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Effects of Semaglutide in Doxorubucin Induced Cardiotoxicity in Wistar Rat

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ABSTRACT:

Cardiovascular disease remains the leading cause of death worldwide, and drug-induced cardiotoxicity is an important and growing contributor to cardiac morbidity. Doxorubicin, a widely used anthracycline anticancer agent, is limited in clinical practice by a dose-dependent and cumulative cardiotoxicity that is driven principally by oxidative stress, mitochondrial dysfunction, and disruption of calcium homeostasis in cardiomyocytes. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist widely used in the management of type 2 diabetes mellitus and obesity, has been reported to exert antioxidant, anti-inflammatory and cardioprotective actions in addition to its established metabolic effects.

The present study is designed to evaluate the protective effect of semaglutide against doxorubicin-induced cardiotoxicity in Wistar albino rats. Cardiotoxicity will be induced in rats using doxorubicin, and the protective potential of three graded doses of semaglutide (3, 7 and 14 mg/kg) will be assessed against a verapamil-treated standard group and untreated control groups. In addition, an in-silico molecular docking study will be carried out to explore the interaction of semaglutide with key proteins implicated in cardiac oxidative and apoptotic signalling, namely NF-κB, Bax, Bcl-2 and NRF2.

Cardioprotection will be assessed using serum cardiac injury markers (LDH, CK-MB, cTn-T), inflammatory cytokines (TNF-α, IL-6, IL-10), cardiac tissue oxidative stress parameters (MDA/TBARS, GSH, SOD, catalase, TAC), heart-to-body weight ratio, myocardial infarct size and histopathological examination of cardiac tissue. The outcome of this study is expected to generate scientific evidence on whether semaglutide, beyond its metabolic benefits, can attenuate doxorubicin-induced cardiac injury, thereby supporting its potential adjunct use in patients receiving anthracycline chemotherapy.

Keywords: Semaglutide; Doxorubicin; Cardiotoxicity; Wistar rats; Oxidative stress; Molecular docking; GLP-1 receptor agonist.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide, accounting for an estimated 17.9 million deaths each year [1]. A preventable part of this burden is drug-induced cardiac injury, of which anthracycline cardiotoxicity is a prominent example. Doxorubicin remains one of the most effective and widely used antineoplastic agents, acting through DNA intercalation and topoisomerase II inhibition, but its use is constrained by a cumulative, dose-dependent cardiomyopathy that may stay subclinical for years before presenting as heart failure [2,3].

The cardiotoxic mechanisms of doxorubicin are interlinked. Redox cycling of its quinone moiety and iron-catalysed Fenton chemistry generate reactive oxygen species; inhibition of topoisomerase IIβ, mitochondrial accumulation, disturbed sarcoplasmic reticulum calcium handling, and activation of NF-κB-driven inflammation and Bax/Bcl-2-mediated apoptosis converge on cardiomyocyte death. The heart is especially vulnerable because of its high mitochondrial density and limited endogenous antioxidant reserve. Dexrazoxane, the only agent approved for this indication, has a restricted label [4], so effective and well-tolerated cardioprotective strategies are still needed.

Semaglutide is a long-acting GLP-1 receptor agonist approved for type 2 diabetes and obesity, and it reduces major adverse cardiovascular events in clinical trials [5,6]. Experimental data suggest direct cardioprotective actions, including anti-inflammatory and antioxidant effects, modulation of the Bax/Bcl-2 balance and activation of the NRF2 pathway. Semaglutide has been reported to ameliorate doxorubicin-induced cardiac dysfunction in rodents by correcting BNIP3-mediated mitochondrial dysfunction [7], and the related agonist exenatide protects through the SIRT1 pathway [8]; a further study examined semaglutide in doxorubicin cardiotoxicity in Wistar rats [9]. A systematic dose-ranging evaluation that combines biochemical, structural and histopathological endpoints with an active comparator and a mechanistic in silico analysis is, however, lacking.

The present study therefore evaluated the effect of three graded doses of semaglutide on doxorubicin-induced cardiotoxicity in Wistar rats, using verapamil, a calcium-channel blocker, as the standard comparator, and used molecular docking to explore the interaction of semaglutide with NF-κB, Bax, Bcl-2 and NRF2.

