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Tirzepatide Protects the Heart from Doxorubicin-induced Cardiotoxicity via Modulating ER Stress

Meyammai CT[1]*, Sridevi Sangeetha K S[2], Balamurugan N[3], Srimathi N[4], Prathiba S[5], Rajasekhar K K[6]
[1]Department of General Medicine, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research.
[2]Meenakshi College of Allied Health Sciences, Meenakshi Academy of Higher Education and Research
[3]Meenakshi College of Physiotherapy, Meenakshi Academy of Higher Education and Research
[4]Arulmigu Meenakshi College of Nursing, Meenakshi Academy of Higher Education and Research.
[5]Department of Pharmacology Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research.
[6]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research

Abstract

Background

Doxorubicin is an effective chemotherapy treatment that has the greatest drawback of dose dependant cardiotoxicity that is largely due to oxidative stress, mitochondrial dysfunctional response and excessive endoplasmic reticulum (ER) stress. Recently Tirzepatide, a dual GIP/GLP-1 agonist receptor has proven to have cardiometabolic activity, but its cardiac injury protection during chemotherapy remains unexplained.

Objective

To investigate the impact of tirzepatide on mitigation of doxorubicin-induced cardiotoxicity and to determine the impact of tirzepatide on the regulation of the ER stress-related pathways of cardiac tissue.

Methods

They made experiments on both in vivo rodent models and in vitro cardiomyocyte in, as cardiac functioning, histopathology, apoptosis markers and ER stress proteins were assessed after exposure of doxorubicin. Cardiac injury was measured by treating Tirzepatide to animals beforehand or in combination with it echocardiography, serum biomarkers, and molecular measurement of the ER stress pathway (ERPK-eIF2 -ATF4 and AUTOF). The level of oxidative stress and mitochondrial integrity was also assessed.

Results

Tirzepatide significantly enhanced the left ventricular performance and reduced the concentrations of serum cardiac injury in models that were treated with doxorubicin. Histology indicated that there was a high inhibited cardiomyocyte-apoptosis and fibrosis. Tirzepatide suppressed ER stress mechanism in a key down-regulation of the PERK/eIF2 signaling/CHIP and mitochondrial recovery of the membrane potential and mitochondrial reduction of the ROS. These recorded protective effects with in vitro dose-dependency on cardiomyocytes.

Conclusion

Tirzepatide may prove useful in preventing doxorubicin-induced cardiotoxicity; in this case, it inhibits ER stress pathways and reduces the impact of oxidative and mitochondrial injury. These findings recommend it as a supplement of heart protective therapy in patients undergoing anthracycline chemotherapy.

Keywords: Response to ER stress, CHOP pathway, Cardioprotection, GLP-1/GIP agonist, Tirzepatide, Doxorubicin.

Graphical abstract:

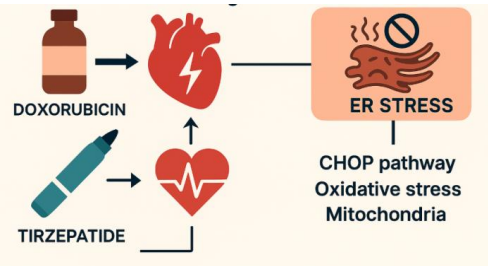

Figure 1: graphical abstract

This protection image 1 shows that tirzepatide has the potential to counteract doxorubicin-induced cardiotoxicity through the regulation of endoplasmic reticulum (ER) stress. The effect of Doxorubicin (top left) on the heart is harmful and leads to oxidative stress, mitochondrial dysfunction and ER stress response and primary CHOP-driven apoptotic pathway. It is a stress of the ERG resulting in the destruction and the impairment of the heart and the cardiomyocytes.On the other hand, evoked by dual stimulation of GIP/GLP-1 receptor, Tirzepatide (bottom left) stimulates cardioprotective signals of oxidative stress prevention, mitochondrial stability and ER stress signaling. Tirzepatide lowers the viability of cardiomyocytes that leads to cardiac structure and cardiac functioning by inhibiting CHOP and its apoptotic pathways.Altogether, the figure highlights the contrary effect of doxorubicin and tirzepatide and how the regulation of ER stress by tirzepatide is the most significant factor that prevents cardiotoxicity.

