Original Article

Linagliptin Renoprotective Role in Rats with Cisplatin-induced Nephrotoxicity

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Abstract

Background: Nephrotoxicity is a common type of toxicity associated with the use of many chemotherapeutic agents, especially cisplatin. The prevalence of cisplatin nephrotoxicity is about 28% to 36% after a single dose. Cisplatin is an important agent for treating a wide range of solid tumors, so nephroprotection is very important. Linagliptin is an antidiabetic drug that acts by inhibiting the enzyme dipeptidyl peptidase-4. This group of drugs has pleiotropic effects that may reduce nephrotoxicity caused by cisplatin. **Objectives:** To evaluate the nephroprotective effect of linagliptin against cisplatin-induced nephrotoxicity. **Materials and Methods:** A total of 28 male rats were divided into four groups: control, cisplatin alone, cisplatin with linagliptin, and linagliptin alone. The rats were administered cisplatin (7 mg/kg, IP single dose on day 8) alone or in combination with linagliptin (3 mg/kg/day, orally for 14 days) and the control group received only distal water. After 2 weeks, blood samples were collected for measurement of tumor necrotic factor-α, caspase-3, total antioxidant capacity, urea, and creatinine. Animals were then sacrificed and the kidney was removed for histopathological studies. Data are expressed as the mean ± standard error of the mean. **Results:** Linagliptin treatment significantly minimized cisplatin-induced nephrotoxicity and improved kidney function by reducing serum urea, creatinine, caspase-3, and TNF-α levels and increasing serum total antioxidant capacity level. In addition, linagliptin improved histopathological changes induced by cisplatin administration. **Conclusion:** Linagliptin may serve as a nephron-protectant when administered concomitantly with cisplatin.

Keywords: Cisplatin, linagliptin, nephroprotection, nephrotoxicity

Introduction

The kidney is one of the major organs in the body and it is responsible for the concentration and excretion of many toxins and drugs from the body. Many of the medications available in the market have the potential to cause nephrotoxicity, which subsequently limits their clinical usefulness. Despite the development in medical research on this type of disorder, there is a high risk of morbidity and mortality still associated with acute kidney injury (AKI).[1,2,3] The main signs and symptoms of AKI are the accumulation of urea, creatinine, and toxins due to sudden deterioration in kidney function over several hours to days.[4]

Drug-induced nephrotoxicity is one of the essential causative factors of AKI.[5] One of these drugs is cisplatin. Cisplatin is an important anticancer drug that is used for the treatment of a wide range of cancer types such as cervical cancer, non-small cell lung cancer, bladder cancer, squamous cell carcinoma of the neck and head, esophageal, testicular, ovarian, uterine, colon, and breast cancers.[6-12] One of the important causes that limit the clinical usefulness of cisplatin is nephrotoxicity as it accumulates in the kidney. The cisplatin-induced nephrotoxicity is dose-dependent and it usually occurs in 30%–40% of patients receiving cisplatin.[6,13,14] A single dose of cisplatin may produce reversible kidney injury, whereas multiple or large doses may produce permanent kidney damage.[15] Cisplatin-induced nephrotoxicity

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occurs through the following mechanisms: oxidative stress, apoptosis, and inflammation.[16]

Oxidative stress plays an important role in cisplatin-induced nephrotoxicity, as the studies show that cisplatin causes an increase in malondialdehyde (MDA), 3-nitrotyrosine, and 4-hydroxy, 8-hydroxydeoxyguanosine, and cause a reduction in the antioxidant level such as catalase (CAT) and superoxide dismutase (SOD).[17] The pathogenesis of cisplatin-induced nephrotoxicity also involves an inflammatory response. Indeed, cisplatin induction of inflammation includes activation of tumor necrotic factor-α (TNF-α), which regulates the activation of a wide range of pro-inflammatory cytokines like transforming growth factor-β1 (TGF-β1), interleukin 1, 4, 6 (IL-1β, IL-4, IL-6), and monocyte chemotactic protein-1 (MCP-1).[18] Furthermore, cisplatin can activate both intrinsic and extrinsic apoptotic pathways. The last two pathways cause the activation of specific proteases known as executioner caspases (caspase 7 and caspase 3), which result in certain morphological changes of apoptosis-like cell shrinkage, DNA fragmentation, and membrane blistering.[14,19]

