anti-inflammatory, and tissue-protective qualities. The goal of this study was to examine sitagliptin's potential nephroprotective efficiency in decreasing cyclosporine-induced kidney damage and to clarify the mechanisms underlying its protective effects.

Methods: Adult male rats were assigned to four experimental groups: Group 1 (Control) got the vehicle; Group 2 received cyclosporine (CsA); Group 3 received sitagliptin; and Group 4 was given both CsA and sitagliptin. Blood levels of urea, creatinine, and cystatin-C (CYS-C) were measured. Additionally, renal oxidative stress indicators such as MDA, CAT, SOD, and GSH were assessed. Kidney tissue samples underwent histological investigation.

Results: We revealed that sitagliptin reduced CsA-induced increases in serum urea, creatinine, cystatin-C, and renal MDA while preventing CsA-induced decreases in renal CAT, SOD, and GSH. It mitigated the enhanced degenerative renal tissue damage induced by CsA.

Conclusion: Sitagliptin may protect the kidneys from CsA-induced damage by reducing inflammation and oxidative stress while also boosting antioxidant defenses.

Introduction

Cyclosporine A (CsA), an immunosuppressive agent, is employed in solid organ transplantation to avert rejection of the transplanted organ. CsA is also employed in the treatment of autoimmune disorders, including rheumatoid arthritis and psoriasis (1–3). Nonetheless, the renal impairment associated with CsA is a major adverse effect that limits its application in medical situations (4). CsA-induced renal injury is characterized by the accumulation of inflammatory cells, damage to kidney tubules, arteriolopathy, increased immunogenicity, and tubulointerstitial fibrosis (5). Various pathways contribute to CsA-induced kidney injury, with oxidative stress being a major factor in the initiation and worsening of the illness. The increased production of reactive oxygen species (ROS), together with ensuing oxidative damage and lipid toxicity, are the principal indicators of kidney damage associated with CsA. In this context, reactive oxygen species (ROS) levels were increased in human kidney mesangial cells subjected to cyclosporine A (CsA) treatment

(7,8). Research indicates that oxidative stress, specifically superoxide (O2), a potent free radical produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-1 (NOX1) in the kidneys, may contribute to renal damage (9&10). Furthermore, studies indicate that hypertensive persons receiving CsA medication exhibit increased plasma hydroperoxide levels (2,10). Furthermore, LLC-PK1 tubular cells have demonstrated diminished levels of renal antioxidants, including reduced glutathione (GSH) (2&11). The mechanisms underlying CsA-induced kidney impairment are intricate, with inflammation significantly contributing to the deterioration of the condition (12&13). Inflammation is typically viewed as a defensive reaction that aids in removing harmful agents and provides time for tissue recovery. Conversely, heightened inflammation and the creation of pro-inflammatory cytokines like TNF-α and IL-1β have been associated with more severe kidney damage. CsA therapy has been demonstrated to enhance TNF-alpha mRNA levels, raise the count of dendritic cells, and augment the expression of MHC class II antigens (1&14). By increasing the production of inflammatory substances such as TNF-α and TGF-β, cyclosporine may damage kidney tissues. In lupus nephritis, TNF-α enhances the production of chemokines and cytokines, activates innate immune responses, and aids in the development of dendritic cells (15&16). TNF-α is a cytokine that exhibits multiple functions and is both pro-inflammatory and immunomodulatory. It can cause tissue injury by initiating an inflammatory response. A significant factor in the expression of pro-inflammatory genes such as cytokines, the nuclear factor-kappa B (NF-κB) pathway is regarded as a crucial pro-inflammatory signalling pathway. Chemokines and adhesion proteins (17). CsA therapy led to elevated levels of iNOS and NF-κB in the kidneys (18). DPP-4 inhibitors have been demonstrated to decrease protein levels in urine by alleviating kidney inflammation in individuals with diabetes. Numerous studies have been conducted to determine whether analogous effects might occur in kidney diseases that are not related to diabetes. These studies demonstrated that DPP-4 inhibitors substantially reduce protein levels in urine without impacting glucose metabolism, evidenced by enhancements in various kidney inflammation markers (19&20). Sitagliptin was the inaugural DPP-4 inhibitor sanctioned by the US FDA for managing type 2 diabetes, receiving approval in 2006. Clinical research has shown that sitagliptin is well tolerated, has a minimal risk of inducing low blood sugar, does not significantly affect body weight, and can be used by those with chronic kidney disease (21&22). Due to its anti-inflammatory and anti-apoptotic properties, sitagliptin could play a crucial role in slowing the progression of diabetic kidney disease (DN) (23&24). Moreover, sitagliptin enhanced renal health and alterations in tissue, reduced inflammation, oxidative stress, remodeling of kidney tissue, and scarring, while activating the PI3K/AKT pathway, underscoring its protective role on kidneys in different rat models of diabetic kidney disease (25–27). Studies have shown that sitagliptin possesses protective, antioxidant, and anti-inflammatory properties. Consequently, it can mitigate the detrimental impacts of deltamethrin on the kidneys by eliminating free radicals and functioning as a potent antioxidant. (28). Furthermore, sitagliptin demonstrated considerable protection against kidney damage produced by methotrexate (29), gentamicin (30), acute ischemia-reperfusion injury (31&32), and adenine-induced kidney disease in rats (33). This study aimed to examine the potential protective benefits of sitagliptin against CsA-induced kidney injury and to obtain a more comprehensive understanding of the underlying mechanisms. The efficacy of the selected drug and the extent of kidney injury were evaluated through biochemical, pathological, and protein expression investigations.

Material and Methods

Animals

The study comprised 24 adult male Wistar albino rats, each of which weighed 200±20 g. In a laboratory that consisted of a 12-hour light and 12-hour dark cycle, as well as standard temperature and humidity levels, the rats were permitted to adjust to their new environment for a period of 10 days. They were granted unlimited access to water and food. The National Research Council's Guide for the Care and Use of Laboratory Animals was adhered to in all experimental methods and animal welfare practices, and the Beni-Suef University (BSU-IACUC) Faculty of Pharmacy's Research Ethics Committee granted approval (approval number 022-360).

Drug and Chemicals

We bought hesperidin, sitagliptin, and cyclosporine from Sigma-Aldrich in St. Louis, Missouri. The study's other chemicals were all analytical grade.

Animal Trial:

A total of four separate categories were assigned to the six animals who were a part of the experiment. In Group 1 (G1), the vehicle was given to the rats being used as controls for a period of fourteen days. Over the course of seven days, rats in Group 2 (G2) were given an intraperitoneal injection of CsA at a dose of 25 mg/kg/day (1&34) in a stock solution of saline. A total of fourteen days were spent giving rats in Group 3 (G3) a dosage of sitagliptin that was mixed with saline and supplied orally at a rate of thirty milligrams per kilogram each day. There are 35 and 36. In the same way as was stated before for Group 4 (G4), CsA and sitagliptin were given to rats in the same environment. Seven days before to beginning CsA therapy, sitagliptin was administered, and each of the two treatments continued for an additional seven days between them. While the individual was under intraperitoneal pentobarbital anesthesia (35 mg/kg), blood was drawn from the retro-orbital plexus without the use of heparinized tubes. This was done immediately after the experiment. The serum was separated by centrifugation at a speed of 4000 revolutions per minute for a period of five minutes after the blood samples had clotted for a period of thirty minutes. After the serum was collected, it was transferred to a freezer at a temperature of -80 degrees Celsius for further analysis. Immediately after the cervical dislocation that was used to kill the animals, the kidneys were extracted and washed three times with ice-cold normal saline. During the preparation of the left kidneys, 500

mg of tissue was crushed in 5 mL of phosphate buffer with a concentration of 0.1 M and a pH of 7.4. In order to conduct biochemical analysis, the supernatants that were produced from the centrifugation of the homogenates have been collected and kept at a temperature of -80 degrees Celsius. In preparation for immunohistochemical and histological testing, the right kidneys were fixed with neutral buffered formalin at a concentration of 10%.

