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Research Article
Effect of Tirzepatide on Cisplatin and Doxorubicin-Induced Cardiotoxicity and Nephrotoxicity

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Abstract

Background and Objective: Tirzepatide (TIRZ) is a drug recently approved for treating obesity and type 2 diabetes. It is an agonist of the Glucagon-Like Peptide-1 (GLP-1) receptor that regulates glucose levels and aids in weight loss. The TIRZ is also reported to reduce cardiotoxicity caused by doxorubicin (DOX). The cisplatin (CIS) and DOX are chemotherapeutic agents that are administered to treat different cancers. On the other hand, CIS and DOX were also reported to develop adverse reactions like nephrotoxicity as well as cardiotoxicity. Present research evaluates the protective action of TIRZ against CIS or the development of cardiotoxicity and nephrotoxicity. **Materials and Methods:** Sixty rats weighing 225-260 g were split into six groups, each with ten animals. The control animals received saline. The TIRZ group was administered three doses of 1.35 mg/kg. The CIS group received three doses (8 mg/kg), while DOX-treated animals received three doses (4 mg/kg). The CIS+TIRZ group received three doses (8 and 1.35 mg/kg). The DOX+TIRZ group received three doses (4 and 1.35 mg/kg). All injections were administered using an intraperitoneal injection route. The animals were observed for mortality and body weight and blood samples were obtained to quantify troponin I, CK-MB, BUN and creatinine via electrochemiluminescence (ECL) and compared the results to the control non-treated group using one-way ANOVA. **Results:** The survival rate decreased when TIRZ was combined with CIS or DOX. Troponin I, CK-MB, BUN and the BUN/creatinine ratio showed a notable rise in CIS and DOX groups, whereas creatinine levels decreased. However, this increase was not reversed when TIRZ was combined with CIS or DOX. Rats receiving CIS or DOX showed more mortality compared to control animals **Conclusion:** The study's findings indicate that CIS and DOX can cause cardiotoxicity and nephrotoxicity. However, co-treatment with TIRZ synergizes this elevation and increases the toxicity of CIS and DOX in the heart and kidney.

Key words: Tirzepatide, cisplatin, doxorubicin, cardiovascular, nephrotoxicity

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Cardiac or renal injury is distinctly characterized by a rapid decline in cardiac output and renal function that impacts the structural integrity of cardiac or renal tissues-assessing the levels of troponin I, CK-MB and BUN as well as creatinine, in addition to the BUN/creatinine ratio[1,2]. The higher troponin I and CK-MB values, along with increased BUN and creatinine, is a prevalent approach for evaluating cardiac and renal function[2,3]. Chemotherapy agents such as doxorubicin and cisplatin have been shown to induce cardiotoxicity by enhancing troponin I levels as well as CK-MB, as well as nephrotoxicity indicated by elevated BUN and creatinine levels post-treatment[4,5].

Cisplatin is a potent and versatile chemotherapy agent commonly employed in the management of numerous solid forms of tumors such as those located in the testicles, head, ovary, lung, bladder, cervix including lymphomas and melanomas[6]. Cisplatin demonstrates anticancer effects through various mechanisms, the most recognized of which involves its interaction with DNA purine bases. This interaction inhibits transcription and replication, resulting in the arrest of the cell cycle, eventually causing cancer cell apoptosis[7]. The clinical application of CIS is constrained by adverse effects, including cardiac and renal toxicity, as well as electrolyte imbalance[8,9].

Doxorubicin (DOX) is a prominent and potent anticancer anthracycline antibiotic that has been extensively utilized in treating different tumors localized in the lungs, prostate and breast[10]. Unfortunately, the application of DOX in chemotherapy is constrained by its detrimental effects on vital organs such as the heart and kidneys[11]. The NADPH-dependent reductases and non-enzymatic reactions, such as the interaction between DOX and iron also enhance the production of free radicals[12]. However, the precise mechanisms behind DOX-induced cardiotoxicity and nephrotoxicity are still not completely understood. The free radical may engage in redox cycling, leading to the formation of O_2 and H_2O_2[13]. In the presence of iron, DOX can form complexes with itself[14]. These complexes subsequently contribute to the enhancement of the transformation of H_2O_2 into various forms of reactive oxygen species (ROS) like hydroxyl ions[15]. The heightened generation of ROS results in deterioration of biomolecules like proteins as well as lipids, causing damage and toxicity in heart and kidney tissues[16].