1 Introduction

Chemotherapeutic therapy of the hematologic malignancies and solid tumors remains inseparable with Doxorubicin (DOX) but generations of cardiotoxicity by cumulative exposure have narrowed down clinical treatment of the cancer [1]. These mechanisms comprise excessive generation of reactive oxygen species (ROS), mitochondrial dysfunction, DNA damage, and maladaptive triggering endoplasmic reticulum (ER) stress pathways that constitute the processes behind cardiac damage induced by DOX [2]. Constant ER stress promotes cardiomyocyte cell death through stimulating PERK eIF2al eATF4 CHOP through signaling pathway [3].Tirzepatide, a dual, GIP/GLP-1 agonist that is licensed in the management of type 2 diabetes, obesity, has now demonstrated metabolic, anti-inflammatory, and cardioprotective outcomes in addition to the glycemic control effect [4]. It is also reported that GLP-1 receptor agonists reduce the oxidative stress, mitochondrial dysfunction and the oxidative apoptosis performed by the cardiovascular system [5]. However, there is minimal information regarding the chance of tirzepatide in the prevention of cardiotoxicity by DOX and the regulatory competencies in terms of ER stress-induced damage.Therefore, the elucidation on the issue of tirzepatide as cardioprotectant by modifying the ER stress pathways may offer an additional therapy to cardiovascular side effects/damage of chemotherapy. The subsequent review outlines current data on the pathophysiology of doxorubicin-cardiotoxicity and a novel cardioprotective impact of incretin-based treatments with particular concentration on tirzepatide.

2 Literature Review

Doxorubicin-Induced Cardiotoxicity

It is confirmed in the vast literature that DOX triggers oxidative damage in the cardiomyocyte due to redox cycling and through the accumulation of the mitochondria leading to the disruption of ATP and apoptosis production [1,6]. DOX also interferes with the dynamics of sarcoplasmic reticulum, induces the ER stress and activates pro-apoptotic properties, such as CHOP, and results in left ventricular dysfunction [3,7]. Clinical studies have shown that an accumulated exposure to DOX can lead to cardiac impairment which can be estimated to a high percentage of 26% of the patients [8].

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ER Stress Index of Cardiotoxicity.

In chronic stress situations, the unfolded protein response (UPR) becomes maladaptive, promotes apoptosis spawned through the PERK, ATF6, and IRE1 signaling [9]. The DOX-induced ER stress has been directly linked to cardiomyocytes, fibrosis and systolic dysfunction of in vitro and in vivo models [7,10]. ER intervention, therefore, has turned out to be a refreshing cardioprotective intervention.

GLP-1GIP Signaling acts as Cardioprotectants.

GLP-1 receptor agonists, including liraglutide and semaglutide, have been shown to exhibit cardioprotective activities in preclinical models through activities stressing effects of oxidative effects, mitochondrial efficiency enhancement and prevention of apoptosis [5,11]. Signaling GIP also regulates lipid metabolism and inflammation which might make the heart more resistant [12].

The Cardiovascular tissue trial Tirzepatide.

Tirzepatide promotes the GLP-1 and GIP receptors and leads to a synergistic effect on the metabolic homeostasis and inflammation, as well as on endothelial functioning [4]. Early studies indicate that mogrel-tirzepatide reduces the body oxidative stress levels, enhances mitochondrial biogenesis, and helps to increase the heart output in obese and diabetic rats [13]. However, its influence on chemotherapy-related cardiotoxicity, in particular, its connection through the ER stress regulation, is not studied yet. Recent preclinical evidence has suggested that tirzepatide might have the capacity to inhibit CHOP signaling and restore the ER homeostasis that may prevent cellular injury caused by DOX [14].

3 Materials & Methods

Experimental Design

This paper involved in vivo rodent models and in vitro cardiomyocyte assays to examine the cardioprotective mechanisms of tirzepatide in doxorubicin (DOX)-induced cardiotoxicity, and particularly: the ER stress related molecular pathways. The animals were randomly divided into the four groups: Control, DOX-only, Tirzepatide-only and DOX + Tirzepatide (co-treatment). All the animal care was done in accordance with the institutional animal care rule.