Biochemical analysis:

Serum level of urea and creatinine

To prepare the left kidneys, 500 mg of tissue was crushed and then placed in 5 mL of phosphate buffer with a concentration of 0.1 M and a pH of 7.4. The supernatants of the centrifuged homogenate were collected and kept at a temperature of -80 degrees Celsius for the purpose of conducting biochemical tests. The right kidneys were preserved with 10% neutral buffered formalin so that histological and immunohistochemical investigations could be performed to analyze them.

Serum cystatin C

In accordance with the instructions provided by the manufacturer (Elabscience Biotechnology Co., Ltd., Wuhan, Hubei, China), a Rat Cys-C ELISA reagent purchased from a commercial supplier (Catalogue No. E-EL-R0304) was used in order to determine the levels of cystatin-C in the blood.

Determination of tissue malondialdehyde (MDA)

In renal tissue, MDA, which is a marker of lipid peroxidation, was measured by using a colorimetric technique that was developed by Ohkawa et al. (1979). Following the steps outlined in a kit that is available for purchase (CAT. No. MD 2529, Biodiagnostic, Giza, Egypt) wasa the method that was used to successfully complete the approach.

Determination of glutathione reduced (GSH)

A commercially available reagent (Catalog Number: GR 2511, Biodiagnostic, Giza, Egypt) was used in conjunction with the methodology that was outlined by Beutler et al. (1963) in order to determine the amount of GSH that was present in kidney tissue. This process involves reducing 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) with glutathione (GSH), which results in the production of a yellow chromogen. An absorbance of 405 nm is shown to have a direct correlation with the chromogen intensity, which is directly proportional to the GSH concentration.

Determination of catalase (CAT) activity

The Aebi (1984) technique and a commercial colorimetric reagent (CAT. No.: CA 2517, Biodiagnostic, Giza, Egypt) were employed in this study.

The SOD activity

A total SOD activity was determined by blocking the reduction of nitro blue tetrazolium (NBT) using the xanthine/xanthine oxidase system (43). This was done in order to measure the total SOD activity. In order to create the ethanol phase of the serum, 1.0 milliliters of an ethanol/chloroform combination with a volume-to-volume ratio of 5:3 was combined with an equal amount of the sample that had been centrifuged. One unit of superoxide dismutase (SOD) activity was defined as the quantity of enzyme required to lower the rate of NBT degradation by fifty percent. The SOD activity was measured in terms of protein units per gram. In order to carry out the test, a colorimetric kit that is readily available for purchase was used (Catalog Number: SD 2521, Biodiagnostic, Giza, Egypt).

Histopathological examination

A solution consisting of 40 mL of paraformaldehyde, 125 mL of phosphate buffer (0.2 M, pH 7.4), 37.5 mL of saturated picric acid, 0.5 mg of calcium chloride, 1.25 mL of 25% glutaraldehyde, and distilled water was used to preserve the kidney tissues of each rat. The total volume of the solution was 250 mL. In the beginning, the specimens were fixed with Wrobel-Moustafa for a period of twenty-four hours. After that, they were rinsed three times with seventy percent ethanol for a period of twenty-four hours. First, the specimens were cleaned, and then they were encapsulated in paraffin wax. In order to segment specimens of a size ranging from 5 to 7 µm, a Reichert Leica RM2125 microtome was used. For the purpose of histological evaluation and scoring, the paraffin sections were stained with hematoxylin and eosin (H&E). This was done in order to determine the extent of the degradation and thickness of the glomerular basement membrane.

Statistical analysis

The mean ± standard error is employed to represent the entire dataset. Statistical analyses were conducted using GraphPad Prism 8, employing one-way ANOVA with Tukey's post-hoc test. Statistical significance was established as a p-value below 0.05.

Results

The serum levels of urea and creatinine

Both serum urea (as shown in Figure 1A) and creatinine (as shown in Figure 1B) levels were found to be considerably higher after the administration of CsA in contrast to the control group ($p<0.001$). When compared to the administration of CsA alone, the combination of sitagliptin and CsA proved to be considerably effective in lowering blood levels of urea and creatinine ($p<0.001$). Sitagliptin on its own did not have a significant impact on the metabolic parameters that were being studied, in contrast to the control group that was given the vehicle.

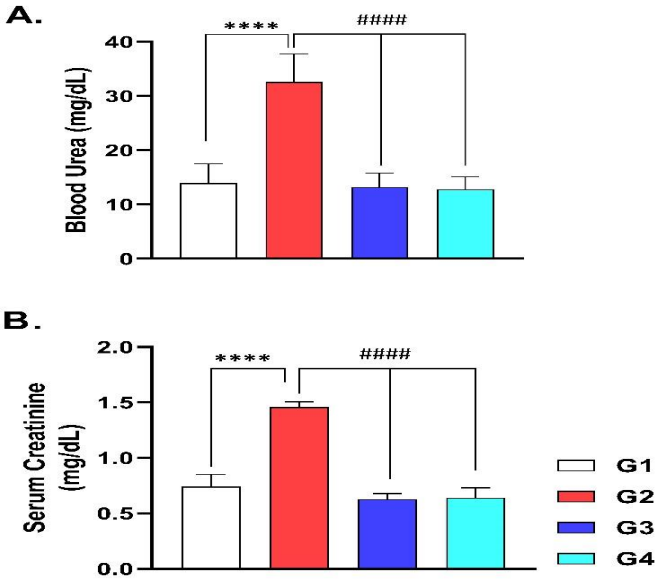

Fig. (1) Creatinine (B) and serum urea (A) levels are impacted by the treatment of sitagliptin and cyclosporine. The data (n=6) is displayed as mean ± SEM. (Groups G1 and G2 represent the control group, CsA-treated rats, Sitagliptin-treated rats, and Sitagliptin + CsA group, respectively). **** ### compared to G2 rats; ### compared to G1 rats ($p<0.0001$).

The levels of serum cystatin-C (CYS-C)

Figure 2 illustrates that CsA therapy resulted in a significant increase in Cystatin-C (CYS-C) levels ($p<0.0001$). Sitagliptin significantly diminished this increase in contrast to animals administered with CsA ($p<0.0001$). Moreover, as illustrated in Figure 2, sitagliptin administration did not yield any significant variations in cystatin-C levels relative to the control group.

Kidney MDA and GSH

MDA, a lipid peroxidation marker, was significantly elevated in the renal tissue of rats treated with CsA in comparison to the control group ($p<0.0001$). (Fig. 3A). The combination of sitagliptin and CsA markedly reduced the CsA-induced elevation in MDA levels in rats ($p<0.0001$) in comparison to CsA administered alone. Furthermore, compared to control rats, CsA therapy significantly lowered renal tissue glutathione (GSH) levels ($p<0.0001$). Figure 3B shows that sitagliptin and CsA co-administration improved antioxidant defense and conserved kidney GSH levels ($p<0.0001$). MDA and GSH levels remained near to normal during this therapy, and sitagliptin had no noticeable influence on them (Fig. 3A, B)

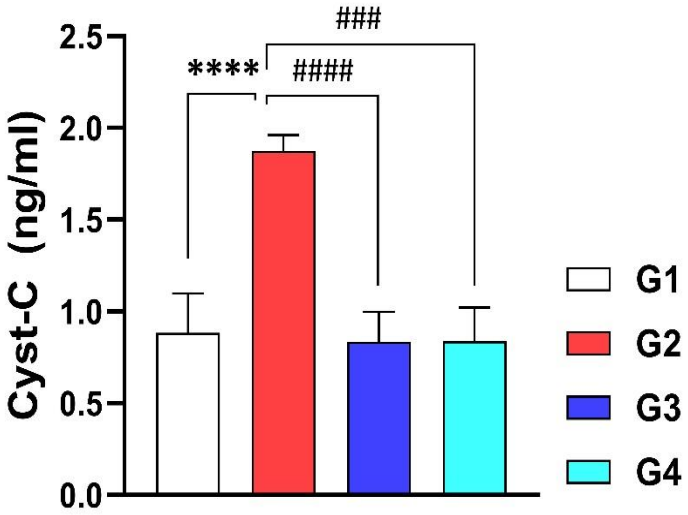

Fig. (2) Impact of cyclosporine and sitagliptin therapy on serum cystatin-C (Cys-C) concentrations. The data is presented as mean ± SEM (n=6). G1 represents the control group, G2 denotes rats administered with CsA, G3 signifies sitagliptin, and G4 indicates sitagliptin combined with CsA. **** ($p < 0.0001$) relative to G1, ### ($p < 0.001$) and #### ($p < 0.0001$) relative to G2.