2. Materials and Methods

2.1 Drugs and chemicals

Semaglutide, doxorubicin hydrochloride and verapamil hydrochloride were used as test, inducing and standard drugs, respectively Kits for LDH, CK-MB and cTn-T, rat-specific ELISA kits for TNF-α, IL-6 and IL-10, Ellman's reagent (DTNB), thiobarbituric acid, nitroblue tetrazolium/pyrogallol, hydrogen peroxide, FRAP reagents and Bradford/Lowry reagents were used for biochemical estimation. All other chemicals were of analytical grade.

2.2 Experimental animals and ethics

Healthy male Wistar albino rats (200–250 g) were housed in polypropylene cages (not more than three per cage) at 22 ± 2 °C, 50–60% relative humidity and a 12 h light/dark cycle, with a standard pellet diet and water *ad libitum*. Animals were acclimatised for at least 7 days before dosing, and animals showing signs of illness were excluded. The study followed CPCSEA guidelines and the 3Rs principle and was approved by the Institutional Animal Ethics Committee (IAEC approval no. IAEC NO:2308/PO/Re/ S/2024/CCSEA). Humane endpoints (weight loss above 20% of baseline, marked lethargy, laboured breathing or inability to access food and water) were applied.

2.3 Molecular docking

The three-dimensional structure of semaglutide was retrieved from PubChem (SDF) and energy-minimised in ChemBio3D Ultra 14.0. Crystal structures of NF-κB (PDB 4KV1), Bax (4S0O), Bcl-2 (1G5M/1GJH) and NRF2 (4IFL) were obtained from the RCSB Protein Data Bank. Water molecules, extraneous chains and heteroatoms were removed, and polar hydrogens, Kollman charges and missing atoms were added in AutoDockTools 1.5.6. Blind docking was performed with AutoDock 4.0 using a grid of 96 × 86 × 90 points (0.5 Å spacing) and the Lamarckian genetic algorithm with a maximum of 25 conformers. Binding energies, inhibition constants (Ki) and interacting residues were recorded, and poses were visualised in BIOVIA Discovery Studio Visualizer 2019.

2.4 Induction of cardiotoxicity and experimental design

Animals were randomly allocated to six groups (n = 6 each): Group I, vehicle control (normal saline, 0.5 mL/kg, oral); Group II, doxorubicin (200 mg/kg, cumulative) with saline; Groups III, IV and V, doxorubicin plus semaglutide at 3, 7 and 14 mg/kg, respectively; and Group VI, doxorubicin plus verapamil (20 mg/kg/day (oral or intraperitoneal), doxorubicin dosing schedule, semaglutide dosing frequency and the exact treatment duration (14–28 days in the thesis). The cumulative doxorubicin dose of 200 mg/kg is far above the 15–25 mg/kg usually used in rat models; please verify the unit and dose before submission.

2.5 Sample collection

Twenty-four hours after the last dose, body weight was recorded and blood was collected under light anaesthesia for serum preparation. Animals were then euthanised by CPCSEA-approved methods, and hearts were excised, rinsed in ice-cold saline, blotted and weighed. Part of the tissue was fixed in 10% neutral buffered formalin for histopathology and TTC staining, and the remainder was homogenised for biochemical assays.

2.6 Biochemical estimations

Serum LDH (kinetic NADH-based method) and CK-MB (immunoinhibition kinetic method) were measured with diagnostic kits, and serum cTn-T, TNF-α, IL-6 and IL-10 by sandwich ELISA read at 450 nm. In cardiac homogenates, lipid peroxidation was measured as thiobarbituric acid reactive substances (MDA; 532 nm), reduced glutathione by Ellman's method (412 nm), SOD by inhibition of pyrogallol autoxidation or NBT reduction (560–570 nm), catalase by the rate of H_2O_2 decomposition (240 nm), total antioxidant capacity by the FRAP assay (593 nm), and total protein by the Lowry or Bradford method using bovine serum albumin as standard. Tissue parameters were expressed per mg protein. Assays were run in duplicate or triplicate, with blanks and standards, and samples from all groups were processed in the same batch where feasible.