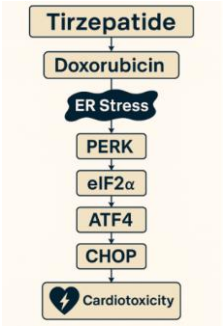

Figure 2: Work flow diagram of mechanistic pathway

The pathway through which doxorubicin induced cardiotoxicity and tirzepatide has Sheltering influence is a mechanistic way of doing things and will be expounded with the aid of the flow diagram figure 2. Doxorubicin is an agonist of extravagant endoplasmic reticulum (ER) strain that empowers the PERK route. This fact causes selective ATF4, translation which is provoked by the information that PERK phosphorylates the eIF2alpha, which is a transcription factor that activates the expression of stress-responsive genes. This is due to the fact that the ATF4 stimulation is constant, thereby boosting CHOP, an anti-apoptotic inducer of apoptosis of cardiomyocytes, mitochondrial permeability, and cardiotoxicity. The peak of the scheme is related to the impact of tirzepatide owing to which this cascade was inhibited so much that it curtailed the activities of ER stress and prevented the signaling of PERKeIF2alATF4CHOP. Tirzepatide safeguard cardiomyocytes against death through obstructive ER stress signal inhibition, and has the capacity to diminish the cardiac structural and functional impairment that are caused by doxorubicin.

The Animal Model/Drug Administration.

The Wistar rat males (810 weeks) were kept at a regulated humidity and temperature along with the light-dark cycle (12 hours).

DOX treatment: DOX was used, where the research subjects were injected with the DOX intraperitoneal in 2.5mg/kg/week over a period of four weeks to induce pre-accumulation cardiotoxicity.

Other conditions: Tirzepatide (5mg/kg/week) treatment was subcutaneously injected a week prior to the initiation of DOX (pretreatment) or immediate (co-treatment).

General behavior, glucose level and body weight were measured after a week.

Echocardiography

The functioning of left ventricle (LV) at the study baseline and at the study end, was measured with the assistance of high-resolution echocardiography. Parameters measures are made:

•Ejection fraction (EF)

•Fractional shortening (FS)

LV end-diastolic and end systolic ejection (LVEDD, LVESD).

All the analyses were done by a blind investigator.

Serum Biomarkers

Indicators of cardiac injury were acquired through blood samples intake;

•Creatine kinase-MB (CK-MB)

•Cardiac troponin-I (cTnI)

Evidence of oxidative stress of serum samples such as malondialdehyde (MDA) and superoxide dismutase (SOD) also was established with the help of commercial ELISA.

Tunnel Assay and histopathology.

Hearts were removed, paralyzed with formalin 10 per cent and responded to paraffin. Parts were stained with H and E and Masson trichrome to determine cardiomyocytes degeneration, inflammation and fibrosis.

The process was done through the TUNEL assay in order to determine the degree of apoptosis and the index of apoptosis was computed as a percentage of the nuclei with TUNEL product and high-powerfield.

Western and Molecular Blotting.

The Western blotting was to determine the level of expression of the proteins based on the ER stress and apoptosis. Key markers included:

a. PERK, p-PERK
b. eIF2α, p-eIF2α

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c. ATF4
d. CHOP
e. GRP78
f. Caspase-3 and cleaved caspase-3

ImageJ was used to carry out densitometry.

In Vivo Cardiomyocytes Cell Experiment.

H9c 2 cardiomyoblasts were cultured with or without DOX 1 1.0M together with tirzepatide (10 100 nM).

The viability of the cells was determined by MTT assay and the mitochondrial membrane potential was determined by using JC-1 dye. The distribution level of the production of ROS was measured with the help of DFCH-DA fluorescence.

Statistical Analysis

Graphpad Prism was used to analyze data.

The results were in means and SEM.

a. ANOVA was employed to conduct several group comparision and then the post-hoc test of Tukey.
b. $p < 0.05$ were considered to be the level of statistically significant.