Kidney CAT activity

The CAT activity of rats that were treated with CsA was found to be significantly lower compared to the activity of control rats that were treated with vehicle (Fig. 3C, $p<0.0001$). A significant preservation of kidney CAT activity was observed when sitagliptin was administered in conjunction with CsA, as demonstrated in Figure 3C ($p < 0.0001$). There was no discernible effect of sitagliptin on the activity of CAT in renal tissues when it was administered alone.

Kidney SOD activity

In the renal tissues of rats that were treated with CsA, the level of superoxide dismutase (SOD) activity was found to be considerably reduced compared to the control group (Fig. 3D, $p<0.0001$). Compared to rats that had renal damage caused by CsA, the treatment of sitagliptin in conjunction with CsA was able to stabilize superoxide dismutase (SOD) activity, ensuring that levels remained at or near normal levels ($p < 0.0001$). As illustrated in Figure 3D, the activity of SOD was not substantially impacted by sitagliptin in comparison to that of control rats.

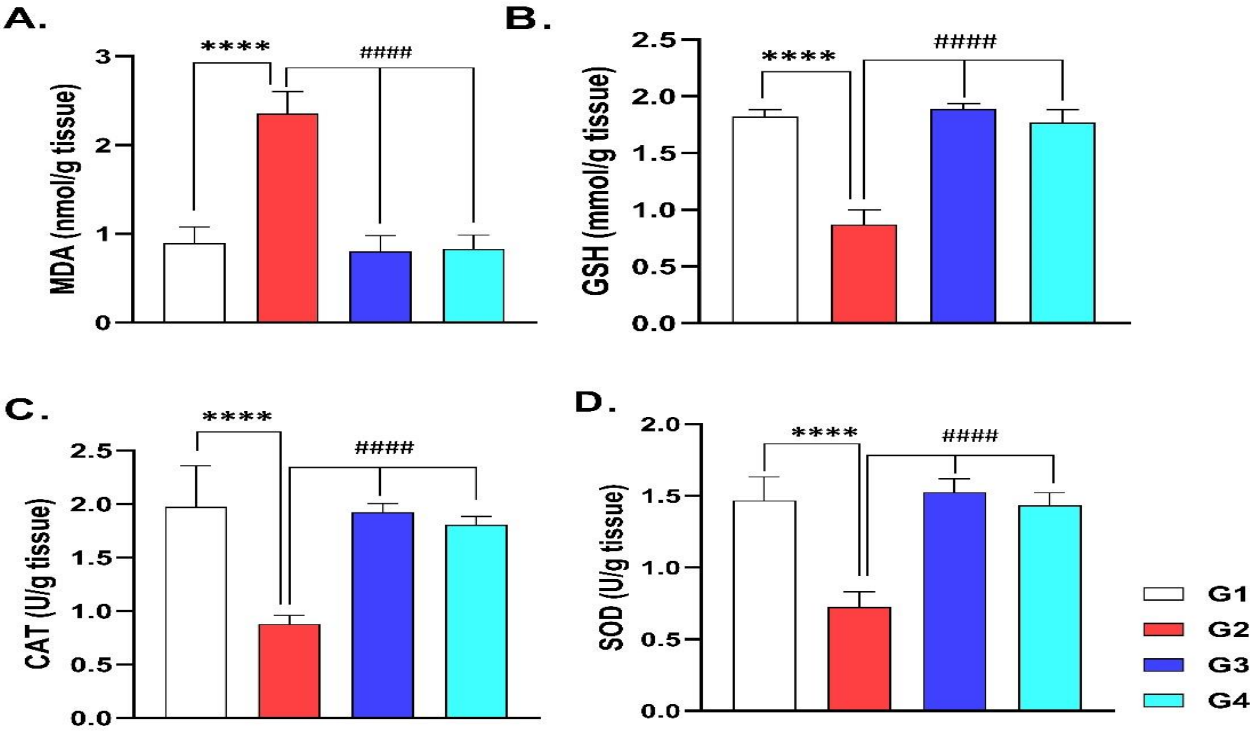

Fig. (3) The effect of CsA and sitagliptin treatment on kidney tissue levels of MDA, GSH, CAT, and SOD. Data are shown as mean ± SEM (n=6). MDA: Malondialdehyde, GSH: Reduced glutathione, CAT: Catalase, SOD: Superoxide dismutase, CsA: Cyclosporine A. (G1=Control, G2=CsA-treated rats, G3=Sitagliptin, G4=Sitagliptin + CsA). **** ($p<0.0001$) shows a significant difference from normal control rats, #### ($p<0.0001$) shows a significant difference from CsA-treated rats.

Histopathological examination

The renal cortex demonstrated normal proximal and distal convoluted tubules, as well as normal glomeruli with an exceptional Bowman's capsule, in photomicrographs of renal slices taken from control rats (Fig. 4). Rats administered CsA showed visible symptoms in their renal cortex slices, including renal corpuscles, reduced Bowmen's space, and

glomerular atrophy. Some tubules' lining epithelium had been destroyed, causing dilation and severe necrosis. The renal tubules demonstrated dilation in addition to the presence of macrophage giant cells, interstitial haemorrhage, vascular congestion, and interstitial inflammatory cells around blood vessels (Fig. 4). These findings were much more visible than in the control mice (Fig. 4). When kidney slices from the other groups were compared to CsA-treated rats, it was discovered that sitagliptin treatment caused no major pathological abnormalities. The development of kidney injury was reduced by sitagliptin and CsA treatment in comparison to the nephrotoxicity group. This effect was more pronounced when sitagliptin and CsA were administered in combination (Fig. 4).

