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Vildagliptin Nephroprotective Effect in Rats Model with Cisplatin-Induced Nephrotoxicity

Abeer T. Watife*, Ahsan F. Bairam, Nibras H. Al-Ghuraibawi

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Kufa, Iraq.
*Correspondence to: Abeer T. Watife, (E-mail: abeer.tariq@uobabylon.edu.iq)
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Abstract

Objective: To evaluate the nephroprotective effect of vildagliptin against cisplatin-induced nephrotoxicity in rats.

Methods: Twenty-eight male rats have been divided into four groups: Control (received distal water), cisplatin treated group (received single dose of cisplatin (7 mg/kg) intraperitoneally (IP) on day eight), vildagliptin plus cisplatin treated group (received vildagliptin 10 mg/kg/day orally for 14 days, seven days before and seven days after the dose of cisplatin on day eight), and vildagliptin treated group (received the same dose and duration of vildagliptin mentioned previously). At the end, blood samples were collected to evaluate tumor necrotic factor-α (TNF-α), caspase-3, total antioxidant capacity (TAOC), urea, and creatinine. The serum levels of these biomarkers were expressed as mean ± standard error of mean. Additionally, kidneys were fixed in formalin for histopathological examination.

Results: Vildagliptin treatment significantly reduced the serum levels of TNF-α, caspase-3, urea, and creatinine as well as increased the TAOC level in rats treated with vildagliptin plus cisplatin when compared with cisplatin treated group. Histopathological examination further supported the nephroprotective effect of vildagliptin in rats with cisplatin induced nephrotoxicity.

Conclusion: Vildagliptin improved kidney function and reduced cisplatin nephrotoxicity which may highlight the nephroprotective effect of this DPP-4 inhibitor against cisplatin-induced nephrotoxicity.

Keywords: Nephrotoxicity, vildagliptin, cisplatin, TNF-α, caspase-3, TAOC

Introduction

Kidney is one of the body's primary organs, which is responsible for the filtration and elimination of several poisons and medications. Numerous drugs available for clinical use have the potential to cause nephrotoxicity, which reduces their clinical benefit. Acute kidney injury (AKI) continues to be associated with a significant risk of morbidity and mortality despite advances in medical research on this type of illness.[1,2] Due to a decrease in glomerular filtration and damage to tubules, urea, creatinine and other toxic materials that are eliminated by the kidney could be accumulated in blood.[3]

The most important causative factor for nephrotoxicity is drug-induced nephrotoxicity. Cisplatin is a chemotherapeutic agent used for the treatment of several types of tumors such as esophageal,[4] breast,[5] uterine cancer,[6] and squamous cell carcinoma of the neck and head.[7] It is a platinum molecule that consists of a central atom of platinum with two chloride and two ammonium molecules. The mechanism of action of cisplatin highly relays on the formation of reactive electrophilic molecules that react with nucleophilic groups of DNA resulting in the formation of inter and intra-strand cross-linking, this causes a defect in DNA templates and impairs the DNA synthesis and replication.[8] Nephrotoxicity, which occurs when cisplatin builds up in the kidney, is one of the main factors that restrict the clinical usefulness of this drug.[7] It is reported that cisplatin-induced nephrotoxicity may occur through induction of inflammation, apoptosis, and oxidative stress in renal tissue. The inflammatory response involves the activation of TNF-α which is an important cytokine responsible for the systemic inflammation and acute phase of nephrotoxicity induced by cisplatin. By acting on TNF receptor type 1 (TNFR1), TNF-α can directly stimulate tubular cell death and tissue damage, also it can indirectly stimulate a strong inflammatory response by its action on TNF receptor type 2 (TNFR2).[9]

The apoptosis involves the stimulation of both extrinsic and intrinsic pathways. Cell shrinkage, DNA fragmentation, and membrane blistering are some of the morphological changes of apoptosis brought on by the activation of certain proteases known as executioner caspases (caspases 3 and 7).[10] The other mechanism by which cisplatin causes nephrotoxicity is oxidative stress. Because cisplatin is an electrophilic molecule and has a high affinity toward nucleophilic molecules, it reacts with thiol-containing antioxidants, such as metallothionein and glutathione, in renal tubular cells and inactivates or degrades them. In addition, it also causes an inhibition of some antioxidant enzymes such as glutathione reductase, glutathione peroxidase, and superoxide dismutase (SOD), which may result in an increase in the level of reactive oxygen species (ROS).[11]