DPP-4 inhibitors are antidiabetic drugs that act by stimulating glucose-dependent insulin secretion from pancreatic β cells through inhibition of the DPP-4 enzyme that causes degradation of the endogenous incretin hormones.[20] In addition to their anti-diabetic effect, DPP-4 inhibitors have a pleiotropic effect that involves antioxidant, antiapoptotic, and anti-inflammatory effects.[21] Linagliptin is a potent DPP-4 inhibitor that is administered orally once daily. Linagliptin has a large volume of distribution, and it has good penetration into kidney tissues.[22] A number of experimental studies have shown that the nephroprotective effect of DPP-4 inhibitors in diabetic and nondiabetic patients occurs through antioxidant, anti-inflammatory and antiapoptotic effects.[21]

Based on that, the aim of this study is to evaluate the reno-protective effect of linagliptin against cisplatin-induced nephrotoxicity in rats.

Materials and Methods

Materials

Drugs: Cisplatin vial: each 50 mL vial contains 50 mg cisplatin (Korea United Pharma). Linagliptin tablet: 5mg tablet from Boehringer Ingelheim, Germany.

Stain: Hematoxylin and eosin.

Kits: TNF-α, caspase-3, total antioxidant capacity, urea, and creatinine kits.

The kits of TNF-α and caspase-3 are ELISA-based assays obtained from Elabscience (Houston, TX, USA). The total antioxidant capacity kit is colorimetric, which is also obtained from Elabscience. Urea and creatinine kits are colorimetric and obtained from Cromatest (Montgat-Barcelona, Spain). All biomarker procedures are carried out in accordance with the manufacturer's guidelines.

Animals

A total of 28 healthy adult albino male rats weighing 170–220 g and aged between 10 and 14 weeks were used in the study. These animals were placed in plastic cages that were embedded with wooden shelves, at room temperature (24–25°C). The animals were kept under 12-h natural light and 12-h dark cycle, and the humidity was maintained between 60% and 65%. The rats were fed with a standard diet and tap water. These animals were placed in the animal house in the Faculty of Pharmacy/Kufa University for 2 weeks before starting the experiment in order to accommodate them for laboratory conditions and reduce the stress resulting from a changing environment. This study was carried out according to the national guidelines for the use and care of laboratory animals. All the experimental protocols were ratified by the Institutional Animal Care and Use Committee (IACUC).

Methods

The animals were randomly divided into four groups (7 rats/group), and received treatment for 15 days, 7 days before and after cisplatin administration.

Group 1 (Control): Rats were administered distal water (1 mL/kg/day) orally for 2 weeks.

Group 2 (Cisplatin): Rats received only a single dose of cisplatin (7 mg/kg) by IP route on day 8 of the experiment.[23]

Group 3 (Cisplatin plus linagliptin): Rats were given linagliptin orally in a dose of 3 mg/kg/day for 2 weeks, one before and one after cisplatin single dose of 7 mg/kg at day 8.

Group 4 (Linagliptin): Rats were given only linagliptin orally for 15 days at a dose of 3 mg/kg/day. Linagliptin dose was used based on previous studies.[24]

Collection of blood samples

After 24 h from the last dose of linagliptin, the body weight of each rat was measured. After that, the animals were anesthetized by using ketamine in a dose of (100 mg/kg) and xylazine in a dose of (10 mg/kg), both given by IP route. Then the blood samples were collected directly from the heart through a heart puncture. The blood samples were placed in gel tubes (with clot activator gel). The serum was obtained after centrifugation at 5000 rpm for 10 min. This serum was used to measure the TNF-α, total antioxidant capacity, urea, creatinine, and caspase-3.

Histopathological examination

For histopathology, the kidney was saved and fixed in 10% formalin for 24–48 h and then washed with ethanol (80%,

95%, and 100%) to dehydrate the sample. Then to remove alcohol the sample was washed with xylene and embedded in liquid paraffin. The sample was sliced by microtome and stained with hematoxylin and eosin.