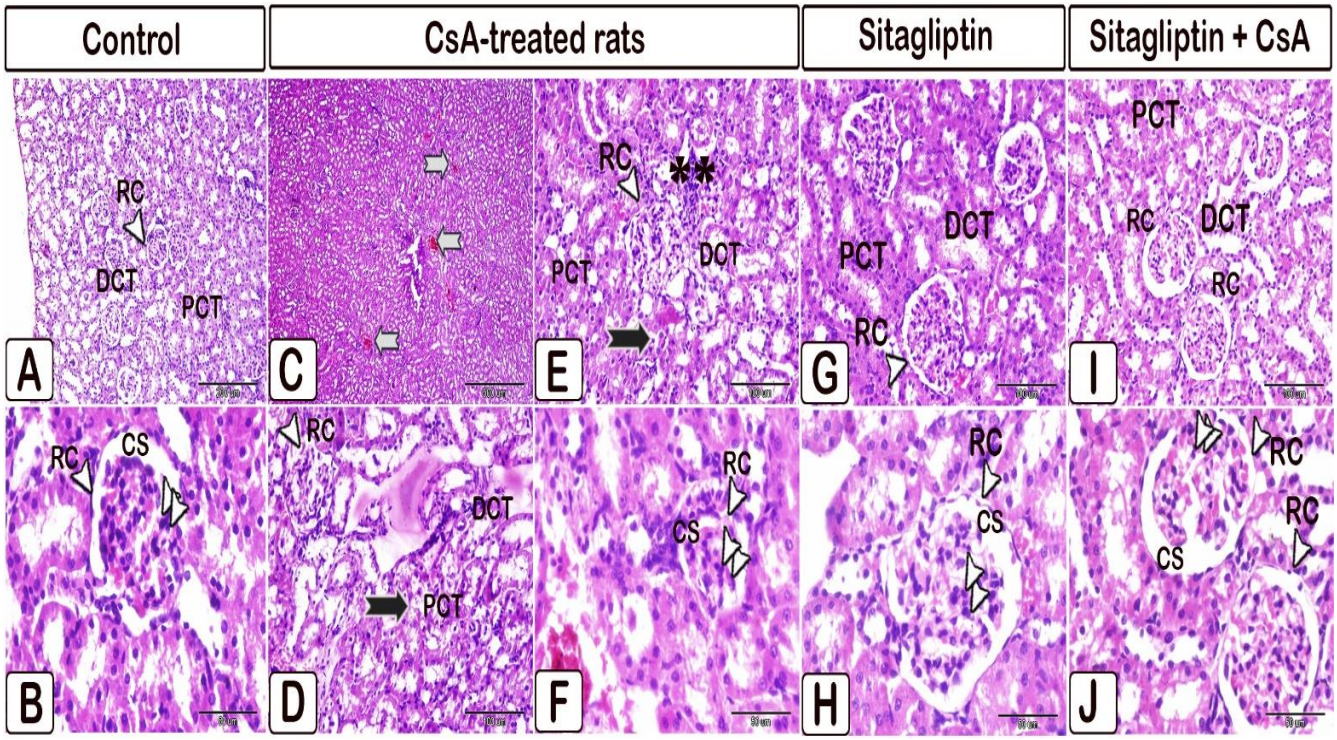

Fig. (4) Paraffin-embedded kidney tissue slices from the control group were photographed using haematoxylin and eosin (HE) staining. A, B: Histological analyses of the kidney tissues from control rats that were given the vehicle revealed that the proximal and distal convoluted tubules, in addition to the renal glomeruli, were all normal. The structural features of the renal corpuscle (RC), which is made up of Bowman's capsules, are distinct and reliable. Proximal (PCT) and distal convoluted tubules (DCT) are present in a normal epithelial cell. It is significant that there are so many glomerular cell nuclei (shown by two arrowheads). The phrase "capsular space" (CS) was used. C, D, E, and F: Typical photomicrographs of kidney tissue paraffin slices from the CsA. congestion of the vascular (white arrows). Inflammatory cell infiltration (**) and tubular degeneration with epithelial cell necrosis (black arrows) are examples of pathological findings. The proximal (PCT) and distal convoluted tubules of the kidney tissue exhibit necrosis. Alongside this necrosis, the capsular space (CS) narrows and the size of the glomeruli within the renal corpuscle (RC, arrowheads) decreases. G, H, I, J: Figures of the kidney cortex of experimental groups 3 and 4 at low and high magnification levels display the typical histological characteristics of renal corpuscles (RC), kidney tubules (PCT and DCT), and a capsular space (CS) that has been recreated inside the cortex to match the control group. It is evident that there are several glomerular cell nuclei (shown by two arrowheads).

Discussion

Cyclosporine A (CsA)'s principal side effect is nephrotoxicity (42). This might show as chronic renal failure or transitory acute kidney damage (43). It includes disorders like interstitial fibrosis and tubular atrophy (44). Numerous strategies have been developed to protect patients with autoimmune disorders and organ transplants from the adverse effects of cyclosporine therapy (3). The specific mechanism of cyclosporine-related nephrotoxicity remains uncertain. Cyclosporine induces oxidative stress, which causes tissue damage via many routes. The initial characterization of the infiltration of inflammatory

cells into the kidneys is an increase in the synthesis and release of inflammatory cytokines and chemokines (45). This is a common component. The present investigation is designed to evaluate the protective effects of hesperidin and sitagliptin on the kidneys of rats in response to cyclosporine. The goal was to discover a novel strategy for maintaining kidney structure and function following organ transplantation or cyclosporine therapy for autoimmune disorders. Rats receiving cyclosporine showed considerably elevated blood levels of kidney-related biochemical indicators, such as urea and creatinine, which validates findings from previous research using cyclosporine to cause kidney injury in experimental animals (19,46&23). Cyclosporine considerably raised blood creatinine (Cr), blood urea nitrogen (BUN), and urine protein levels while dramatically decreasing serum albumin levels (48&49). Animals fed CsA had increased neutrophil infiltration, which was connected to greater tissue levels of the enzyme MPO. The spike in MPO activity shows that inflammatory leukocytes are present in the kidneys, causing structural damage to the renal tissue (50). Daily dosages of CsA caused a marked deterioration in kidney function, as seen by higher blood creatinine, urea, and cystatin C levels (51). Our data showed that cyclosporine-A therapy significantly increased renal MDA levels and decreased renal GSH, as well as elevated serum Cyst-C levels, indicating compromised kidney function compared to control rats. Other investigations have revealed a considerable increase in oxidative markers in the renal tissues and serum of cyclosporine-treated mice compared to controls (52&53). Cyclosporine-A-induced kidney impairment was validated by substantial alterations in renal function tests, oxidative stress indicators, and renal histology. Administering CsA to rats caused a significant disturbance in redox equilibrium, as evidenced by an increase in the lipid peroxidation marker MDA and a reduction in tissue antioxidants, including GSH and SOD. CsA's effects are thought to stem from altering mitochondrial oxidative phosphorylation, which causes an increase in ROS generation (2&8). Cyclosporine-A elevates reactive oxygen species (ROS) production across several cell types, disrupting oxidative equilibrium, diminishing antioxidant levels, and enhancing lipid peroxidation (11&55). The antioxidant enzymes SOD and GSH-Px serve as the principal defense against oxidative damage generated by reactive oxygen species (ROS). In order to protect cells from the potentially damaging effects of free oxygen radicals, superoxide dismutase (SOD) is thought to be the primary defense agent. Several more investigations have also shown a decrease in renal tissue SOD activity following CsA delivery (56), and therapy with the SOD mimic tempol was beneficial in halting kidney issues induced by CsA (57). The levels of blood SOD activity were also shown to be lower in rats that were administered CsA (58). CsA administration to test animals resulted in an increase in the amounts of MDA found in kidney tissues and a reduction in the activity of CAT (42). Additionally, the levels of key antioxidant enzymes, such as CAT, SOD, and GPx, were significantly decreased as a result of the treatment with CsA. On the other hand, the levels of MDA and nitric oxide (NO) in the tissue were not affected by the therapy. CsA-treated mice had substantially greater serum creatinine, LDH, BUN, and kidney MDA levels than controls, but lower kidney SOD and GSH levels. Furthermore, CsA has been shown to raise ROS levels in the kidneys, which directly contributes to CsA-induced kidney injury. Growing data suggests that apoptosis is critical to the detrimental effects of CsA on the kidneys (58&59). By inducing oxidative stress, mitochondria-based mechanisms can start cell apoptosis (60). In contrast, rats administered CsA showed mesangial lobulation, a larger capsular gap, and fewer, closely packed glomeruli. As inflammatory cells penetrated the stroma, the tubules exhibited extensive degeneration, localized tubular atrophy, and tubular enlargement (1). Chronic CsA-induced kidney diseases are distinguished by tubule and surrounding tissue destruction. Based on the findings of our research, it was determined that the administration of CsA to rats led to an increase in the oxidative damage that was caused to the kidney tissues. This was shown by the presence of greater levels of MDA and lower levels of GSH, SOD, and CAT. This was connected to a greater inflammatory response and increased cellular infiltration. Tissue structural abnormalities included tubular degeneration, shrinkage, thickening of basement membranes, inflammatory cell infiltration, and modifications in the renal parenchyma.These findings are consistent with previous investigations. The kidneys have the largest quantities of the enzyme DPP-4, which is suppressed by sitagliptin (61). DPP-4 inhibitors improve glucose metabolism and raise circulating GLP-1 levels, resulting in diabetes-fighting benefits (62). When the GLP-1R in blood arteries is activated, smooth muscle relaxes, leading to increased blood flow to the kidneys (63). GLP-1 stimulates GLP-1R in a healthy kidney, causing natriuresis and water loss (64). DPP-4 inhibitor medication increases GLP-1 levels, which has a number of benefits for kidney protection. These include an improvement in glomerular filtration rate (GFR), less inflammation and oxidative stress, better mesangial development, and lower blood glucose and cholesterol levels (65). Sitagliptin's kidney-protective actions against renal ischemia/reperfusion (I/R) damage, including the restoration of normal blood sugar levels, might be due to a variety of processes (66). The results that we obtained from a number of different experimental models, including diabetic nephropathy (67), ischemia-reperfusion injury (31), gentamicin nephrotoxicity (68), and cisplatin-induced nephrotoxicity in mice (69), are in agreement with the findings of other study that have demonstrated the effectiveness of sitagliptin in enhancing kidney function and minimizing tissue changes. In rats, sitagliptin substantially reduced creatinine, cyst-C, and blood urea levels in comparison to the nephrotoxicity group, as evidenced by previous research. The kidney tissues of the CsA-treated group exhibited significantly lower levels of catalase and SOD in comparison to the control group. Nonetheless, the pairing of sitagliptin and CsA significantly enhanced these antioxidant enzymes. Comparable results have been noted in additional studies (70). Sitagliptin provides kidney protection from ischemia-reperfusion injury by mitigating oxidative stress (71). It also improves cardiac mitochondrial dysfunction in insulin-resistant mice (72) and lowers brain mitochondrial dysfunction (73) in the same model (68). In 2K1C animals,