Tirzepatide is an agonist for the GLP-1 receptor that performs important action in diabetes type-II and obesity management[17]. It has been claimed that TIRZ stimulates the incretin hormone, which in turn reduces hunger and the amount of food consumed, resulting in a reduction in body weight[18]. An earlier study found that the combination of TIRZ and DOX was effective in lowering oxidative stress and inflammation, as well as improving cardiac function and lowering the chance of developing heart failure[19].

Therefore, the present research sought to explore the possible prophylactic activity of TIRZ in mitigating cardiotoxicity and nephrotoxicity induced by CIS or DOX in rats, as well as to clarify the mechanisms involved in these toxicities and the associated protective effects. It also assessed the effect of TIRZ on cardiac and renal functions in rats undergoing chronic treatment with CIS or DOX.

MATERIALS AND METHODS

Study duration: The study was conducted from May, 2024 to July, 2024 at a Pharmacology Laboratory in the College of Pharmacy at Qassim University, Saudi Arabia.

Chemicals and drugs: The doxorubicin injection (2 mg/mL) and cisplatin (1 mg/mL) were sourced from Ebewe Pharma Ges.m.b.H. Nfg.KG in Unterach am Attersee, Austria. Tirzepatide (Mounjaro 7.5 mg/0.5 mL Prefilled Pen 4s) was obtained Eli Lilly Saudi Arabia Ltd Riyadh, Saudi Arabia.

Animals: Sixty rats, ranging in age (10-12 weeks) and weight ranging between 225-260 g, procured from the College of Pharmacy's animal house belonging to Qassim University, were housed in individual chambers inside an environment that rotated between light and dark cycles lasting 12 hrs, with the lights being turned on at 6 o'clock in the morning. Pelletized food and water were available to the animals throughout the day. The survival rate of the experimental rats was monitored daily and the body weight was taken every 2 days. The research adhered to the institution's ethical standards for animal experiments.

Experimental procedure including treatment protocol: The experimental animals in this research were divided into six groups, each containing 10 animals. Normal saline is administered intraperitoneally as the control. Administration of treatment involves intraperitoneal delivery of TIRZ at a concentration of 1.35 mg/kg thrice during the study protocol, with a three-day interval between each administration. The second treatment involved administering CIS (8 mg/kg) intraperitoneal delivery in three doses. The fourth treatment involved administering DOX (4 mg/kg) intraperitoneal delivery in three doses. The fifth treatment involved a combination of medications of TIRZ (1.35 mg/kg) and CIS (8 mg/kg).

Finally, the sixth group was administered three doses of TIRZ (1.35 mg/kg) and DOX (4 mg/kg). After completion of the treatments, the animals were euthanized and blood samples were collected from six animals in each group. The experimental rats were closely observed daily to ensure accurate documentation of their survival or mortality rates and body weights every two days. After that, the animals underwent biochemical assays[20].

Electrochemiluminescence (ECL): On day eleven, the rats were euthanized using carbon dioxide (CO_2) humanely and their heads were decapitated from their necks. This occurs after complete drug administration. Then, blood samples were collected from both the control as well as treatment groups, including those receiving TIRZ, CIS, DOX and CIS+TIRZ, as well as DOX+TIRZ. The collected blood samples were placed into Ethylenediaminetetraacetic Acid (EDTA) tubes. The tubes were centrifugated at a speed of 12,000×g for 10 min. The plasma was immediately transferred into 200 µL glass containers. Then, the plasma components were analyzed for troponin I, CK-MB, BUN and creatinine levels using an automatic electrochemiluminescence (ECL) analyzer (Roche Diagnostics, a company based in Germany). The ECL is a highly sensitive technology that detects and quantifies biomolecules, such as proteins, through immunoassays[21].

Ethical consideration: The work was permitted by the Institutional Committee on Animal Protection and Use of Qassim University's Deanship for Scientific Research (approval numbers 23-67-05 and 23-69-07).

Statistical analysis: A test known as an One-way Analysis of Variance (ANOVA) was performed on the results of the *in vivo* research procedure. A presentation of the investigation's findings was made using the mean plus or minus the Standard Error of the Mean (SEM). This resulted in the implementation of a Tukey analysis, which was used for comparing the data on an individual basis. The statistical significance levels were established at a p-value lesser than 0.05.

RESULTS

TIRZ effect on DOX or CIS on rats' survival rate: A model established to understand better whether TIRZ improves the rate of survival in animals was administered with CIS or DXR. A Kaplan-Meier test was utilized to achieve this parameter. Based on the results, an analysis of the survival rate was conducted on rats treated with different combinations of TIRZ and CIS or TIRZ and DXR, it was observed that the findings indicated DOX resulted in 20% mortality and CIS 10% throughout the study duration. However, a combination of TIRZ with CIS caused 50% mortality and TIRZ with DOX caused 30% mortality. Thus, the study's results indicated that adding TIRZ to CIS or DOX may have a synergistic effect, whereas the control and TIRZ groups maintained a 100% survival rate (Fig. 1).