2.7 Heart-to-body weight ratio, infarct size and histopathology

The heart-to-body weight ratio was calculated as (wet heart weight/terminal body weight) × 100. Infarct size was determined by triphenyltetrazolium chloride (TTC) staining of transverse sections and expressed as a percentage of left ventricular area using image analysis software. For histology, formalin-fixed tissue was processed, embedded in paraffin, sectioned at 4–5 µm and stained with haematoxylin and eosin. Myofibrillar disarray, vacuolisation, inflammatory infiltration, interstitial oedema and necrosis were scored 0–4 (0 = absent, 4 = severe) by an observer blinded to group allocation.

2.8 Statistical analysis

Data are presented as mean ± SEM (n = 6). Groups were compared by one-way ANOVA followed by Tukey's post hoc test, and $p < 0.05$ was considered significant. Each group was compared with the doxorubicin group (Group II), and Group V was compared with Group VI. Histopathological scores are semi-quantitative and are reported descriptively [or state Kruskal–Wallis/Dunn's test results if the raw scores were analysed]. [State the software used, e.g. GraphPad Prism version.]

3. Results

3.1 Molecular docking

Semaglutide showed favourable predicted binding to all four targets (Table 1, Figure 1). The strongest interaction was with NF-κB (−7.42 kcal/mol; Ki 3.60 μM), followed by Bcl-2 (−7.16 kcal/mol; 5.52 μM), Bax (−6.85 kcal/mol; 9.65 μM) and NRF2 (−6.57 kcal/mol; 15.20 μM). Docking alone cannot establish functional modulation of these proteins.

Table 1. Docking results of semaglutide against selected cardiac signalling proteins.

Target	PDB ID	Binding energy (kcal/mol)	Ki (μM)	Key interacting residues
NF-κB	4KV1	−7.42	3.60	Lys144, Arg246, Glu241, Asn244
Bax	4S0O	−6.85	9.65	Arg145, Glu69, Leu70, Asp71
Bcl-2	1G5M / 1GJH	−7.16	5.52	Arg143, Tyr105, Phe112, Ala146
NRF2	4IFL	−6.57	15.20	Lys150, Arg415, Glu413, Asn414

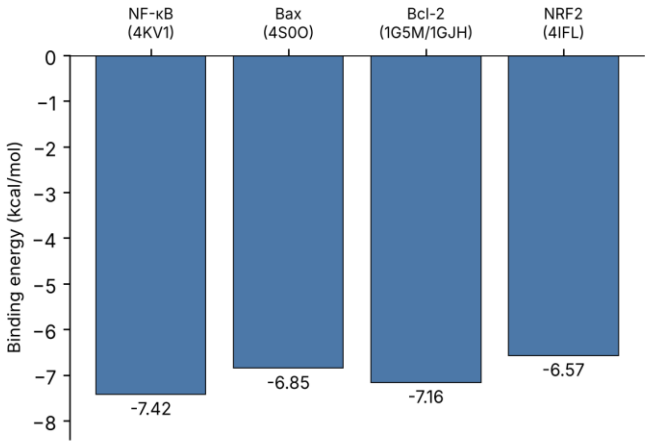


Figure 1. Predicted binding energies of semaglutide against NF-κB, Bax, Bcl-2 and NRF2. More negative values indicate stronger predicted binding.

3.2 Body weight, heart weight and heart-to-body weight ratio

Terminal body weight fell in the doxorubicin group (183.6 ± 4.7 g) compared with control (224.8 ± 5.3 g), and this was attenuated dose-dependently by semaglutide (Table 2). Absolute heart weight did not differ materially between groups. The heart-to-body weight ratio rose from 0.365 ± 0.015% in controls to 0.468 ± 0.018% with doxorubicin, and was significantly lower in the 14 mg/kg semaglutide group (Table 2, Figure 5A).

Table 2. Body weight, heart weight and heart-to-body weight ratio.