sitagliptin administration was able to restore the elevated plasma levels of oxidative stress indicators, including MDA, NO, and advanced protein oxidation products, to their normal state, which were higher than those of sham-operated mice (74). The administration of sitagliptin resulted in a significant reduction in the amount of total protein excreted in urine, as well as in serum BUN and creatinine levels, in rats that had been treated with gentamicin. Additionally, in contrast to the group that was given gentamicin, sitagliptin was able to restore the levels of GSH, GPx, SOD, CAT, and MDA (68). Likewise, in rats undergoing methotrexate treatment, sitagliptin administration notably reduced lipid peroxidation while boosting kidney SOD, GPx, and catalase activities (29). These results align with previous studies, which demonstrated that sitagliptin decreases MDA levels while enhancing SOD and GSH levels in an ovalbumin-induced asthma model (75). Consequently, sitagliptin might decrease oxidative stress by diminishing ROS production (49). Moreover, sitagliptin lowered the death rate of renal tubular cells induced by gentamicin, as shown by a significant reduction in Bax-positive immunoreactive cells in kidney tissues (68). In comparison to control mice, streptozotocin-induced diabetic mice exhibited substantial renal alterations, such as tubular dilation, mesangial matrix expansion, and tubulointerstitial fibrosis, as evidenced by histological examination. These issues were substantially alleviated by sitagliptin treatment, which reduced morphological damage. Moreover, sitagliptin has demonstrated the ability to restore and preserve renal histological integrity in various acute kidney injury models. Our research demonstrated that sitagliptin effectively addresses kidney toxicity caused by cyclosporine (CsA). Renal function indicators like serum creatinine and blood urea concentrations normalized following the combination of sitagliptin with CsA. In addition, rats that were administered both sitagliptin and CsA experienced a decrease in blood cystatin-C levels when contrasted with those that were administered CsA alone. Through the reduction of lipid peroxidation, sitagliptin was discovered to be able to maintain the oxidant/antioxidant balance of the kidney, as was established by biochemical experiments. Biochemical studies showed that sitagliptin preserved the kidney's oxidant/antioxidant equilibrium by lowering lipid peroxidation, evidenced by reduced MDA levelsby improving the efficiency of essential antioxidant enzymes including catalase and superoxide dismutase (SOD) and by elevating levels of GSH. Histopathological analysis confirmed these results, showing that sitagliptin, given prior to or simultaneously with CsA, significantly diminished kidney injury. The renal tissue exhibited fewer structural problems, including reduced tubular and glomerular damage and minimal inflammatory cell infiltration, when compared with the CsA-only treatment group. This highlights sitagliptin's capacity to enhance renal cell protection against oxidative stress. Sitagliptin has the potential to function as a preventative therapy for kidney impairment that is caused by CsA. This is because sitagliptin has anti-inflammatory, antioxidant, and anti-apoptotic capabilities. These properties maintain the integrity of renal tissue and a virtually normal overall histological structure.

Conclusion

The biochemical and histological analyses conducted in this research indicate that the combination of sitagliptin and cyclo sporine (CsA) offers significant nephroprotection. Sitagliptin effectively safeguarded renal tissues from damage caused by CsA by decreasing oxidative stress and inflammation while i nhibiting apoptosis.

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Conflict of Interest

The authors are under no obligation to disclose any relevant financial or non-financial interests.

Data availability

The corresponding author can provide the datasets created and/or examined during the current study upon reasonable request.

Authorship contribution

Each author contributed to the study's concept and design. B.A.S.M., A.M.A., H.H.A., and S.M.M prepared the materials, collected the data, and conducted the analysis. A.M.A., S.M.M, and H.H.A. composed the manuscript's initial draft. The final editing and review were accomplished by S.M.M, A.M.A., and B.A.S.M.

Ethical approval

The study was approved by the Ethics Committee for Animal Experimentation at the Faculty of Pharmacy at Beni-Suef University (BSU-IACUC) in accordance with the guide for the care and use of laboratory animals published by the National Institutes of Health in the United States (NIH Publication No. 85–23, revised 1996) (Approval Number: 022-360).

References

1.Ateyya H. Amelioration of cyclosporine induced nephrotoxicity by dipeptidyl peptidase inhibitor vildagliptin. Int Immunopharmacol. 2015 Jul 30;28(1):571–7.

2.Wu Q, Wang X, Nepovimova E, Wang Y, Yang H, Kuca K. Mechanism of cyclosporine A nephrotoxicity: Oxidative stress, autophagy, and signalings. Food Chem Toxicol [Internet]. 2018 Aug 1 [cited 2023 May 19];118:889–907. Available from: https://pubmed.ncbi.nlm.nih.gov/29960018/

3.El-Sheikh AAK, Morsy MA, Abdel-latif RG. Modulation of eNOS/iNOS by nebivolol protects against cyclosporine A-mediated nephrotoxicity through targeting inflammatory and apoptotic pathways. Environ Toxicol Pharmacol [Internet]. 2019 Jul 1 [cited 2023 Apr 14];69:26–35. Available from:

https://pubmed.ncbi.nlm.nih.gov/30927701/

4.O'Connell S, Slattery C, Ryan MP, McMorrow T. Identification of novel indicators of cyclosporine A nephrotoxicity in a CD-1 mouse model. Toxicol Appl Pharmacol [Internet]. 2011 Apr 15 [cited 2023 Jul 7];252(2):201–10. Available from: https://pubmed.ncbi.nlm.nih.gov/21354196/

5.Hye EY, Chul WY. Established and newly proposed mechanisms of chronic cyclosporine nephropathy. Korean J Intern Med [Internet]. 2009 [cited 2023 Apr 14];24(2):81–92. Available from: https://pubmed.ncbi.nlm.nih.gov/19543484/

6.Josephine A, Amudha G, Veena CK, Preetha SP, Rajeswari A, Varalakshmi P. Beneficial effects of sulfated polysaccharides from Sargassum wightii against mitochondrial alterations induced by Cyclosporine A in rat kidney. Mol Nutr Food Res [Internet]. 2007 Nov [cited 2023 Jul 7];51(11):1413–22. Available from: https://pubmed.ncbi.nlm.nih.gov/17918168/

7.O'Connell S, Tuite N, Slattery C, Ryan MP, McMorrow T. Cyclosporine A–Induced Oxidative Stress in Human Renal Mesangial Cells: A Role for ERK 1/2 MAPK Signaling. Toxicol Sci [Internet]. 2012 Mar 1 [cited 2023 Jul 7];126(1):101–13. Available from: https://dx.doi.org/10.1093/toxsci/kfr330

8.Vangaveti S, Das P, Kumar VL. Metformin and silymarin afford protection in cyclosporine A induced hepatorenal toxicity in rat by modulating redox status and inflammation. J Biochem Mol Toxicol [Internet]. 2021 Jan 1 [cited 2023 May 19];35(1). Available from: https://pubmed.ncbi.nlm.nih.gov/32886845/

9.Joshi S, Peck AB, Khan SR. NADPH oxidase as a therapeutic target for oxalate induced injury in kidneys. Oxid Med Cell Longev [Internet]. 2013 [cited 2023 Jul 7];2013. Available from: https://pubmed.ncbi.nlm.nih.gov/23840917/