Statistical analysis

The statistical analysis was achieved using the graph pad prism version 10. The statistics were presented as a mean value ± standard error of the mean (SEM). To compare the mean between two groups or more, the Analysis of Variance (ANOVA) test was used followed by a Tukey's *post hoc* test. The difference is considered significant when the P value < 0.05.

Ethical approval

This experiment followed the national criteria for laboratory animal care and use. All protocols, followed by the Institutional Animal Care and Use Committee (IACUC) in the University of Kufa, Iraq, according to document number 2239, on March 21, 2023.

Results

Impact of Linagliptin on serum TNF-α level

The mean value of the TNF-α is markedly elevated in the serum of cisplatin-treated rats as compared to the control group (P < 0.001). Animals treated with linagliptin plus cisplatin showed a significant decrease in their mean value of TNF-α in comparison to that in cisplatin-treated rats (P < 0.001). Additionally, no significant differences were seen in TNF-α mean value between rats received linagliptin alone and the control group, as demonstrated in Figure 1.

Impact of Linagliptin on serum caspase-3 level

The mean value of serum caspase-3 level showed a significant increase in animals treated with cisplatin alone (P < 0.001), whereas animals treated with linagliptin plus cisplatin demonstrated a significant decrease in their serum caspase-3 level compared to cisplatin-treated rats (P < 0.001). No significant difference was noticed between the linagliptin-administered group (group 4) and control, as shown in Figure 2.

Impact of Linagliptin on serum total antioxidant capacity level

The mean value of T-AOC level is significantly decreased in cisplatin-treated group (group 2) (P < 0.01). Furthermore, linagliptin plus cisplatin-treated animals (group 3) showed significant elevation in their T-AOC compared to the cisplatin-administered group (P < 0.01). Additionally, serum T-AOC level in rats administered linagliptin plus cisplatin or linagliptin alone was even higher than that in control animals, see Figure 3.

Impact of Linagliptin on serum urea and creatinine levels

The dose of cisplatin in rats treated with cisplatin caused a significant elevation in the mean value of serum urea and creatinine levels compared to the control group (P < 0.001). The mean value of serum urea and creatinine were significantly decreased in linagliptin plus cisplatin treated animals compared to rats treated with cisplatin alone (P < 0.001), however, these corresponding animals still have urea and creatinine concentrations above normal (Control), as shown in Figures 4 and 5.

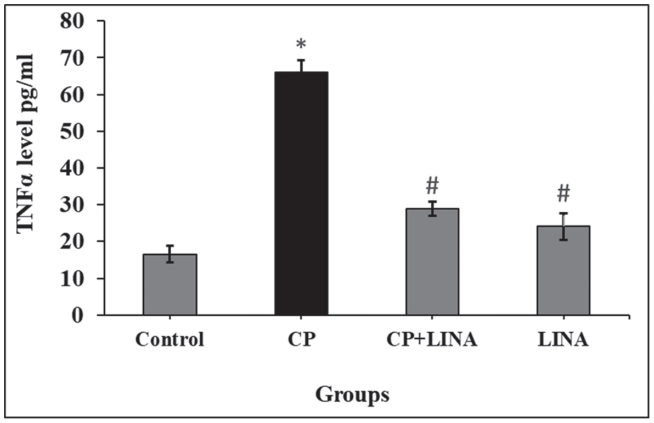

Figure 1: Serum level of tumor necrosis factor α among the study groups. Data are expressed as mean ± standard error of the mean (SEM). CP refers to rats received cisplatin single dose (7 mg/kg) by IP route on day 8 of the experiment. CP+LINA refers to rats received linagliptin orally in a dose of (3 mg/kg/day) for 2 weeks, one before and one after single dose cisplatin (7 mg/kg) at day 8. LINA refers to rats received linagliptin orally for 15 days at a dose of 3 mg/kg/day. *Refers to significant finding versus control (P < 0.001). #Refers to significant finding versus CP group (P < 0.001)