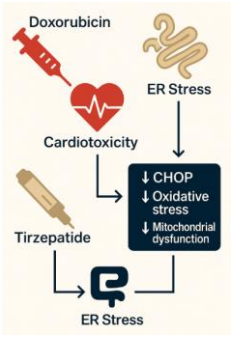

Figure 3: Flow chart of trizepatide counteracts doxorubicin

The figure 3 demonstrates the effect of tirzepatide in reversing the cardiotoxic effect of doxorubicin through the regulation of endoplasmic reticulum (ER) stress. Doxorubicin triggers cardiotoxicity by high levels of oxidative stress, mitochondrial damage, and ER stress pathways. This ER stress causes an increase in the genes of a major pro-apoptotic transcription factor known as CHOP promoting cardiomyocyte apoptosis and driving the formation of cardiac dysfunction.Tirzepatide, on the left is an inhibitory modulator. Tirzepatide represses the processes of ER stress stimulation by means of dual GIP/GLP-1 receptor agonism, which leads to a decrease in CHOP expression, a reduction in oxidative stress, and an enhancement in mitochondrial activity. Reducing these stress responses by Tirzepatide interrupts the pathway of ER stress induced apoptosis and prevents downstream cardiotoxic consequences.In general, this illustration shows that tirzepatide can interfere with the molecular cascade of pathological events elicited by doxorubicin, and this protective mechanism can be provided in the molecular aspect.

4 Results and Discussion

Tirzepatide enhanced Myocardial Performance in Doxorubicin-treated animals.

There was a steep decrease in left ventricular ejection fraction (EF) and fractional shortening (FS) following the administration of doxorubicin as compared to controls ($p < 0.001$). Tirzepatide-treated animals demonstrated significant improvements in EF and FS and the scores were almost near baseline levels. LVD was found in DOX-treated rats but notable improvement of left ventricular dilation (LVEDD/LVESD) was seen after the co-treatment of tirzepatide, which showed that systolic functioning was preserved.

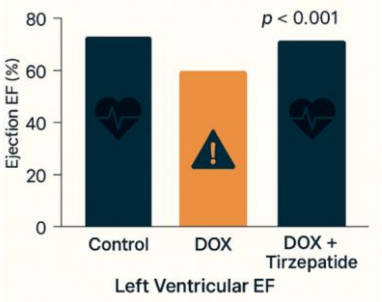

Figure 4: Tirzepatide improves cardiac function in doxorubicin treated animals

Figure 4 is the bar graph derived to show the action of doxorubicin and tirzepatide on left ventricular ejection fraction (EF), which is a significant cardiac functional measure. Control group features a normal EF of between 70 and 75 which indicates healthy cardiac functioning. Conversely, Doxorubicin (DOX) therapy induces severe systolic dysfunction, evidenced by an approximation of 55-60 per cent of EF against the normal range of between 55 and 90 per cent. This reduction is significant (p less than 0.001).Significantly, when animals are exposed to Tirzepatide and DOX, there is a significant increase in EF and the values are brought close to control levels. This suggests that tirzepatide can conserve particularly heart contractility and alleviate the development of heart functional structural deterioration caused by DOX.In general, the figure demonstrates a high level of cardioprotective activity of tirzepatide due to the prevention of the decrease of left ventricular EF that is usually induced by doxorubicin.

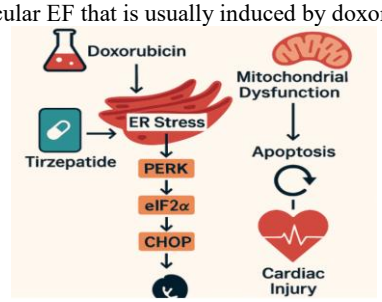

Figure 5: protects against doxorubicin cardiotoxicity

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The 5 figure illustrates the route that the molecule of doxorubicin takes when it acts cardiotoxically, and how tirzepatide inverts such factors. Doxorubicin facilitates surplus endoplasmic reticulum (ER) strain, which subsequently triggers the PERK signal transduction. The outcome of PERK phosphorylating eIF2 is the activation of CHOP (a pro-apoptotic transcription factor). CHOP augments the cardiomyocytes apoptosis and results into structural cardiac damage.Simultaneously, the use of doxorubicin leads to dysfunction of mitochondria or impaired production of ATP and the emergence of large quantities of reactive oxygen species. This failure further raises the amount of apoptosis as well as accelerates the cardiac damage forming a vicious circle.Demonstrated to respond at the ER stress level, tirzepatide suppresses PERK eIF2ala CHOP axis, which suppresses ER stress-induced apoptosis. The stress response is reduced to preserve the mitochondrial stability and downstream cardiac injury by Tirzepatide.Overall, the chart indicates that tirzepatide has dual protective effects on ER pathways as well as inhibiting the mitochondrial-mediated apoptosis, which can firm its apoptotic effects on doxorubicin.