TIRZ combined with CIS or DOX reduces body mass: As per Fig. 2, the body mass (weight) of the TIRZ, CIS, DXR, CIS+TIRZ and DXR+TIRZ treated animals was reduced in comparison to saline treatment. The study measured modifications in body weight from the start to the experiment's conclusion, which showed a significant decrease in TIRZ (mean 93), CIS (mean 82), DOX (mean 89), CIS+TIRZ (mean 79) and DXR+TIRZ (mean 86) when comparison was done with saline group (mean 117).

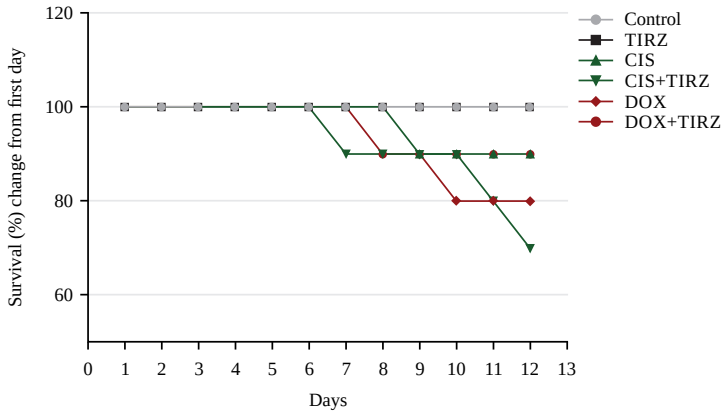

Fig. 1: Role of CIS, DXR, TIRZ and combination on the survival rate

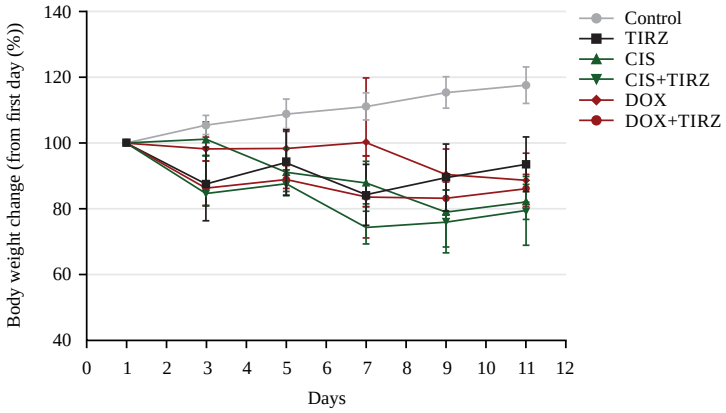

Fig. 2: Role of CIS, DXR, TIRZ and combination on the body weight

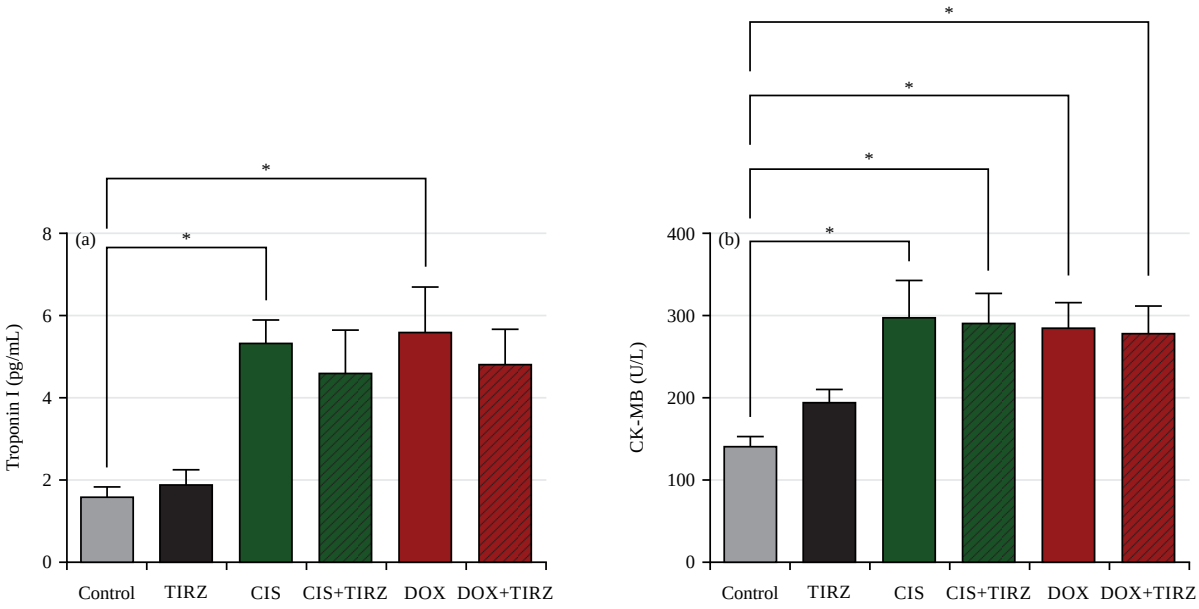

Fig. 3(a-b): Role of CIS, DOX, TIRZ and the combination of TIRZ with CIS or DOX on troponin I and CK-MB levels, (a) Treatment with CIS (24 mg/kg) or DOX (12 mg/kg) i.p (intraperitoneal) injection resulted in observed enhancement of troponin I levels when compared to normal animals, (b) Administration with CIS (24 mg/kg) or DOX (12 mg/kg, intraperitoneal injection) showed a marked elevation in CK-MB levels in comparison with saline group. The combination of CIS or DOX with TIRZ induced a slight reduction in levels of troponin I and CK-MB, but they were insignificant when compared to normal treatment animals (*p<0.05) related to the control group

TIRZ effect on CIS or DOX on troponin I and CK-MB: The observation of the ECL test showed a marked increase in troponin I and CK-MB concentrations in the CIS and DOX groups. However, when TIRZ was combined with CIS and DOX, this increase was not improved when compared with control animals (Fig. 3a-b). Thus, this outcome suggests TIRZ had no positive effect against CIS or DOX-induced cardiotoxicity.

TIRZ effect on CIS or DOX on BUN, creatinine and BUN/creatinine ratio: The observation of the ECL test showed a marked increase in BUN concentrations in the CIS and DOX groups. However, when TIRZ was combined with CIS and DOX, this increase was not improved when compared with control animals (Fig. 4a). On the contrary, it was found that there was a significant decrease in creatinine concentrations in the CIS