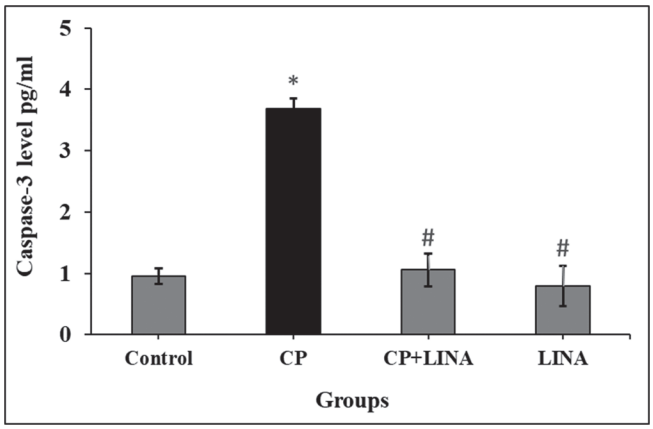

Figure 2: Serum level of caspase-3 among the study groups. Data are expressed as mean ± standard error of the mean (SEM). CP refers to rats received cisplatin single dose (7 mg/kg) by IP route on day 8 of the experiment. CP+LINA refers to rats received linagliptin orally in a dose of (3 mg/kg/day) for 2 weeks, one before and one after a single dose of cisplatin (7 mg/kg) at day 8. LINA refers to rats received linagliptin orally for 15 days at a dose of 3 mg/kg/day. *Refers to significant finding versus control (P < 0.001). #Refers to significant finding versus CP group (P < 0.001)

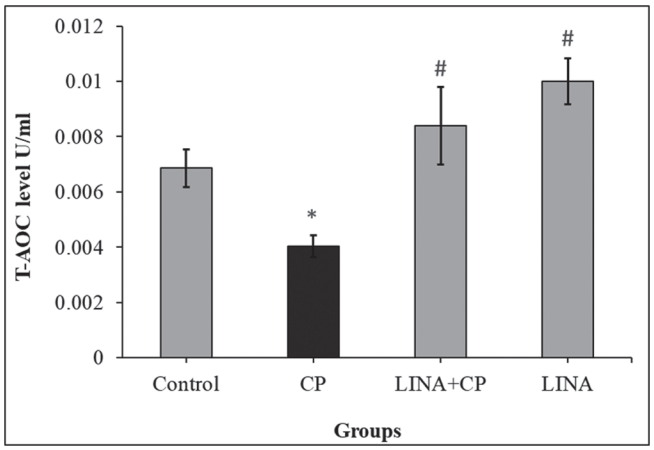

Figure 3: Serum level of total antioxidant capacity among the study groups. Data are expressed as mean ± standard error of the mean (SEM). CP refers to rats received cisplatin single dose (7 mg/kg) by IP route on day 8 of the experiment. CP + LINA refers to rats received linagliptin orally in a dose of (3 mg/kg/day) for 2 weeks, one before and one after a single dose of cisplatin (7 mg/kg) at day 8. LINA refers to rats received linagliptin orally for 15 days at a dose of 3mg/kg/day. *****Refers to significant finding versus control ($P < 0.01$). **#**Refers to significant finding versus CP group ($P < 0.01$)

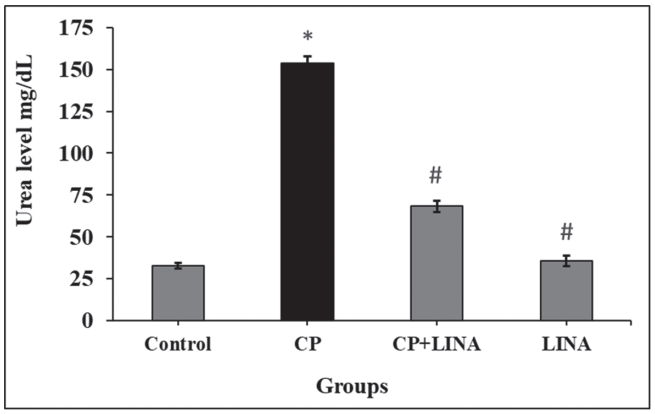

Figure 4: Serum level of urea among the study groups. Data are expressed as mean ± standard error of the mean (SEM). CP refers to rats received cisplatin single dose (7 mg/kg) by IP route on day 8 of the experiment. CP+LINA refers to rats received linagliptin orally in a dose of (3 mg/kg/day) for 2 weeks, one before and one after a single dose of cisplatin (7 mg/kg) at day 8. LINA refers to rats received linagliptin orally for 15 days at a dose of 3 mg/kg/day. *****Refers to significant finding versus control ($P < 0.001$). **#** Refers to significant finding versus CP group ($P < 0.001$)