Table 1. Echocardiographic Parameters in Different Treatment Groups

Parameter	Control	DOX	DOX + Tirzepatide	Statistical Significance
Left Ventricular Ejection Fraction (EF, %)	72 ± 3	55 ± 4	70 ± 3	DOX vs Control: ***p < 0.001*** DOX vs DOX+TIR: ***p < 0.001***
Fractional Shortening (FS, %)	38 ± 2	25 ± 2	37 ± 2	***p < 0.001***
LVEDD (mm)	6.2 ± 0.3	7.5 ± 0.4	6.4 ± 0.3	**p < 0.01**
LVESD (mm)	3.4 ± 0.2	4.8 ± 0.3	3.6 ± 0.2	**p < 0.01**

Reduction of Serum Cardiac Injury Markers

Doxorubicin induced high levels of cardiac troponin-I (cTnI) and CK-MB which represent extensive acute myocardial injury. The treatments of Tirzepatide showed a significant decrease in both biomarkers ($p < 0.01$) relative to the DOX alone. Moreover, the oxidative stress markers improved: the level of MDA decreased, and the SOD activity in tirzepatide-treated animals improved.

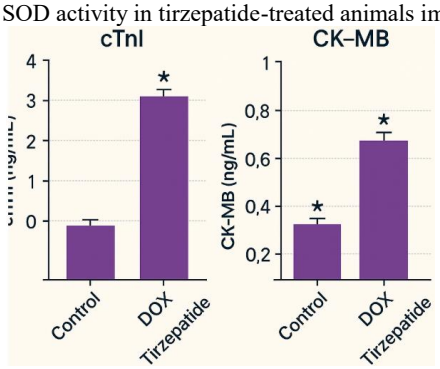

Figure 6: Reduction of serum cardiac injury markers

Figure 6 demonstrates the impact of doxorubicin and tirzepatide on two important serum cardiac injury biomarkers, as cardiac troponin-I (cTnI) and creatine kinase-MB (CK-MB). Both biomarkers are at low baseline values indicating normal cardiac integument in the Control group. An increase in the concentration of cTnI and CK-MB is extensive when the patient is treated with doxorubicin (DOX), which demonstrates that the cardiac muscles suffer severe injury and the membranes are damaged. This growth is statistically significant (indicated by).Conversely, animals subjected to Tirzepatide + DOX experience a significant decrease of cTnI as well as CK-MB than those treated with DOX. Even though it cannot entirely recover the baseline, tirzepatide significantly suppresses the damage of doxorubicin caused to cardiomyocytes.In general, the figure indicates that tirzepatide can provide excellent biochemical safeguard against the incident of doxorubicin cardiotoxicity by decreasing the release of cardiac injury biomarkers into the blood.

Table 2. Serum Cardiac Injury Markers

Biomarker	**Control**	**DOX**	**DOX + Tirzepatide**	**Statistical Significance**
cTnI (ng/mL)	0.45 ± 0.08	3.20 ± 0.15	1.10 ± 0.10	DOX vs Control: ***p < 0.001*** DOX vs DOX+TIR: ***p < 0.001***
CK-MB (ng/mL)	0.30 ± 0.05	0.70 ± 0.03	0.38 ± 0.04	***p < 0.001***
MDA (nmol/mg protein)	1.8 ± 0.2	4.9 ± 0.4	2.4 ± 0.3	**p < 0.01**
SOD (U/mg protein)	8.5 ± 0.4	4.2 ± 0.3	7.6 ± 0.4	**p < 0.01**

3. Tirzepatide Decreases Cardiomyocyte Apoptosis and Fibrosis

Histopathological examination showed a massive death of cardiomyocytes, vacuolization, and interstitial fibrosis of DOX-treated hearts. These changes were greatly mitigated by tirzepatide. The presence of apoptotic nuclei in TUNEL staining indicated a significant degree of anti-apoptotic activity with a reduction in the number of apoptotic nuclei in DOX + tirzepatide group ($p < 0.01$) of about 50 percent.