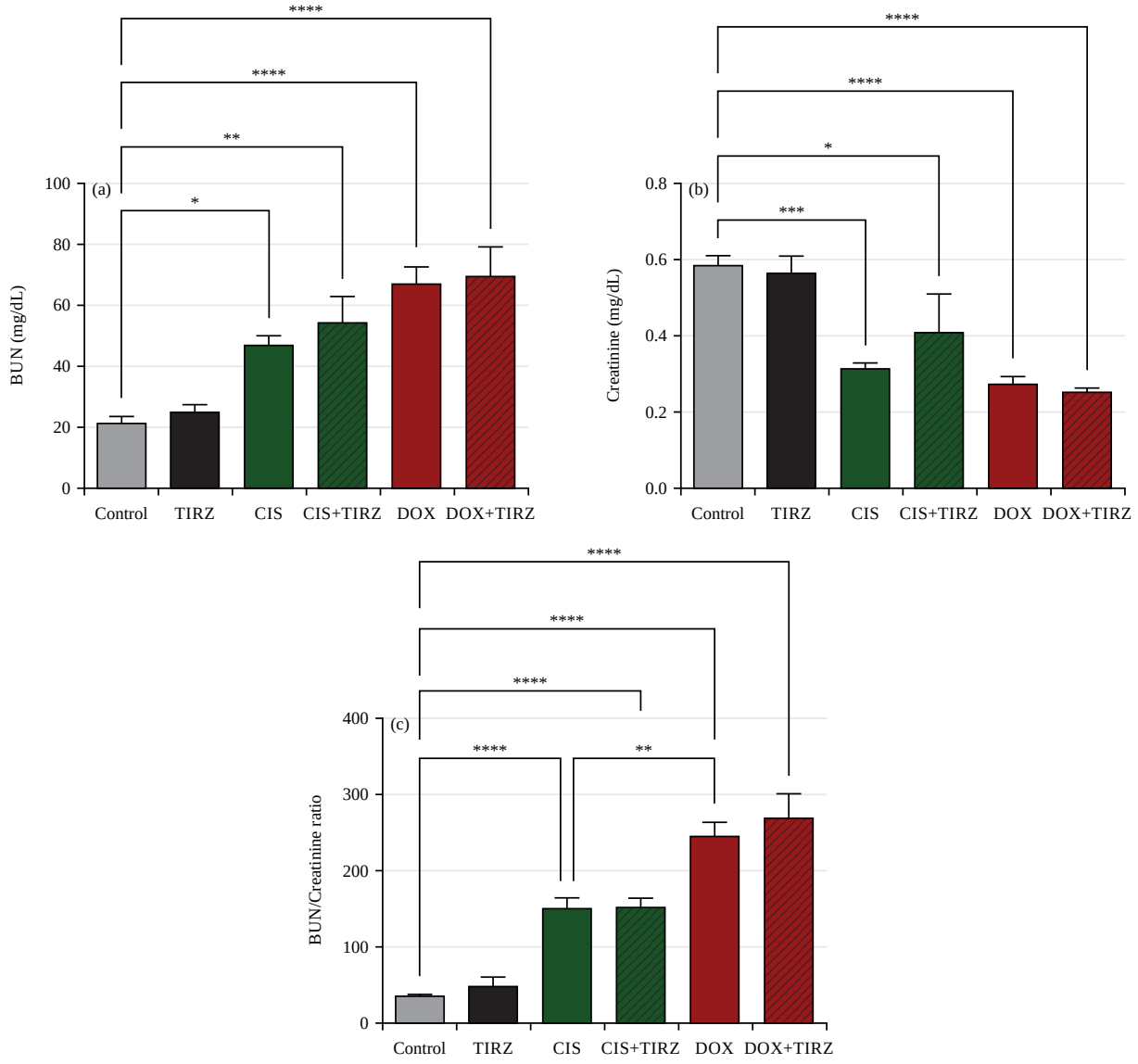

Fig. 4(a-c): Role of CIS, DOX, TIRZ and combination of TIRZ with CIS or DOX on BUN and creatinine levels and their ratio, (a) Treatment with CIS (24 mg/kg) or DOX (12 mg/kg) i.p injection resulted in an observable enhancement of BUN levels, (b) Decrease in creatinine levels upon comparison with the saline group and (c) Administration with CIS (24 mg/kg) or DOX (12 mg/kg) intraperitoneal injection produced a marked elevation in the BUN/creatinine ratio when compared to saline-treated animals (*p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001) different from the control rats or other treated rats

and DOX groups. However, this decrease was not improved when TIRZ was combined with CIS or DOX in comparison with control rats (Fig. 4b). Furthermore, it was recorded a significant ($p<0.001$) increase in the BUN/creatinine ratio in the CIS and DOX-treated groups. However, when TIRZ was combined with CIS or DOX, this increase was not improved compared to the control group (Fig. 4c). Thus, this outcome suggests TIRZ had no positive effect against CIS or DOX-induced nephrotoxicity.

DISCUSSION

The present study used cisplatin (CIS) and doxorubicin (DOX) to treat experimental rats to induce cardiotoxicity and nephrotoxicity, aiming to assess the protective effects of TIRZ against these toxicities. The investigation specifically concentrated on its influence on troponin I, CK-MB, BUN and creatinine levels. The CIS and DOX can interact with DNA

replication by causing damage to the DNA in CIS and inhibiting topoisomerase II, an enzyme essential for both transcription and replication processes[22,23]. Various mechanisms contribute to the development of cardiac and renal failure induced by CIS or DOX, including direct damage to cardiomyocytes and kidney cells, oxidative stress and inflammation[24,25]. Collectively, these factors are thought to be associated with injury to cardiac and renal tissues[8,11]. These modifications lead to variations in troponin I as well as CK-MB from the heart, as well as BUN and creatinine levels due to compromised renal function[5,26,27]. Tirzepatide acts as a receptor agonist for GLP-1 and has demonstrated protective effects on cardiac tissue subjected to chemotherapy in animal studies by mitigating oxidative stress[19]. Reports indicate that tirzepatide may assist in reducing diabetic hyperglycemia through the activation of GLP-1[18]. The TIRZ has been shown to improve glycaemic control through increased stimulation of insulin secretion and enhanced insulin sensitivity[28]. The present research sought to assess the preventive action of TRIZ toward cardiotoxicity and nephrotoxicity induced by CIS and DOX. However, the findings revealed an opposing effect on the heart and kidneys due to the synergistic interaction of TRIZ with CIS or DOX.