To maintain the clinical usefulness of cisplatin, it is crucial to reduce the corresponding nephrotoxicity. Vildagliptin is an antidiabetic drug that belongs to dipeptidyl peptidase-4 inhibitors. These drugs act by inhibiting peptide hormones that cause the degradation of endogenous incretins. These incretins decrease the blood glucose level by stimulating insulin secretion from pancreatic β cells after ingestion of food. There are two incretins that are detected as blood glucose-lowering peptides, including gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1).[12]

Based on the above, the aim of this study is to evaluate the nephroprotective effect of vildagliptin against cisplatin-induced nephrotoxicity in rats.

Animals, Materials, and Methods

Animals

Twenty-eight adult albino male rats, ranging in age from 10 to 14 weeks and weighing between 170 and 220 g, were used in the study. The animals were kept in plastic cages with

hardwood shelves implanted at room temperature (24–25°C) in the cages. The animals were housed in a cycle of 12 hours of natural light and 12 hours of darkness. The humidity was held steady at (60–65%). The rats were given a typical meal along with tap water to drink. To prepare for laboratory conditions and lessen stress brought on by a change in habitat, the animals were housed in the animal house of the Faculty of Pharmacy/University of Kufa for two weeks prior to the experiment. National standards for the use and care of laboratory animals were followed during the conduct of this investigation. The Institutional Animal Care and Use Committee (IACUC) approved all of the experimental protocols.

Materials

Drugs: Cisplatin vial: each 50 ml vial contains 50 mg cisplatin (Korea united pharma). Vildagliptin powder was obtained from CHICO company/China
Stain: Eosin and hematoxylin.
Kits: The ELISA kits for caspase and TNF- were purchased from Elabscience USA. The colorimetric total antioxidant capacity kit is also available from Elabscience. Colorimetric urea and creatinine kits are available from Cromatest Spain.
Note: The manufacturer's instructions are followed for every biomarker procedure.
Biochemical Determination: After collecting blood samples, serum was utilized for determination of biomarkers, including serum TNF-α, caspase-3, T-AOC, urea and creatinine. Procedures were done depending on manufacturer instructions.

Methods

The animals were randomly divided into four groups, seven animals each. The control group received distal water orally for two weeks and a single IP dose of distal water was given on day eight of the experiment. The cisplatin-treated group received a single dose of cisplatin (7 mg/kg) by IP injection on day eight of the study.[13] The vildagliptin plus cisplatin-treated group: received vildagliptin (10 mg/kg/day) orally for two weeks one before and one after the single dose of cisplatin. The last group received only vildagliptin (10 mg/kg)[14] orally for two weeks.

Samples Collection

Collection of Blood Samples

Each rat's body weight was measured 24 hours after the previous vildagliptin dose. Following that, the animals were given IP doses of 10 mg/kg of xylazine and 100 mg/kg of ketamine to induce anesthesia. Later, the cardiac puncture was used to obtain blood samples straight from the heart. The gel tubes, containing clot activator gel, were used to collect the blood samples. After 10 minutes of centrifugation at 5000 rpm, the serum was collected and the levels of TNFα-, caspase-3, TAOC, urea and creatinine were all measured.

Histopathological Examination

The kidney was kept and fixed in 10% formalin for 24–48 hours for histology. The kidney was then rinsed with ethanol (80%, 95%, and 100%) to dehydrate the sample. After that, the sample was then rinsed with xylene to remove the alcohol, and then it was embedded in liquid paraffin. Hematoxylin and eosin were used to stain the sample after it had been microtome-sliced.

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). GraphPad Prism version 10 was used to conduct the one-way analysis of variance (ANOVA) and tukey's post hoc analysis to determine the statistical significance. A probability of less than 0.05 ($P < 0.05$) was considered significant.