10.El-Naga RN. Pre-treatment with cardamonin protects against cisplatin-induced nephrotoxicity in rats: impact on NOX-1, inflammation and apoptosis. Toxicol Appl Pharmacol [Internet]. 2014 Jan 1 [cited 2023 Apr 14];274(1):87–95. Available from: https://pubmed.ncbi.nlm.nih.gov/24211271/

11.De Arriba G, Calvino M, Benito S, Parra T. Cyclosporine A-induced apoptosis in renal tubular cells is related to oxidative damage and mitochondrial fission. Toxicol Lett [Internet]. 2013 Mar 7 [cited 2023 Apr 14];218(1):30–8. Available from: https://pubmed.ncbi.nlm.nih.gov/23347876/

12.Lee S, Kim W, Kim DH, Moon SO, Jung YJ, Lee AS, et al.Protective effect of COMP-angiopoietin-1 on cyclosporine-induced renal injury in mice. Nephrol Dial Transplant [Internet]. 2008 Sep [cited 2023 Jul 7];23(9):2784–94. Available from: https://pubmed.ncbi.nlm.nih.gov/18463324/

13.Nam HK, Lee SJ, Kim MH, Rho JH, Son YK, Lee SM, et al.Rosuvastatin attenuates inflammation, apoptosis and fibrosis in a rat model of cyclosporine-induced nephropathy. Am J Nephrol [Internet]. 2013 [cited 2023 Jul 7];37(1):7–15. Available from: https://pubmed.ncbi.nlm.nih.gov/23258196/

14.Carlos CP, Sonehara NM, Oliani SM, Burdmann EA. Predictive usefulness of urinary biomarkers for the identification of cyclosporine A-induced nephrotoxicity in a rat model. PLoS One [Internet]. 2014 Jul 29 [cited 2024 Mar 16];9(7). Available from: https://pubmed.ncbi.nlm.nih.gov/25072153/

15.M A, C Z, WB G, P P, G S, W U, et al. TNF is an essential mediator in lupus nephritis | Request PDF [Internet]. Arthritis Rheum. 2002 [cited 2023 Apr 16]. p. 3418–9. Available from: https://www.researchgate.net/publication/230556983_TNF_is_an_essential_mediator_in_lupus_nephritis

16.Ibrahim SRM, Abdallah HM, El-Halawany AM, Mohamed GA, Alhaddad AA, Samman WA, et al. Natural Reno-Protective Agents against Cyclosporine A-Induced Nephrotoxicity: An Overview. Molecules [Internet]. 2022 Nov 1 [cited 2023 Jul 7];27(22). Available from: https://pubmed.ncbi.nlm.nih.gov/36431872/

17.Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol [Internet]. 2009 [cited 2023 May 14];1(6). Available from: https://pubmed.ncbi.nlm.nih.gov/20457564/

18.Magendiramani V, Umesalma S, Kalayarasan S, Nagendraprabhu P, Arunkumar J, Sudhandiran G. S-allylcysteine attenuates renal injury by altering the expressions of iNOS and matrix metallo proteinase-2 during cyclosporine-induced nephrotoxicity in Wistar rats. J Appl Toxicol [Internet]. 2009 Aug 1 [cited 2023 May 13];29(6):522–30. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jat.1437

19.Penno G, Garofolo M, Del Prato S. Dipeptidyl peptidase-4 inhibition in chronic kidney disease and potential for protection against diabetes-related renal injury. Nutr Metab Cardiovasc Dis [Internet]. 2016 May 1 [cited 2023 Apr 19];26(5):361–73. Available from: https://pubmed.ncbi.nlm.nih.gov/27105869/

20.Nicotera R, Casarella A, Longhitano E, Bolignano D, Andreucci M, De Sarro G, et al. Antiproteinuric effect of DPP-IV inhibitors in diabetic and non-diabetic kidney diseases. Pharmacol Res. 2020 Sep 1;159:105019.

21.Arjona Ferreira JC, Marre M, Barzilai N, Guo H, Golm GT, Sisk CMC, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care [Internet]. 2013 May [cited 2023 Jul 7];36(5):1067–73. Available from: https://pubmed.ncbi.nlm.nih.gov/23248197/

22.Plosker GL. Sitagliptin: a review of its use in patients with type 2 diabetes mellitus. Drugs [Internet]. 2014 [cited 2023 Apr 14];74(2):223–42. Available from: https://pubmed.ncbi.nlm.nih.gov/24407560/

23.Mega C, Teixeira-de-Lemos E, Fernandes R, Reis F.

Renoprotective Effects of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin: A Review in Type 2 Diabetes. J Diabetes Res. 2017;2017:5164292.

24.Al-Qabbaa SM, Qaboli SI, Alshammari TK, Alamin MA, Alrajeh HM, Almuthnabi LA, et al. Sitagliptin Mitigates Diabetic Nephropathy in a Rat Model of Streptozotocin-Induced Type 2 Diabetes: Possible Role of PTP1B/JAK-STAT Pathway. Int J Mol Sci [Internet]. 2023 Apr 1 [cited 2023 Jul 7];24(7). Available from: https://pubmed.ncbi.nlm.nih.gov/37047505/

25.Jo CH, Kim S, Park JS, Kim GH. Anti-Inflammatory Action of Sitagliptin and Linagliptin in Doxorubicin Nephropathy. Kidney Blood Press Res [Internet]. 2018 Jun 1 [cited 2023 Jul 7];43(3):987–99. Available from: https://pubmed.ncbi.nlm.nih.gov/29913457/

26.Wang D, Zhang G, Chen X, Wei T, Liu C, Chen C, et al. Sitagliptin ameliorates diabetic nephropathy by blocking TGF-β1/Smad signaling pathway. Int J Mol Med [Internet]. 2018 May 1 [cited 2023 Jul 7];41(5):2784–92. Available from: https://pubmed.ncbi.nlm.nih.gov/29484381/

27.Mohamed RH, Sedky AA, Hamam GG, Elkhateb L, Kamar SA, Adel S, et al. Sitagliptin's renoprotective effect in a diabetic nephropathy model in rats: The potential role of PI3K/AKT pathway. Fundam Clin Pharmacol [Internet]. 2022 Apr 1 [cited 2023 Jul 7];36(2):324–37. Available from: https://pubmed.ncbi.nlm.nih.gov/34735026/

28.Shi W, Zhang D, Wang L, Sreeharsha N, Ning Y. Curcumin synergistically potentiates the protective effect of sitagliptin against chronic deltamethrin nephrotoxicity in rats: Impact on pro-inflammatory cytokines and Nrf2/Ho-1 pathway. J Biochem Mol Toxicol [Internet]. 2019 Oct 1 [cited 2023 May 19];33(10):e22386. Available from: https://pubmed.ncbi.nlm.nih.gov/31454128/

29.Afkhami Fard L, Malekinejad H, Esmaeilzadeh Z, Jafari A, Khezri MR, Ghasemnejad-Berenji M. Protective effects of sitagliptin on methotrexate-induced nephrotoxicity in rats. J Environ Sci Heal Part C, Toxicol Carcinog [Internet]. 2023 Apr 3 [cited 2023 May 19];1–14. Available from: https://pubmed.ncbi.nlm.nih.gov/37010136/

30.Al Suleimani YM, Abdelrahman AM, Karaca T, Manoj P, Ashique M, Nemmar A, et al. The effect of the dipeptidyl peptidase-4 inhibitor sitagliptin on gentamicin nephrotoxicity in mice. Biomed Pharmacother [Internet]. 2018 Jan 1 [cited 2023 May 19];97:1102–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29136947/

31.Chen YT, Tsai TH, Yang CC, Sun CK, Chang LT, Chen HH, et al. Exendin-4 and sitagliptin protect kidney from ischemia-reperfusion injury through suppressing oxidative stress and inflammatory reaction. J Transl Med [Internet]. 2013 Oct 25 [cited 2023 Apr 19];11(1). Available from: https://pubmed.ncbi.nlm.nih.gov/24161164/