Parameter	I: Control	II: DOX	III: SEM 3 + DOX	IV: SEM 7 + DOX	V: SEM 14 + DOX	VI: VRP + DOX
Initial body weight (g)	202.4 ± 4.8 ns	201.8 ± 5.1	202.1 ± 4.6 ns	203.0 ± 5.2 ns	202.6 ± 4.9 ns	201.9 ± 5.0 ns
Terminal body weight (g)	224.8 ± 5.3 ***	183.6 ± 4.7	195.8 ± 5.0 ns	202.7 ± 4.8 ns	210.9 ± 5.2 **	205.6 ± 4.9 *

Parameter	I: Control	II: DOX	III: SEM 3 + DOX	IV: SEM 7 + DOX	V: SEM 14 + DOX	VI: VRP + DOX
Heart weight (g)	0.82 ± 0.03 ns	0.86 ± 0.03	0.84 ± 0.03 ns	0.83 ± 0.03 ns	0.82 ± 0.02 ns	0.83 ± 0.03 ns
Heart/body wt ratio (%)	0.365 ± 0.015 **	0.468 ± 0.018	0.429 ± 0.017 ns	0.409 ± 0.016 ns	0.389 ± 0.014 *	0.404 ± 0.016 ns

Mean ± SEM, n = 6. Symbols denote Tukey comparison against Group II (DOX): *p < 0.05, **p < 0.01,** *p < 0.001, ns = not significant.

3.3 Serum cardiac injury markers

Doxorubicin significantly raised serum LDH, CK-MB and cTn-T compared with control (all p < 0.001; Table 3, Figure 2). Semaglutide reduced all three markers in a stepwise, dose-dependent manner. LDH was lowered to 389.6 ± 15.7, 324.8 ± 13.4 and 264.3 ± 11.8 U/L at 3, 7 and 14 mg/kg, respectively (about 44% below the doxorubicin value at the highest dose). The 3 mg/kg dose reduced LDH but not CK-MB or cTn-T significantly, whereas the 7 and 14 mg/kg doses were effective for all three markers. Semaglutide 14 mg/kg did not differ significantly from verapamil.

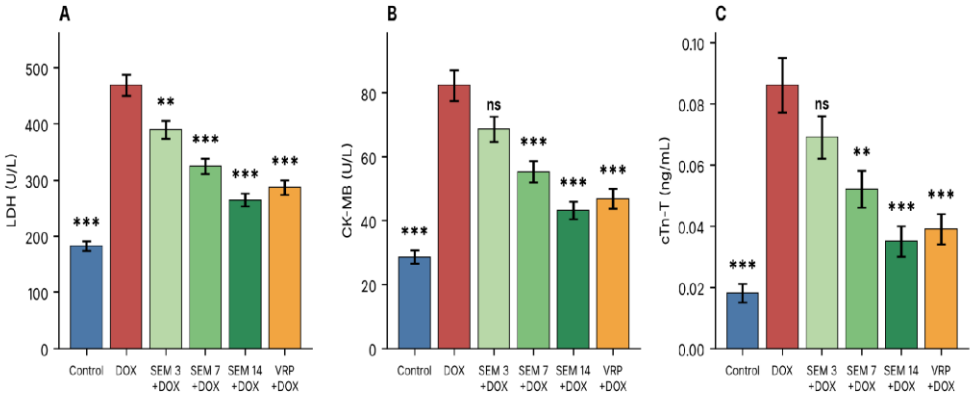


Figure 2. Serum LDH (A), CK-MB (B) and cTn-T (C). Mean ± SEM, n = 6. Symbols show comparison against the DOX group (Tukey): *p < 0.05, **p < 0.01,** *p < 0.001, ns = not significant. SEM, semaglutide (mg/kg); VRP, verapamil.

3.4 Serum inflammatory cytokines

Doxorubicin increased TNF-α (96.8 ± 3.7 vs 42.6 ± 2.1 pg/mL) and IL-6 (78.5 ± 3.2 vs 31.4 ± 1.8 pg/mL) and reduced the anti-inflammatory cytokine IL-10 (18.6 ± 1.2 vs 38.7 ± 1.9 pg/mL). Semaglutide lowered TNF-α and IL-6 and restored IL-10 in a dose-dependent manner; at 14 mg/kg, TNF-α was 55.3 ± 2.4 pg/mL, IL-6 43.8 ± 2.1 pg/mL and IL-10 34.2 ± 1.8 pg/mL (Table 3, Figure 3). Verapamil gave similar values.

Table 3. Serum cardiac injury markers and cytokines.