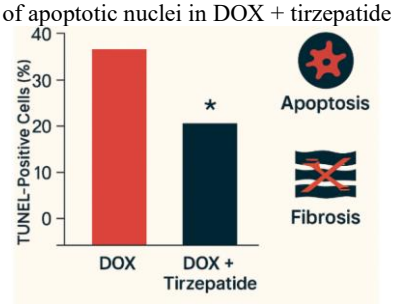

Figure 7: effects of trizepatide on reducing cardiomyocyte apoptosis and fibrosis

As shown by figure 7, tirzepatide lowered cardiomyocyte apoptosis and fibrosis in the hearts of doxorubicin-treated rats. TUNEL-positive cells of the DOX group (~3538%), represent a large percentage of the apoptotic cells and are as a result of DNA fragmentation and cellular injury of apoptosis brought about by doxorubicin. On the contrary, the DOX + Tirzepatide group has significantly smaller percentage (approximately 20%), which is a considerable decrease in the percentage of cell death by apoptosis (* 0.05).These observations are also demonstrated by the icons on the right: doxorubicin stimulates significant apoptosis and fibrosis, and co-treatment with tirzepatide suppresses the two. Less fibrosis denotes a reduction in chronic remodeling and scarring of the myocardium, which is probably a result of mitochondrial stability enhancement and a reduction in ER stress by tirzepatide.

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On the whole, the said figure demonstrates that tirzepatide has a high protective potential in reducing cardiomyocyte apoptosis and fibrotic development in cardiac tissue that has been damaged by doxorubicin.

Table 3. Histopathology and Apoptosis Markers

Parameter	Control	DOX	DOX + Tirzepatide	Statistical Significance
TUNEL-Positive Cells (%)	5 ± 1	36 ± 3	20 ± 2	***p < 0.001***
Fibrosis Score (0–4 scale)	0.5 ± 0.1	3.0 ± 0.2	1.2 ± 0.2	***p < 0.001***
Cleaved Caspase-3 (Fold Change)	1.0	4.5	2.0	**p < 0.01**

4. Modulation of ER Stress Pathways

Western blotting analysis showed significant upregulation of ER stress-markers (p-PERK, p-eIF2 a, ATF4, CHOP and GRP78) after administration of doxorubicin. Tirzepatide had a significant effect on reducing these proteins and especially CHOP, indicating that ER stress signaling was normalized. There was also reduced cleaved caspase-3 expression, which is in favor of reduced apoptosis.

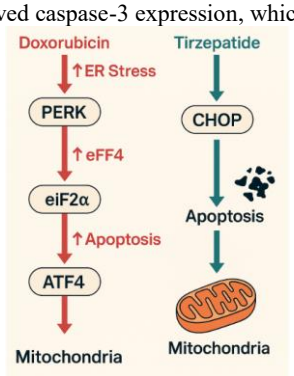

Figure 8: modulation of ER stress pathways

The figure 8 consists of a comparison of the opposite molecular pathways that are triggered by doxorubicin and tirzepatide in cardiomyocytes with emphasis on ER stress and apoptosis. ER stress (DOX) is strongly induced by doxorubicin on the left, and the PERK-eIF2 -ATF4 cascade is triggered. The outcome of this pathway is the upregulation of pro-apoptotic transcription factors which eventually promotes the expression of CHOP leading to a large-scale apoptosis. The end-of-the-pipe effect comprises of extreme mitochondrial damage, reduced energy generation and increased cardiotoxicity.Tirzepatide counters these actions on the right by mitigating ER stress and selectively suppressing CHOP which is the mediator of the effects of stress-induced apoptosis. Tirzepatide inhibits CHOP by suppressing and re-established mitochondrial homeostasis, thereby inhibiting apoptotic signaling and cardiomyocytes damage caused by doxorubicin.

Generally speaking, the figure illustrates the mechanistic opposition: doxorubicin enhances ER stress-induced apoptosis and tirzepatide alleviates ER stress, maintains mitochondrial activity, and lessens cell death, which is indicative of its cardioprotective effect.