Impact of Cisplatin and Linagliptin on kidney histopathology

Depending on histopathological results, the control group (received only distal water) showed no morphological changes in their renal tissues and no significant occupied lesion, as demonstrated in Figure 6A. In contrast, the cisplatin-treated group displayed significant damage to glomeruli, renal tubules, and blood vessels. Cisplatin caused severe necrotic changes (Liquefactive necrosis) in

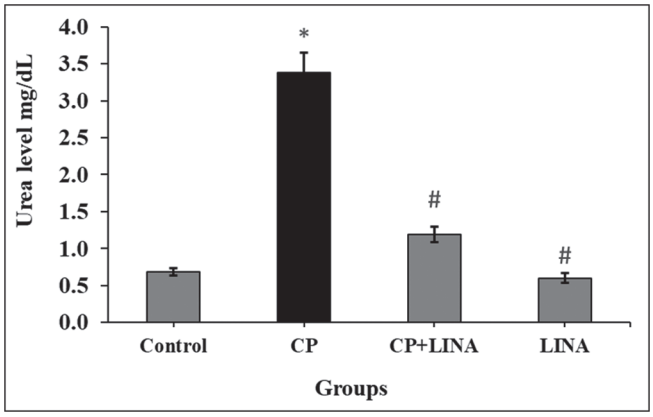

Figure 5: Serum level of creatinine among the study groups. Data are expressed as mean ± standard error of the mean (SEM). CP refers to rats received cisplatin single dose (7 mg/kg) by IP route on day 8 of the experiment. CP+LINA refers to rats received linagliptin orally in a dose of (3 mg/kg/day) for 2 weeks, one before and one after a single dose of cisplatin (7 mg/kg) at day 8. LINA refers to rats received linagliptin orally for 15 days at a dose of 3 mg/kg/day. *****Refers to significant finding versus control ($P < 0.001$). **#**Refers to significant finding versus CP group ($P < 0.001$)

renal tissue resulting in clear damage in renal tubules and glomerulus, see Figure 6B.

On the other hand, the administration of linagliptin before and after the dose of cisplatin resulted in significant amelioration of cisplatin nephrotoxicity, as shown in Figure 6C, mild degenerative changes in renal tubules and glomeruli were seen. Finally, the administration of linagliptin alone revealed no pathological effect on rat's kidney tissues, as appeared in Figure 6D.

Discussion

Cisplatin is a widely used anticancer drug used for the treatment of a wide range of solid tumors. The most common limitation that restricts the clinical usefulness of cisplatin is nephrotoxicity. This toxicity affects the quality of life of cancer patients and results in dose reduction or drug discontinuation.[13] Numerous processes, such as oxidative stress, inflammation, and activation of apoptotic pathways, were implicated in the pathogenesis of cisplatin-induced nephrotoxicity.[25,26]

Widely prescribed anti-hyperglycemic medications called DPP-4 inhibitors work to improve pancreatic beta-cell activity by preventing the inactivation of GLP1. The pleiotropic extra pancreatic effects of DPP-4 inhibitors have received a lot of attention recently due to their possible use in treating number of medical conditions.[27] Based on that, the present study aimed to assess the nephroprotective effect of linagliptin against cisplatin-induced nephrotoxicity in rats.

In this study, cisplatin caused a significant increase in inflammatory biomarker tumor necrotic