Results

Effect of Vildagliptin on Serum TNF-α Level

As shown in Figure 1, the mean value of TNF-α is markedly elevated in the serum of the cisplatin-treated group as compared to the control rats ($P < 0.001$). Pretreated with vildagliptin before and after cisplatin administration significantly decreased the mean value of TNF-α in the corresponding groups versus cisplatin-treated rats ($P < 0.001$). However, vildagliptin plus cisplatin-treated rats showed significantly higher levels of TNF-α in comparison with control at $P < 0.05$. In addition, no significant differences were found concerning TNF-α serum levels in vildagliptin alone treated groups versus control.

Effect of Vildagliptin on Serum Caspase-3 Level

As demonstrated in Figure 2, the level of caspase-3 is clearly elevated in serum of cisplatin-treated group when compared with control rats ($P < 0.001$). Vildagliptin administration before and after cisplatin IP single dose injection produced significant reduction in the mean value of caspase-3 in vildagliptin plus cisplatin treated rats versus cisplatin treated rats ($P < 0.001$). No significant differences were found corresponding the caspase-3 level in rats treated with vildagliptin weather alone or in combination with cisplatin compared with control animals.

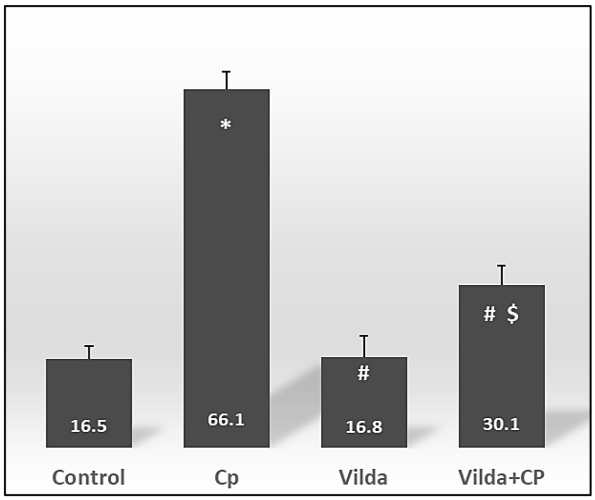

Fig. 1 **Serum level of tumor necrosis factor-α in pg/ml among the study groups. Data are expressed as Mean ± standard error of the mean (SEM). CP refers to rats administered cisplatin (7 mg/kg IP single dose). Vilda refers to rats administered vildagliptin (10mg/kg/day orally for 15 days). Vilda + CP refers to rats administered vildagliptin (10 mg/kg/day orally for two weeks, one before and one after single dose of cisplatin (7 mg/kg) at day eight). *Refers to significant findings versus control ($P < 0.001$). #Refers to significant findings versus cisplatin group ($P < 0.001$). $ refers to significant findings versus control ($P < 0.05$).**

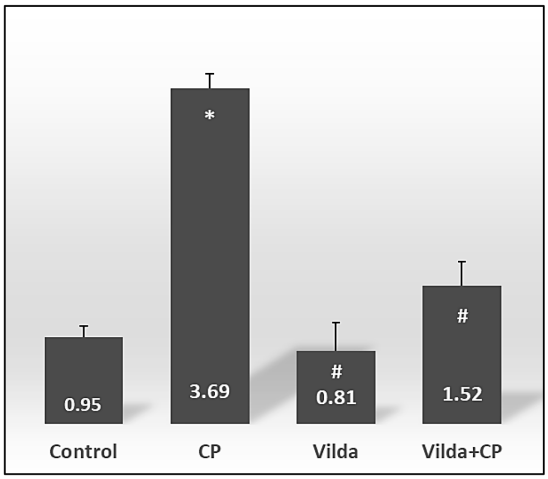

Fig. 2 **Serum level of caspase-3 in pg/ml among the study groups. Data are expressed as Mean ± standard error of the mean (SEM) in pg/ml. CP refers to rats administered cisplatin (7 mg/kg IP single dose). Vilda refers to rats administered vildagliptin (10 mg/kg/day orally for 15 days). Vilda + CP refers to rats administered vildagliptin (10mg/kg/day orally for two weeks, one before and one after single dose of cisplatin (7 mg/kg) at day eight). * Refers to significant findings versus control (*P* < 0.001). #Refers to significant findings versus cisplatin group (*P* < 0.001).**