This investigation utilized a Kaplan-Meier approach to evaluate the survival rate[29]. This approach is essential for pinpointing the toxic effects linked to particular drugs or medical conditions[30]. The recent study has shown that TIRZ alone had no impact on the survival rate, which remained at 100%, consistent with the control group. Following the administration of three doses of CIS or DOX to the subjects (24 and 12 mg/kg, respectively), the survival rate of the rats declined to 90% for CIS and 80% for DOX after 11 days from the initial dose. Nonetheless, the combination of TIRZ with CIS or DOX resulted in an elevated mortality rate, reaching 70% in the CIS-treated animals and 50% in the DOX-administered rats upon comparison with normal rats. The observations indicate that TIRZ might enhance the toxicity of CIS and DOX.

This study involved a comparison of body weight changes from the initial injected dose of TIRZ, CIS, DOX or their combinations throughout the entire treatment period until the endpoint. Our findings indicate that the control group experienced a weight gain exceeding 6% during the study period. However, the body mass was slightly decreased in TIRZ alone. In the CIS group, body mass was decreased by 11%, while the DOX treatment experienced a 10% reduction in body mass. In rats subjected to a combination of CIS and TIRZ, a 15% decline in body mass, while the combination of TIRZ with DOX resulted in a 16% decrease. Consequently, this study found that TIRZ, CIS, DOX and their combination might decrease the body weight when comparison was done with saline-treated animals.

Cardiac dysfunction can arise from various factors, including angina, myocardial infarction and exposure to toxic agents like chemotherapy[4]. Damage to heart tissues can be indicated by troponin I as well as CK-MB levels[31]. With significant damage to the heart tissue, there is an elevation of troponin I as well as CK-MB values in the bloodstream[32]. Troponin I is recognized to rise for several hours following cardiac damage and then diminishes, whereas CK-MB persists for a longer duration[33]. The present study findings indicated that the groups administered with CIS and DOX exhibited marked elevation in troponin I as well as CK-MB levels. Nonetheless, the combination of TIRZ with CIS and DOX resulted in a slight reduction of the toxic impact on troponin I levels, whereas the TIRZ combination did not enhance the effects of CIS or DOX on CK-MB levels.

The present investigation revealed that rats administered CIS or DOX displayed signs of renal dysfunction, indicated by a notable rise in serum BUN and a reduction in creatinine levels, leading to an elevated BUN/creatinine ratio. This finding aligned with our earlier research and additional studies suggest the detrimental effects of cisplatin (CIS) and doxorubicin (DOX) on renal function. Nonetheless, earlier research has indicated that combining a GLP-1 agonist like liraglutide with CIS in murine models can alleviate the nephrotoxic activity induced by CIS. Similarly, the GLP-1 agonist lixisenatide offers protection against DOX-mediated kidney fibrosis in animals. Nonetheless, the impact of TIRZ on safeguarding the kidneys during chemotherapy remains inadequately elucidated. The study revealed a notable synergistic effect of TIRZ on kidney indicators, evidenced by an enhancement in serum BUN and a reduction in creatinine values, leading to an increased BUN/creatinine ratio. This suggests that TIRZ negatively impacts renal function in patients undergoing CIS and DOX treatment. This study has benefits and weaknesses that need consideration. This study investigates the impact of CIS, DOX and their combination with TIRZ on cardiotoxicity and nephrotoxicity by assessing mortality rate and body weight and measuring troponin I, CK-MB, BUN and creatinine levels. The rats in the present research were of identical age, strain, cancer-free and all tests were performed concurrently throughout the experiment to curtail differences. This study assesses the direct effects of CIS, DOX and their combinations with TIRZ, mitigating cancer interference and minimizing potential confounding factors. The doses and frequency were consistent with those delivered clinically to human patients.

CONCLUSION

The use of CIS or DOX results in notable cardiac dysfunction (enhanced troponin I as well as CK-MB values) and a decline in renal function (increased BUN and reduced creatinine), ultimately culminating in cardiotoxicity and renal failure. The combination of TIRZ with CIS or DOX fails to mitigate this toxicity and exacerbates it. Consequently, healthcare professionals need to take this toxicity into account during chemotherapy administration. However, more research is needed to substantiate the present study findings as well as to establish precisely the role of investigational drugs on organ-level toxicity.

SIGNIFICANCE STATEMENT

This research seeks to assess the protective properties of tirzepatide in relation to cardiotoxicity and nephrotoxicity induced by cisplatin and doxorubicin. Previous studies revealed that cisplatin or doxorubicin can induce cardiotoxicity and nephrotoxicity by increasing levels of troponin I, CK-MB, blood urea nitrogen and creatinine levels. The results indicated that rats administered tirzepatide in conjunction with cisplatin or doxorubicin exhibited an increased mortality rate and a reduction in body weight. Furthermore, the combination of tirzepatide with cisplatin or doxorubicin did not enhance the elevation of troponin I, CK-MB, BUN and creatinine levels. Consequently, the results also demonstrated the inability of tirzepatide to mitigate the cardiotoxic and nephrotoxic effects induced by cisplatin or doxorubicin. Additional studies are necessary in the future to assess various treatment time points of tirzepatide following toxicities induced by cisplatin or doxorubicin.