32.Chang MW, Chen CH, Chen YC, Wu YC, Zhen YY, Leu S, et al. Sitagliptin protects rat kidneys from acute ischemia-reperfusion injury via upregulation of GLP-1 and GLP-1 receptors. Acta Pharmacol Sin [Internet]. 2015 [cited 2023 Apr 19];36(1):119–30. Available from: https://pubmed.ncbi.nlm.nih.gov/25500876/

33.Abdelrahman AM, Suleimani Y Al, Za'abi M Al, Ashique M, Manoj P, Hartmann C, et al. The renoprotective effect of the dipeptidyl peptidase-4 inhibitor sitagliptin on adenine-induced kidney disease in rats. Biomed Pharmacother [Internet]. 2019 Feb 1 [cited 2023 Apr 20];110:667–76. Available from: https://pubmed.ncbi.nlm.nih.gov/30553193/

34.Tan, Yong Chia et al. "Apocynin and catalase prevent hypertension and kidney injury in Cyclosporine A-induced nephrotoxicity in rats." *PloS one* vol. 15,4 e0231472. 16 Apr. 2020, doi:10.1371/

35.Oz Gul, Ozen et al. "Comparative genotoxic and cytotoxic effects of the oral antidiabetic drugs sitagliptin, rosiglitazone, and pioglitazone in patients with type-2 diabetes: a cross-sectional, observational pilot study." *Mutation research* vol. 757,1 (2013): 31-5. doi:10.1016

36.Goldshtein, Inbal et al. "Urinary albumin excretion with sitagliptin compared to sulfonylurea as add on to metformin in type 2 diabetes patients with albuminuria: A real-world evidence study." *Journal of diabetes and its complications* vol. 30,7 (2016): 1354-9. doi:10.1016/

37.Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem [Internet]. 1979 [cited 2023 Sep 18];95(2):351–8. Available from: https://pubmed.ncbi.nlm.nih.gov/36810/

38.BEUTLER E, DURON O, KELLY BM. Improved method for the determination of blood glutathione. J Lab Clin Med [Internet]. 1963 May [cited 2023 Apr 17];61:882–8. Available from: https://pubmed.ncbi.nlm.nih.gov/13967893/

39.Aebi H. Catalase in vitro. Methods Enzymol [Internet]. 1984 Jan 1 [cited 2023 Apr 22];105(C):121–6. Available from: https://pubmed.ncbi.nlm.nih.gov/6727660/

40.Sun VI, Oberley L, U' V. 497 2Present address: Radiation Research Laboratory, 14 Medical Laboratories, The University of Iowa. Clin Chem [Internet]. 1988;34(3):497–500. Available from: https://academic.oup.com/clinchem/article-abstract/34/3/497/5661714

41.Saleh SMM, Mahmoud AB, Al-Salahy MB, Mohamed Moustafa FA. Morphological, immunohistochemical, and biochemical study on the ameliorative effect of gallic acid against bisphenol A-induced nephrotoxicity in male albino rats. Sci Rep [Internet]. 2023 Dec 1 [cited 2023 Oct 27];13(1). Available from: https://pubmed.ncbi.nlm.nih.gov/36720896/

42.Gokce M, Yuzbasioglu MF, Bulbuloglu E, Oksuz H, Yormaz S, Altnoren O, et al. Cilostazol and diltiazem attenuate cyclosporine-induced nephrotoxicity in rats. Transplant Proc [Internet]. 2012 Jul [cited 2023 Aug

3];44(6):1738–42. Available from: https://pubmed.ncbi.nlm.nih.gov/22841259/

43.Cattaneo D, Perico N, Gaspari F, Remuzzi G. Nephrotoxic aspects of cyclosporine. Transplant Proc [Internet]. 2004 [cited 2023 Aug 3];36(2 SUPPL.):S234–9. Available from: https://pubmed.ncbi.nlm.nih.gov/15041344/

44.Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. N Engl J Med [Internet]. 1984 Sep 13 [cited 2023 Aug 3];311(11):699–705. Available from: https://pubmed.ncbi.nlm.nih.gov/6382005/

45.Yeboah MM, Hye Khan MA, Chesnik MA, Sharma A, Paudyal MP, Falck JR, et al. The epoxyeicosatrienoic acid analog PVPA ameliorates cyclosporine-induced hypertension and renal injury in rats. Am J Physiol Renal Physiol [Internet]. 2016 [cited 2023 Aug 3];311(3):F576–85. Available from: https://pubmed.ncbi.nlm.nih.gov/27358055/

46.Hashemi SR, Arab HA, Seifi B, Muhammadnejad S. A comparison effects of l-citrulline and l-arginine against cyclosporine-induced blood pressure and biochemical changes in the rats. Hipertens y riesgo Vasc [Internet]. 2021 Oct 1 [cited 2023 May 17];38(4):170–7. Available from: https://pubmed.ncbi.nlm.nih.gov/34561200/

47.Adekunle IA, Imafidon CE, Oladele AA, Ayoka AO. Ginger polyphenols attenuate cyclosporine-induced disturbances in kidney function: Potential application in adjuvant transplant therapy. Pathophysiol Off J Int Soc Pathophysiol [Internet]. 2018 Jun 1 [cited 2023 May 17];25(2):101–15. Available from: https://pubmed.ncbi.nlm.nih.gov/29433768/

48.Ghafil FA, Kadhim SAA, Majeed S, Qassam H, Hadi NR. Nephroprotective effects of Candesartan Cilexetil against Cyclosporine A-induced nephrotoxicity in a rat model. J Med Life [Internet]. 2022 [cited 2023 Aug 3];15(12):1553–62. Available from: https://pubmed.ncbi.nlm.nih.gov/36762326/

49.El-Kashef DH, Serrya MS. Sitagliptin ameliorates thioacetamide-induced acute liver injury via modulating TLR4/NF-KB signaling pathway in mice. Life Sci [Internet]. 2019 Jul 1 [cited 2023 Jul 2];228:266–73. Available from: https://pubmed.ncbi.nlm.nih.gov/31077717/

50.Guo SX, Fang Q, You CG, Jin YY, Wang XG, Hu XL, et al. Effects of hydrogen-rich saline on early acute kidney injury in severely burned rats by suppressing oxidative stress induced apoptosis and inflammation. J Transl Med [Internet]. 2015 Dec 12 [cited 2023 May 20];13(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26047940/

51.Al-Rabia MW, Alfaleh MA, Asfour HZ, Alharbi WS, El-Moselhy MA, Alhakamy NA, et al. 2-Methoxyestradiol TPGS Micelles Attenuate Cyclosporine A-Induced Nephrotoxicity in Rats through Inhibition of TGF-β1 and p-ERK1/2 Axis. Antioxidants (Basel, Switzerland) [Internet]. 2022 Aug 1 [cited 2023 Aug 5];11(8). Available from: https://pubmed.ncbi.nlm.nih.gov/36009218/

52.Sattarinezhad E, Panjehshahin MR, Torabinezhad S, Kamali-Sarvestani E, Farjadian S, Pirsalami F, et al. Protective Effect of Edaravone Against Cyclosporine-Induced Chronic Nephropathy Through Antioxidant and Nitric Oxide Modulating Pathways in Rats. Iran J Med Sci [Internet]. 2017 Mar 1 [cited 2023 May 17];42(2):170–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28360443/

53.Raeisi S, Ghorbanihaghjo A, Argani H, Dastmalchi S, Seifi M, Ghasemi B, et al. Oxidative stress-induced renal telomere shortening as a mechanism of cyclosporine-induced nephrotoxicity. J Biochem Mol Toxicol. 2018 Aug 1;32(8).

54.Parra Cid T, Conejo García JR, Carballo Álvarez F, De Arriba G. Antioxidant nutrients protect against cyclosporine A nephrotoxicity. Toxicology [Internet]. 2003 Jul 15 [cited 2023 Jul 3];189(1–2):99–111. Available from: https://pubmed.ncbi.nlm.nih.gov/12821286/

55.Redondo-Horcajo M, Romero N, Martínez-Acedo P, Martínez-Ruiz A, Quijano C, Loureno CF, et al. Cyclosporine A-induced nitration of tyrosine 34 MnSOD in endothelial cells: role of mitochondrial superoxide. Cardiovasc Res [Internet]. 2010 [cited 2023 Jul 3];87(2):356–65. Available from: https://pubmed.ncbi.nlm.nih.gov/20106845/

56.Mohamadin AM, El-Beshbishy HA, El-Mahdy MA. Green tea extract attenuates cyclosporine A-induced oxidative stress in rats. Pharmacol Res. 2005 Jan 1;51(1):51–7.