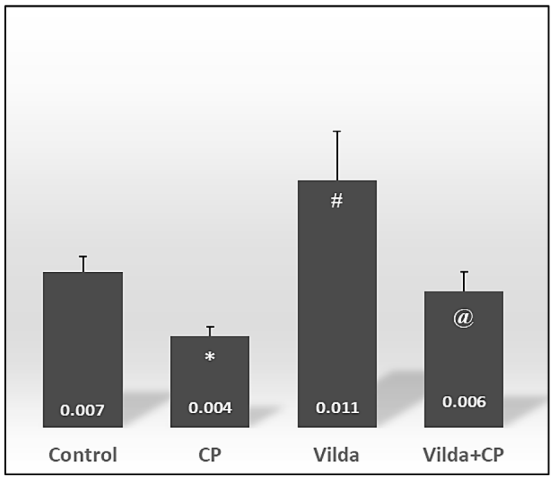

Fig. 3 **Serum level of total antioxidant capacity in U/ml among the study groups. Data are expressed as Mean ± standard error of the mean (SEM). CP refers to rats administered cisplatin (7 mg/kg IP single dose). Vilda refers to rats administered vildagliptin (10 mg/kg/day orally for 15 days). Vilda + CP refers to rats administered vildagliptin (10mg/kg/day orally for two weeks, one before and one after single dose of cisplatin (7 mg/kg) at day eight). *Refers to significant findings versus control (*P* < 0.01). # Refers to significant findings versus cisplatin group (*P* < 0.001). @ Refers to significant findings versus cisplatin group (*P* < 0.05).**

Effect of Vildagliptin on Serum Total Anti-Oxidant Capacity Level

The mean value of T-AOC level is significantly reduced in the cisplatin-treated group ($P < 0.01$). Furthermore, vildagliptin plus cisplatin treated animals showed significant elevation in their T-AOC level compared to the cisplatin-treated rats at $P < 0.05$. Additionally, serum T-AOC level of rats received vildagliptin alone was significantly higher than that in control animals ($P < 0.001$), as shown in Figure 3.

Effect of Vildagliptin on Serum Urea Level

The use of cisplatin in rats produced significant elevation in serum level of urea compared to the control animals ($P < 0.001$). Importantly, the rats treated with vildagliptin before and after cisplatin IP single dose administration possessed significantly lower serum urea levels compared to cisplatin treated group ($P < 0.001$), even though, their urea levels were higher than control animals ($P < 0.001$). Additionally, no significant differences in urea level were noticed between the control animals and rats treated with vildagliptin alone, as seen in Figure 4.

Effect of Vildagliptin on Serum Creatinine Level

The single IP injection of cisplatin in rats made significant increment in serum level of creatinine compared to the control group ($P < 0.001$). Furthermore, animal groups treated with vildagliptin before and after cisplatin administration had significantly lower creatinine levels compared to cisplatin treated group ($P < 0.001$). However, it is seen that rats treated with vildagliptin plus cisplatin had higher serum creatinine concentration than control ($P < 0.05$).

Finally, no significant differences in creatinine level were found between the control group and rats treated with vildagliptin alone, as seen in Figure 5.

Histopathological Study of Kidney

According to histological findings, there are no morphological changes in the renal tissues of the control group (no substantial occupied lesion SOL), as seen in Figure 6A. On day eight of the experiment, cisplatin was administered by IP route in a dose of 7 mg/kg. Because of the cisplatin single dose, the glomeruli, renal tubules, and blood vessels are significantly damaged in the cisplatin-treated group. Indeed, severe necrotic changes (Liquefactive necrosis) in the renal tissue were seen which clearly damaged the renal tubules and glomerulus (Figure 6B).