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REFERENCES

1. Cepoi, M.R., S.T. Duca, A. Chetran, A.D. Costache and M.R. Spiridon *et al*., 2023. Chronic kidney disease associated with ischemic heart disease: To what extent do biomarkers help? Life, Vol. 14. 10.3390/life14010034.
2. Adam, A.M., S.A.R. Nasir, A.Z. Merchant, A.H. Rizvi and A. Rehan *et al*., 2018. Efficacy of serum blood urea nitrogen, creatinine and electrolytes in the diagnosis and mortality risk assessment of patients with acute coronary syndrome. Indian Heart J., 70: 353-359.
3. Braghieri, L., O.Z. Badwan, W. Skoza, M. Fares and V. Menon, 2023. Evaluating troponin elevation in patients with chronic kidney disease and suspected acute coronary syndrome. Cleveland Clinic J. Med., 90: 483-489.
4. Iqbal, M.O., Y. Gu, I.A. Khan, R. Wang and J. Chen, 2023. Evaluation of the *in vitro* antioxidant and antitumor activity of hydroalcoholic extract from *Jatropha mollissima* leaves in Wistar rats. Front. Chem., Vol. 11. 10.3389/fchem.2023.1283618.
5. Afsar, T., S. Razak, A. Almajwal and D. Al-Disi, 2020. Doxorubicin-induced alterations in kidney functioning, oxidative stress, DNA damage, and renal tissue morphology; improvement by *Acacia hydaspica* tannin-rich ethyl acetate fraction. Saudi J. Biol. Sci., 27: 2251-2260.
6. Jafarzadeh, E., V. Montazeri, S. Aliebrahimi, A.H. Sezavar, M.H. Ghahremani and S.N. Ostad, 2022. Combined regimens of cisplatin and metformin in cancer therapy: A systematic review and meta-analysis. Life Sci., Vol. 304. 10.1016/j.lfs.2022.120680.
7. Dasari, S. and P.B. Tchounwou, 2014. Cisplatin in cancer therapy: Molecular mechanisms of action. Eur. J. Pharmacol., 740: 364-378.
8. Dugbartey, G.J., L.J. Peppone and I.A.M. de Graaf, 2016. An integrative view of cisplatin-induced renal and cardiac toxicities: Molecular mechanisms, current treatment challenges and potential protective measures. Toxicology, 371: 58-66.
9. Duan, Z., G. Cai, J. Li and X. Chen, 2020. Cisplatin-induced renal toxicity in elderly people. Ther. Adv. Med. Oncol., Vol. 12. 10.1177/1758835920923430.
10. Rawat, P.S., A. Jaiswal, A. Khurana, J.S. Bhatti and U. Navik, 2021. Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomed. Pharmacother., Vol. 139. 10.1016/j.biopha.2021.111708.
11. Belger, C., C. Abrahams, A. Imamdin and S. Lecour, 2024. Doxorubicin-induced cardiotoxicity and risk factors. IJC Heart Vasculature, Vol. 50. 10.1016/j.ijcha.2023.101332.
12. Wen, S.Y., A. Ali, I.C. Huang, J.S. Liu and P.Y. Chen *et al*., 2023. Doxorubicin induced ROS-dependent HIF1α activation mediates blockage of IGF1R survival signaling by IGFBP3 promotes cardiac apoptosis. Aging, 15: 164-178.
13. Martemucci, G., C. Costagliola, M. Mariano, L. D'andrea, P. Napolitano and A.G. D'Alessandro, 2022. Free radical properties, source and targets, antioxidant consumption and health. Oxygen, 2: 48-78.
14. Gabani, M., D. Castañeda, Q.M. Nguyen, S.K. Choi and C. Chen *et al*., 2021. Association of cardiotoxicity with doxorubicin and trastuzumab: A double-edged sword in chemotherapy. Cureus, Vol. 13. 10.7759/cureus.18194.