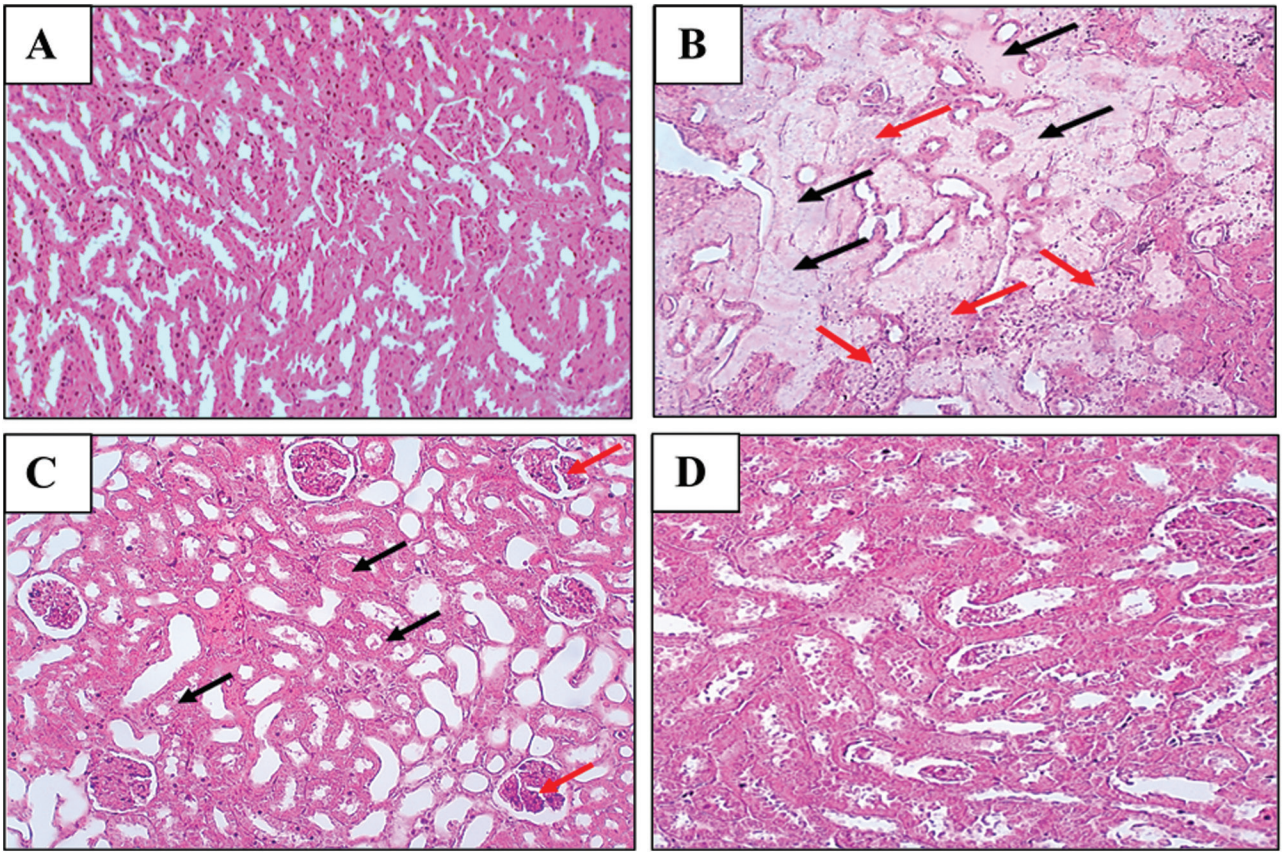

Figure 6: Histopathological examination of kidney tissues of rats treated with cisplatin and/or linagliptin in all groups of the study. (A) Histological section in rat kidney in the control group: it shows normal texture of renal tissue without any significant occupied lesion (SOL). (B) Histopathological section in kidney of rat treated with cisplatin alone (7mg/kg single dose by intraperitoneal route), it shows severe necrotic changes (liquefactive necrosis) in the renal tissue resulting in clear damage in renal tubules (black arrows) and glomerulus (red arrows). (C) Histopathological section in kidney of rat treated with linagliptin (3mg/kg orally) for seven days before and after cisplatin (7mg/kg single dose IP): It shows mild degenerative changes in renal tubules (black arrows) with mild glomeruli degeneration (red arrows). (D) Histological section in kidney of rat treated with linagliptin alone (3 mg/kg orally for 15 days): It shows normal texture of renal tissue (glomeruli and tubules) without any SOL. All slides stained with Hematoxylin and Eosin and the section is captured using a light microscope and digital camera at 10× magnification scale

factor-α compared to the control group. This indicates the inflammatory role of cisplatin in the induction of nephrotoxicity. TNF-α induces the expression of other inflammatory cytokines such as interleukins such as IL-1 and monocyte chemotactic protein-1 (MCP-1).[12] The anti-inflammatory effect of linagliptin is detected by decreasing the level of TNF-α in comparison with cisplatin-treated rats. Interestingly, reducing the level of TNF-α as well as other inflammatory cytokines was reported by previous studies. Also, Linagliptin decreases the infiltration of macrophages into the tubular cells.[28,29,30] However, the importance of the anti-inflammatory effect of linagliptin in reducing the drug-induced nephrotoxicity was stated by other research groups.[31,32]