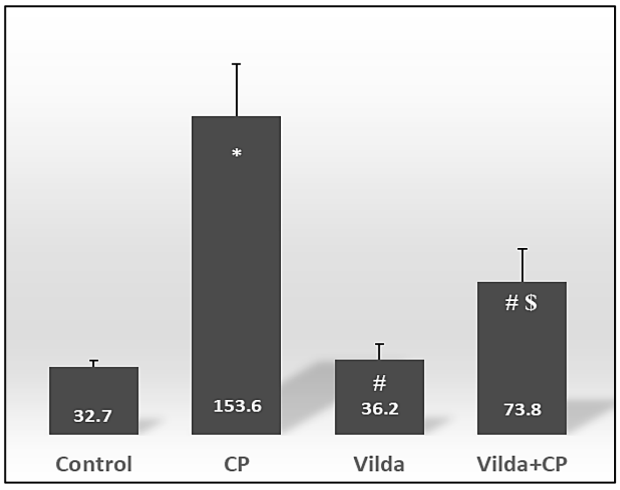

Fig. 4 **Serum level of urea in mg/dl among the study groups. Data are expressed as Mean ± standard error of the mean (SEM). CP refers to rats administered cisplatin (7 mg/kg IP single dose). Vilda refers to rats administered vildagliptin (10 mg/kg/day orally for 15 days). Vilda + CP refers to rats administered vildagliptin (10 mg/kg/day orally for two weeks, one before and one after single dose of cisplatin (7 mg/kg) at day eight). * Refers to significant findings versus control (*P* < 0.001). # Refers to significant findings versus cisplatin group (*P* < 0.001). $ refers to significant findings versus control (*P* < 0.001).**

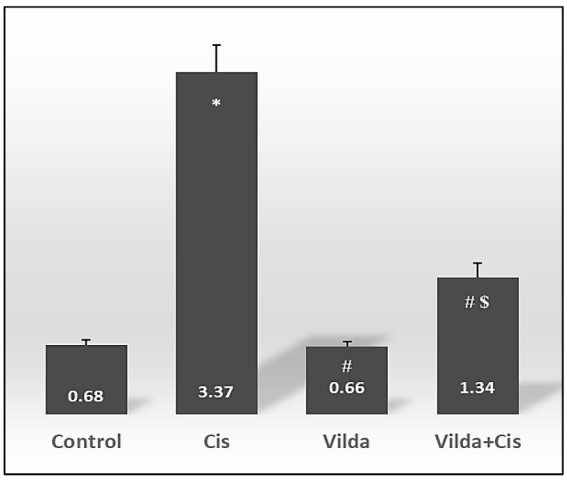

Fig. 5 **Serum level of creatinine in mg/dl among the study groups. Data are expressed as Mean ± standard error of the mean (SEM). CP refers to rats administered cisplatin (7 mg/kg IP single dose). Vilda refers to rats administered vildagliptin (10 mg/kg/day orally for 15 days). Vilda + CP refers to rats administered vildagliptin (10 mg/kg/day orally for two weeks, one before and one after single dose of cisplatin (7 mg/kg) at day eight). * Refers to significant findings versus control ($P < 0.001$). # Refers to significant findings versus cisplatin group ($P < 0.001$). $ refers to significant findings versus control ($P < 0.05$).**

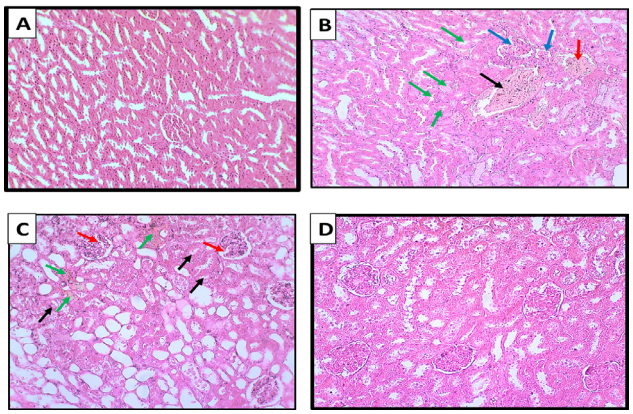

Fig. 6 **Histopathological examination of kidney tissues of rats treated with cisplatin and/or vildagliptin in groups of the study. A: Histological section in kidney of control rat, the renal tissue has normal texture and is free of any substantially occupied lesions (SOL). B: Histopathological section in kidney of rat treated with cisplatin. It reveals severe necrotic alterations (Liquefactive necrosis) in renal tubules (Black arrows) and glomerulus (Red arrows). C: Histopathological section in kidney of rats treated with vildagliptin plus cisplatin, the renal tubules (black arrows) and glomeruli (red arrows) of rats treated with vildagliptin before and after cisplatin dose exhibit mild degenerative alterations. D: Histological section in kidney of rat treated with vildagliptin alone, the renal tissues (glomeruli and tubules) exhibit normal texture without any substantially occupied lesion (SOL). All slides were stained with Hematoxylin and Eosin. Light microscope and digital camera were used to photograph the section at 10X magnification scale.**