15. Checa, J. and J.M. Aran, 2020. Reactive oxygen species: Drivers of physiological and pathological processes. J. Inflammation Res., 13: 1057-1073.
16. Abdur Rauf, A.A. Khalil, S. Awadallah, S.A. Khan and T. Abu-Izneid *et al*., 2024. Reactive oxygen species in biological systems: Pathways, associated diseases, and potential inhibitors-A review. Food Sci. Nutr., 12: 675-693.
17. Jastreboff, A.M., L.J. Aronne, N.N. Ahmad, S. Wharton and L. Connery *et al*., 2022. Tirzepatide once weekly for the treatment of obesity. N. Engl. J. Med., 387: 205-216.
18. Dutta, P., Y. Kumar, A.T. Babu, S.G. Ravindran and A. Salam *et al*., 2023. Tirzepatide: A promising drug for type 2 diabetes and beyond. Cureus, Vol. 15. 10.7759/cureus.38379.
19. Chen, L., X. Chen, B. Ruan, H. Yang and Y. Yu, 2024. Tirzepatide protects against doxorubicin-induced cardiotoxicity by inhibiting oxidative stress and inflammation via PI3K/Akt signaling. Peptides, Vol. 178. 10.1016/j.peptides.2024.171245.
20. Alhowail, A.H., 2024. Pioglitazone ameliorates DOX-induced cognitive impairment by mitigating inflammation, oxidative stress, and apoptosis of hippocampal neurons in rats. Behav. Brain Res., Vol. 457. 10.1016/j.bbr.2023.114714.
21. Alotayk, L.I., M.A. Aldubayan, S.K. Alenezi, M.J. Anwar and A.H. Alhowail, 2023. Comparative evaluation of doxorubicin, cyclophosphamide, 5-fluorouracil, and cisplatin on cognitive dysfunction in rats: Delineating the role of inflammation of hippocampal neurons and hypothyroidism. Biomed. Pharmacother., Vol. 165. 10.1016/j.biopha.2023.115245.
22. Alhowail, A.H., M. Eggert, J. Bloemer, P.D. Pinky and L. Woodie *et al*., 2023. Phenyl-2-aminoethyl selenide ameliorates hippocampal long-term potentiation and cognitive deficits following doxorubicin treatment. PLoS ONE, Vol. 18. 10.1371/journal.pone.0294280.
23. Yang, B., W. Ke, Y. Wan and T. Li, 2021. Targeting RNF8 effectively reverses cisplatin and doxorubicin resistance in endometrial cancer. Biochem. Biophys. Res. Commun., 545: 89-97.
24. Alharbi, I., H. Alharbi, Y. Almogbel, A. Alalwan and A. Alhowail, 2020. Effect of metformin on doxorubicin-induced memory dysfunction. Brain Sci., Vol. 10. 10.3390/brainsci10030152.
25. Zhou, W., A. Kavelaars and C.J. Heijnen, 2016. Metformin prevents cisplatin-induced cognitive impairment and brain damage in mice. PLoS ONE, Vol. 11. 10.1371/journal.pone.0151890.
26. Topal, İ., A.Ö. Bilgin, F.K. Çimen, N. Kurt and Z. Süleyman *et al*., 2018. The effect of rutin on cisplatin-induced oxidative cardiac damage in rats. Anatolian J. Cardiol., 20: 136-142.
27. Dasari, S., S. Njiki, A. Mbemi, C.G. Yedjou and P.B. Tchounwou, 2022. Pharmacological effects of cisplatin combination with natural products in cancer chemotherapy. Int. J. Mol. Sci., Vol. 23. 10.3390/ijms23031532.
28. Thomas, M.K., A. Nikooienejad, R. Bray, X. Cui and J. Wilson *et al*., 2021. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. J. Clin. Endocrinol. Metab., 106: 388-396.
29. Goel, M.K., P. Khanna and J. Kishore, 2010. Understanding survival analysis: Kaplan-Meier estimate. Int. J. Ayurveda Res., 1: 274-278.
30. Dudley, W.N., R. Wickham and N. Coombs, 2016. An introduction to survival statistics: Kaplan-Meier analysis. J. Adv. Pract. Oncol., 7: 91-100.
31. Babuin, L. and A.S. Jaffe, 2005. Troponin: The biomarker of choice for the detection of cardiac injury. Can. Med. Assoc. J., 173: 1191-1202.
32. Alhowail, A.H. and M.A. Aldubayan, 2023. The impact of metformin on the development of hypothyroidism and cardiotoxicity induced by cyclophosphamide, methotrexate, and fluorouracil in rats. Pharmaceuticals, Vol. 16. 10.3390/ph16091312.
33. Aydin, S., K. Ugur, S. Aydin, İ. Sahin and M. Yardim, 2019. Biomarkers in acute myocardial infarction: Current perspectives. Vasc. Health Risk Manage., 15: 1-10.