Cisplatin further caused a significant increase in caspase-3 activity (An apoptosis biomarker). Similarly, cisplatin use by other studies was shown to cause a disturbance in mitochondrial membrane integrity leading to the release of cytochrome-c, which results in the activation of caspases and apoptosis, and subsequent elevation of tissue caspase-3 level after cisplatin administration.[33]

The use of linagliptin with cisplatin produced a decrement in the serum caspase-3 level implying that this drug may have an anti-apoptotic effect. In addition, the histopathological examination also confirmed this anti-apoptotic effect as compared to the cisplatin group. Pretreatment with DPP-4 inhibitors as revealed by similar studies reduced the apoptotic effect of cisplatin through decreasing the level of Bax protein in the kidney.[30-32]

Cisplatin also increases the formation of reactive oxygen species while decreasing the level of natural antioxidant enzymes, resulting in oxidative stress. Cisplatin lowers serum total antioxidant capacity biomarker levels in the current study. The development of oxidative stress is a further mechanism by which cisplatin causes nephrotoxicity, according to this study. This conclusion is consistent with the findings of a previous research group by Al-Thamir *et al*.[34]

Linagliptin combined with cisplatin induces a considerable rise in serum total antioxidant content when compared to cisplatin alone. This effect is related to linagliptin's antioxidant activity, which inhibits the formation of ROS while increasing the level of antioxidant enzymes. GLP-1 prevents renal oxidative stress by inhibiting NADPH oxidase and activating protein kinase A (PKA), resulting in less oxidative stress in glomeruli and tubules.[35] DPP-4 inhibitors also improve superoxide dismutase (SOD) and catalase activity while decreasing MDA and 3-nitrotyrosine activity produced by cisplatin, resulting in less oxidative stress.[32,36,37] In addition, linagliptin varies from other DPP-4 inhibitors in that it includes a xanthine-based scaffold in its chemical structure, which inhibits the xanthine oxidase enzyme, resulting in less ROS formation as reported previously. Linagliptin based on that has stronger antioxidant action than other DPP-4 inhibitors.[38,39]

Regarding urea and creatinine, cisplatin administration significantly reduced kidney function, which is seen through elevating urea and creatine serum levels. Cisplatin induces a considerable increase in blood urea and creatinine due to glomerulosclerosis and proximal tubule injury.[16,40] Concurrent therapy with linagliptin alleviated this effect because it showed a pleiotropic effect (anti-inflammatory, antiapoptotic, and antioxidant effect) and also minimize the damage to glomeruli and proximal tubules as seen by histopathological examination and mentioned by similar studies.[29,32,37]

The current study's histological findings demonstrated considerable nephrotoxicity manifested by tubular degenerative disease and severe necrotic alterations (liquefactive necrosis) in the renal tissue, resulting in evident damage in renal tubules and glomerulus. Cisplatin also caused significant blood vessel congestion. However, similar changes were figured out by previous studies.[29,41] Linagliptin pretreatment afforded nephroprotection against cisplatin-induced nephrotoxicity. With the presence of the bowman capsule and glomerular space, there was only minimal glomerular degradation accompanied by clear improvement of tubular blockage and proximal tubule deterioration. These findings are consistent with other research groups who reported close histopathological results.[22,32]

Finally, linagliptin concomitant administration with cisplatin may protect the renal tissue of people who are in need to receive this cytotoxic chemotherapy. To ascertain linagliptin's protective impact on the human kidneys and other crucial organs, more clinical research is required.

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Nil.

Conflicts of interest

The authors declare that they have no conflict of interest.

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