The renal tubules' diameter is significantly reduced by cisplatin, and some of these tubules were blocked. In addition, renal blood vessels demonstrated significant congestion.

Vildagliptin administration before and after cisplatin dose showed nephroprotective effects as seen by mild tubular and glomerular degenerative alterations on renal tissues, as manifested by Figure 6C. The administration of vildagliptin alone for two weeks revealed no histopathological changes in the studied rats (Figure 6D).

Discussion

Cisplatin is a popular anticancer medication used to treat a variety of solid cancers. Nephrotoxicity is the most frequent factor that limits the clinical usefulness of cisplatin. Cancer patients' quality of life is impacted by this toxicity, which prompts dose reduction or treatment cessation.[15] Numerous mechanisms have been linked to the pathogenesis of cisplatin-induced nephrotoxicity, including oxidative stress, inflammation, and activation of apoptotic pathways.[16,17]

DPP-4 inhibitors, a class of commonly prescribed anti-hyperglycemic drugs, increase pancreatic beta-cell function by halting GLP1 inactivation. DPP-4 inhibitors have been shown to possess pleiotropic extra-pancreatic effects which have recently attracted a lot of interest due to their potential application in the treatment of a number of illnesses.[18] The current study aimed to evaluate vildagliptin activity as a nephroprotective medicine in rats with cisplatin-induced nephrotoxicity.

When compared to the control group, cisplatin significantly elevated the inflammatory biomarker, TNF-α. This in part highlights the role of inflammation in the development of cisplatin-induced nephrotoxicity. Additionally, elevation in TNF-α can elevate levels of other inflammatory cytokines, including interleukins like IL-1 and monocyte chemotactic protein-1 (MCP-1).[15] TNF-α increment due to cisplatin administration was also reported by other similar research studies such as Attia *et al*., 2017 and Kumar *et al*., 2022.[19,20] Furthermore, when compared to rats administered cisplatin alone, pretreatment with vildagliptin has led to a significantly lower TNF-α level in serums of rats administered vildagliptin plus cisplatin. In addition to the antidiabetic effect, DPP-4 inhibitors were announced to possess other biological actions including anti-inflammatory, antiapoptotic, and antioxidant activity.[21] The renal expression of transforming growth factor (TGF)-β and the formation of extracellular matrix (ECM) by NF-kB activation[22] is promoted by oxidative stress and inflammation, which results in glomerulosclerosis and tubulointerstitial fibrosis. Chemokines as monocyte chemoattractant protein (MCP)-1 are stimulated by inflammatory cytokines including TNF_α, IL-6, IL-1β, and IL-18. These chemokines promote macrophage infiltration toward the mesangial cells.[23] DPP-4 inhibitors exert nephroprotection by GLP-1-dependent and independent pathways, they reduce macrophage infiltration to the tubular cells. Also, they reduce the level of TNF-α and other chemokines and cytokines.[24] Consequently, our study demonstrated how important is the anti-inflammatory effect of vildagliptin in lowering the cisplatin-induced nephrotoxicity. These outcomes were similar to that shown by previous studies (Mostafa *et al.,* 2021 and Mostafa *et al.*, 2021).[14,25] The study by (Mostafa *et al*, 2021)[14] demonstrates the anti-inflammatory effect of vildagliptin and its effectiveness in reducing doxorubicin nephrotoxicity. While the study by (Mostafa *et al*, 2021)[25] evaluates the nephroprotective effect of vildagliptin against manganese-induced nephrotoxicity in rats.