57.Tutanc M, Arica V, Yilmaz N, Nacar A, Zararsiz I, Basarslan F, et al. Effects of erdosteine on cyclosporin-A-induced nephrotoxicity. Hum Exp Toxicol [Internet]. 2012 Jun [cited 2023 Nov 26];31(6):565–73. Available from: https://pubmed.ncbi.nlm.nih.gov/21813577/

58.Duru M, Nacar A, Yönden Z, Kuvandik G, Helvaci MR, Koç A, et al. Protective Effects of N-Acetylcysteine on Cyclosporine-A-Induced Nephrotoxicity. http://dx.doi.org/101080/08860220801985942 [Internet]. 2009 May [cited 2023 Aug 5];30(4):453–9. Available from: https://www.tandfonline.com/doi/abs/10.1080/08860220801985942

59.Xiao Z, Shan J, Li C, Luo L, Lu J, Li S, et al. Mechanisms of cyclosporine-induced renal cell apoptosis: a systematic review. Am J Nephrol [Internet]. 2013 [cited 2023 May 19];37(1):30–40. Available from: https://pubmed.ncbi.nlm.nih.gov/23295863/

60.Liu Z, Ren B, Wang Y, Zou C, Qiao Q, Diao Z, et al. Sesamol Induces Human Hepatocellular Carcinoma Cells Apoptosis by Impairing Mitochondrial Function and Suppressing Autophagy. Sci Rep [Internet]. 2017 Apr 4 [cited 2023 May 19];7. Available from: https://pubmed.ncbi.nlm.nih.gov/28374807/

61.Aroor AR, Manrique-Acevedo C, DeMarco VG. The role of dipeptidylpeptidase-4 inhibitors in management of cardiovascular disease in diabetes; focus on linagliptin. Cardiovasc Diabetol [Internet]. 2018 Apr 18 [cited 2023 Jul

1];17(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29669555/

62.Lovshin JA, Zinman B. Blood pressure-lowering effects of incretin-based diabetes therapies. Can J diabetes [Internet]. 2014 [cited 2023 Jul 1];38(5):364–71. Available from: https://pubmed.ncbi.nlm.nih.gov/25284699/

63.Mulvihill EE, Drucker DJ. Pharmacology, Physiology, and Mechanisms of Action of Dipeptidyl Peptidase-4 Inhibitors. Endocr Rev [Internet]. 2014 Dec 1 [cited 2023 Jul 1];35(6):992–1019. Available from: https://dx.doi.org/10.1210/er.2014-1035

64.Von Websky K, Reichetzeder C, Hocher B. Physiology and pathophysiology of incretins in the kidney. Curr Opin Nephrol Hypertens [Internet]. 2014 Jan [cited 2023 Jul 1];23(1):54–60. Available from: https://pubmed.ncbi.nlm.nih.gov/24257158/

65.Li J, Guan M, Li C, Lyv F, Zeng Y, Zheng Z, et al. The dipeptidyl peptidase-4 inhibitor sitagliptin protects against dyslipidemia-related kidney injury in Apolipoprotein E knockout mice. Int J Mol Sci [Internet]. 2014 Jun 26 [cited 2023 Jul 2];15(7):11416–34. Available from: https://pubmed.ncbi.nlm.nih.gov/24972137/

66.Vaghasiya J, Sheth N, Bhalodia Y, Manek R. Sitagliptin protects renal ischemia reperfusion induced renal damage in diabetes. Regul Pept [Internet]. 2011 Jan 17 [cited 2023 Jun 27];166(1–3):48–54. Available from: https://pubmed.ncbi.nlm.nih.gov/20728477/

67.Marques C, Mega C, Gonçalves A, Rodrigues-Santos P, Teixeira-Lemos E, Teixeira F, et al. Sitagliptin prevents inflammation and apoptotic cell death in the kidney of type 2 diabetic animals. Mediators Inflamm [Internet]. 2014 [cited 2023 Apr 20];2014. Available from: https://pubmed.ncbi.nlm.nih.gov/24817793/

68.Abuelezz SA, Hendawy N, Abdel Gawad S. Alleviation of renal mitochondrial dysfunction and apoptosis underlies the protective effect of sitagliptin in gentamicin-induced nephrotoxicity. J Pharm Pharmacol [Internet]. 2016 Apr 1 [cited 2023 May 21];68(4):523–32. Available from: https://pubmed.ncbi.nlm.nih.gov/27019059/

69.shalaby A. Renoprotective Effect of Sitagliptin (Dipeptidyl Peptidase- 4 Inhibitor) aganist Cisplatin Induced Nephrotoxicity in Mice. Br J Pharm Res. 2014 Jan 10;4(9):1116–29.

70.Deger M, Kaya B, Akdogan N, Kaplan HM, Bagir E, Izol V, et al. Protective effect of dapagliflozin against cyclosporine A-induced nephrotoxicity. Drug Chem Toxicol [Internet]. 2022 [cited 2023 May 21];45(6):2637–43. Available from: https://pubmed.ncbi.nlm.nih.gov/34565275/

71.Nuransoy A, Beytur A, Polat A, Samdanci E, Sagir M, Parlakpinar H. Protective effect of sitagliptin against renal ischemia reperfusion injury in rats. Ren Fail [Internet]. 2015 May 1 [cited 2023 Jul 1];37(4):687–93. Available from: https://pubmed.ncbi.nlm.nih.gov/25703705/

72.Apaijai N, Pintana H, Chattipakorn SC, Chattipakorn N. Effects of vildagliptin versus sitagliptin, on cardiac function, heart rate variability and mitochondrial function in obese insulin-resistant rats. Br J Pharmacol [Internet]. 2013 [cited 2023 Jul 1];169(5):1048–57. Available from: https://pubmed.ncbi.nlm.nih.gov/23488656/

73.Pintana H, Apaijai N, Chattipakorn N, Chattipakorn SC. DPP-4 inhibitors improve cognition and brain mitochondrial function of insulin-resistant rats. J Endocrinol. 2013 Jul;218(1):1–11.

74.Alam MA, Hasan Chowdhury MR, Jain P, Sagor MAT, Reza HM. DPP-4 inhibitor sitagliptin prevents inflammation and oxidative stress of heart and kidney in two kidney and one clip (2K1C) rats. Diabetol Metab Syndr [Internet]. 2015 Nov 25 [cited 2023 Jul 3];7(1):107. Available from: /pmc/articles/PMC4658771/

75.Nader MA, El-Awady MS, Shalaby AA, El-Agamy DS. Sitagliptin exerts anti-inflammatory and anti-allergic effects in ovalbumin-induced murine model of allergic airway disease. Naunyn Schmiedebergs Arch Pharmacol [Internet]. 2012 Sep [cited 2023 Jul 2];385(9):909–19. Available from: https://pubmed.ncbi.nlm.nih.gov/22733167/

76.Zhang Q, He L, Dong Y, Fei Y, Wen J, Li X, et al. Sitagliptin ameliorates renal tubular injury in diabetic kidney disease via STAT3-dependent mitochondrial homeostasis through SDF-1α/CXCR4 pathway. FASEB J [Internet]. 2020 Jun 1 [cited 2023 Jul 2];34(6):7500–19. Available from: https://pubmed.ncbi.nlm.nih.gov/32281218/

77.Al Suleimani YM, Abdelrahman AM, Karaca T, Manoj P, Ashique M, Nemmar A, et al. The effect of the dipeptidyl peptidase-4 inhibitor sitagliptin on gentamicin nephrotoxicity in mice. Biomed Pharmacother [Internet]. 2018 Jan 1 [cited 2023 Apr 19];97:1102–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29136947/

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