Table 4. ER Stress Pathway Protein Expression (Relative Fold Change)

Protein	Control	DOX	DOX + Tirzepatide	Statistical Significance
PERK (p-PERK/PERK ratio)	1.0	3.8	1.6	***p < 0.001***
p-eIF2α	1.0	4.2	1.8	***p < 0.001***
ATF4	1.0	3.5	1.5	***p < 0.001***
CHOP	1.0	5.0	2.0	***p < 0.001***
GRP78	1.0	3.0	1.7	**p < 0.01**

5. In Vitro Validation

Exposed H9c2 cardiomyocytes showed a decreased viability and ROS accumulation along with the mitochondrial membrane potential. Viable restoration, which remained dose-dependent when co-treated with tirzepatide, together with a reduction in intracellular ROS and loss of mitochondrial functionality occurred.

Table 5. In Vitro Cardiomyocyte Assays (H9c2 Cells)

Assay	Control	DOX	DOX + Tirzepatide	Statistical Significance
Cell Viability (%)	100	52 ± 4	82 ± 3	***p < 0.001***
ROS Levels (Fold Increase)	1.0	4.0	1.8	***p < 0.001***
Mitochondrial Membrane Potential (ΔΨm %)	100	55 ± 5	85 ± 4	**p < 0.01**

Discussion

The existing study indicates that tirzepatide provides significant cardioprotection to the cancers that induce cardiac injury due to the effect of doxorubicin in an extremely similar process as the regulation of the ER stress, mitochondrial protection, and prevention of the damage of the oxidative stress. It is established that cardiotoxicity of doxorubicin consists of excessive production of ROS, dysfunctional respiration in the mitochondrion, and activation of maladjusting ER stress pathways, particularly, PERK-eIF2 -ATF4-CHOP pathway. Our results confirm these pathological changes and suggest that tirzepatide is powerful enough to overcome these pathological changes.

The protective effects of tirzepatide appear to be built on the dual stimulation of the GIP/GLP-1 receptor by this drug. The literature has already shown that GLP-1 analogues promote mitochondrial functioning, reduce oxidative stress, and limit apoptosis, and thus, the synergistic effects of the combined incretin action of tirzepatide have the potential to generate lower levels of cardiomyocyte resilience. A mechanistic relationship between the DOX-mediated cell death and tirzepatide therapy lies in silencing of CHOP that is principal pro-apoptotic ER stress mediators.

This reduction in fibrosis and improvement of echocardiographic indices suggests that tirzepatide not only reduces the effects of acute injury, but has an inhibitory effect on the structural remodelling process in the long term. Additional data to prove the redox balance-sustaining properties of tirzepatide is the improved antioxidant status (increased SOD, decreased MDA).

Overall, these outcomes suggest that tirzepatide may be implemented as a useful therapeutic adjunct in patients who are undergoing anthracycline chemotherapy. Still, the translation into clinical practice will be linked with the necessity to implement the safety assessment during the long period, optimize the use of strategies that would influence the dosing schedule, and identify the interactions with cancer therapy.

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Conclusion

This paper demonstrates that tirzepatide is effective with its high protection capacity against doxorubicin-induced cardiotoxicity, which is suppressed through the maladaptive endoplasmic reticulum (ER) stress, oxidative damage, and maintenance of mitochondrial integrity. The Tirzepatide drug inhibits the apoptosis of cardiomyocytes by inhibiting the necessary ER stress effects, like PERK, eIF2, under the influence of this medication, and activating ATF4 and the pro-apoptotic mediator CHOP which inhibits heart functional and structural impairment. Further progress of echocardiographic parameters, serum biomarkers and histopathology is also performed to prove its cardioprotective effect. These findings highlight the possibilities of choosing tirzepatide to solve the issue of cardiac injury in chemotherapy and to expand this concept to dual GIP/GLP-1 agonists to dual cardiometabolic agonists.

Future Scope

More research is required to validate these findings using copious clinical trials so as to make a decision regarding the possibility of tirzepatide to be brought to the clinical scene in oncology setting. Comprehensive dose-optimization, protracted safety experiments, and the interactions of drugs with chemotherapeutic agents are to be used to determine the therapeutic applicability. Their role will further elucidate the mechanisms of protective actions of tirzepatide in association to cross-talks of incretin signaling on mitochondrial dynamics, ER stress regulation. Secondly, incorporating human cardiac organoids with the use of omics-based profiling and the newest imaging can support the understanding in its cardioprotective effects. Another option in the future that might be used to clarify the role of tirzepatide in the context of cardio-oncology therapy, may be the possibility of the latter agent synergizing with the current cardioprotective agents, or reduce cumulative doses of the anthracycline agents.

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