In addition, our study demonstrated that cisplatin administration can significantly increase the level of caspase-3 in a cisplatin-treated group compared to the control group. These

findings were comparable with that mentioned by Choi *et al*., 2017[26] which demonstrates the increase in tissue caspase-3 level after cisplatin administration in mice.

The stimulation of apoptosis is another mechanism by which cisplatin causes nephrotoxicity. Cisplatin induces apoptosis of renal proximal tubular cells in vitro via mitochondria-dependent and -independent mechanisms by partially activating caspase-3.[27,28]

The administration of vildagliptin concomitantly with cisplatin implied antiapoptotic activity through lowering rats' serum caspase-3 level which applied nephroprotective activity against cisplatin toxicity. The stimulation of apoptotic cell death in renal tubules is one of the mechanisms through which cisplatin produced nephrotoxicity.[10] DPP-4 inhibitor pretreatment will lessen the apoptotic effect of cisplatin by lowering the level of the Bax protein in the kidney. Additionally, they lower the kidney's levels of cleaved caspase-3.[26] In comparison with the cisplatin-treated group, the histopathological examination of kidneys obtained from rats who received vildagliptin plus cisplatin further supported the antiapoptotic activity of this DPP-4 inhibitor. The antiapoptotic activity of vildagliptin was also reported by similar studies.[14,25,26] The study by Choi et al., 2017[26] indicates the nephroprotective role of gemigliptin against cisplatin-induced nephrotoxicity in mice.

Additionally, cisplatin treatment has been shown to elevate the production of ROS and lower the level of natural antioxidant enzymes, resulting in oxidative stress.[11] Subsequently, oxidative stress acts as an additional mechanism by which cisplatin induces nephrotoxicity. In this study, the serum level of T-AOC in rats who received a single dose of cisplatin has been lowered significantly, which further confirms the role of oxidative stress in the induction of nephrotoxicity. These results are consistent with that conducted by Al-Thamir *et al*., (2012).[29]

In comparison with rats who received cisplatin alone, the rats treated with a combination of vildagliptin plus cisplatin showed significantly higher levels of T-AOC. GLP-1 inhibits NADPH oxidase and activates protein kinase A (PKA), which reduces oxidative stress in glomeruli and tubules and is how it prevents renal oxidative stress.[30] DPP-4 inhibitors also improve catalase and superoxide dismutase (SOD) activity and decrease cisplatin-induced MDA and 3-nitrotyrosine activity, which will lessen the oxidative stress that cisplatin causes.[31] The elevation in T-AOC level asserts the antioxidant activity of vildagliptin that could be due to the decrease in ROS production and/or increase in the level of antioxidant enzymes. Other studies stated that vildagliptin has comparable antioxidant activities against agents with oxidative stress properties.[14,32]

The determination of serum levels of urea and creatinine revealed that cisplatin use significantly reduced kidney function. Because glomeruli and proximal tubules are potentially damaged by cisplatin, there is a considerable rise in serum urea and creatinine levels. These outcomes are in line with a study done by Ozkok and Edelstein in (2014).[33] The study by Ozkok and Edelstein in (2014)[33] indicate the pathogenesis of cisplatin induced nephrotoxicity and how we can reduce this toxicity. Vildagliptin has been shown by several researchers to have a pleiotropic activity (anti-inflammatory, antiapoptotic, and antioxidant effect),[14,19,32] and consequently, it may minimize the injury to glomeruli and proximal tubules improving by that the corresponding renal function.

The biochemical findings of the current study were supported by the histopathological examination of rat's kidneys, which demonstrated considerable nephrotoxicity after cisplatin administration as evidenced by tubular degeneration and severe necrotic alterations (liquefactive necrosis) in the renal tissue. As a result, obvious damage to the renal tubules and glomerulus was noticed. Additionally, cisplatin produced significant congestion in renal blood vessels. These findings are in agreement with earlier research studies.[19,33] Vildagliptin administration produced an important nephroprotective effect against cisplatin-induced nephrotoxicity. Indeed, mild degenerative changes of renal proximal tubules were detected in the kidneys of rats who received vildagliptin. These findings were similarly reported by previous studies which stated that vildagliptin can impose protective effects on tissues exposed to damaging factors.[32]

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgment

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