Parameter	I: Control	II: DOX	III: SEM 3 + DOX	IV: SEM 7 + DOX	V: SEM 14 + DOX	VI: VRP + DOX
LDH (U/L)	182.4 ± 8.6 ***	468.7 ± 18.5	389.6 ± 15.7 **	324.8 ± 13.4 ***	264.3 ± 11.8 ***	286.7 ± 12.6 ***
CK-MB (U/L)	28.6 ± 2.1 ***	82.4 ± 4.8	68.7 ± 3.9 ns	55.3 ± 3.4 ***	43.2 ± 2.8 ***	46.8 ± 3.1 ***
cTn-T (ng/mL)	0.018 ± 0.003 ***	0.086 ± 0.009	0.069 ± 0.007 ns	0.052 ± 0.006 **	0.035 ± 0.005 ***	0.039 ± 0.005 ***
TNF-α (pg/mL)	42.6 ± 2.1 ***	96.8 ± 3.7	82.4 ± 3.1 *	69.7 ± 2.8 ***	55.3 ± 2.4 ***	51.6 ± 2.2 ***
IL-6 (pg/mL)	31.4 ± 1.8 ***	78.5 ± 3.2	66.2 ± 2.9 *	55.1 ± 2.5 ***	43.8 ± 2.1 ***	40.6 ± 1.9 ***
IL-10 (pg/mL)	38.7 ± 1.9 ***	18.6 ± 1.2	23.9 ± 1.4 ns	28.7 ± 1.6 **	34.2 ± 1.8 ***	35.6 ± 1.7 ***

Mean ± SEM, n = 6. Symbols denote Tukey comparison against Group II (DOX).

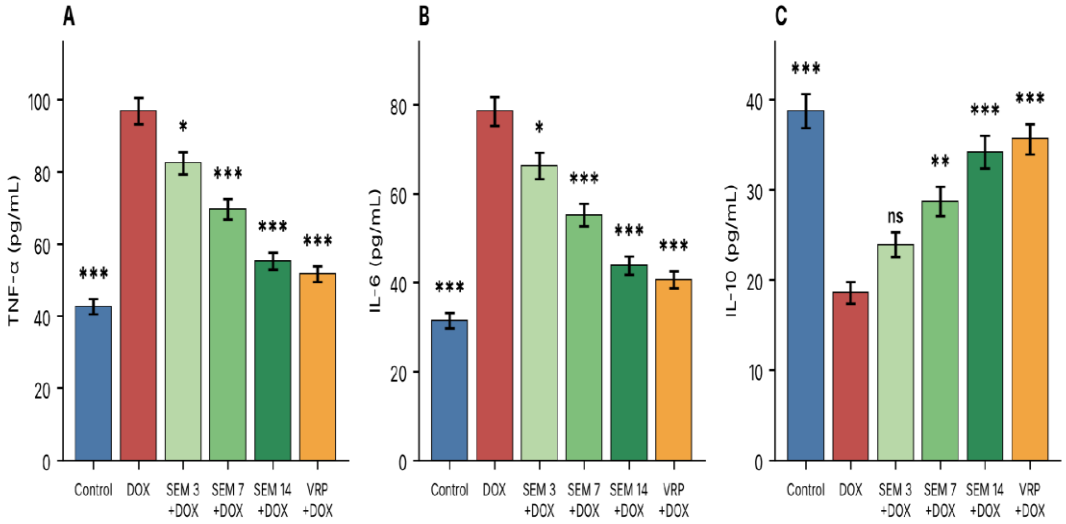


Figure 3. Serum TNF-α (A), IL-6 (B) and IL-10 (C). Statistics and abbreviations as in Figure 2.

3.5 Cardiac oxidative stress and antioxidant status

Doxorubicin approximately doubled lipid peroxidation (MDA/TBARS 5.96 ± 0.21 vs 2.84 ± 0.12 nmol/mg protein) and halved GSH, SOD, catalase and TAC, with a reduction in tissue protein (Table 4, Figure 4). Semaglutide reversed these changes dose-dependently. At 14 mg/kg, MDA fell to 3.38 ± 0.14 nmol/mg protein, and GSH (6.91 ± 0.29 µg/mg protein), SOD (7.52 ± 0.32 U/mg protein), catalase (6.18 ± 0.27 U/mg protein) and TAC (1.67 ± 0.08 µmol/g tissue) approached control and verapamil values. MDA was reduced even at 3 mg/kg, while the antioxidant enzymes and TAC became significantly different from doxorubicin from 7 mg/kg.

Table 4. Cardiac tissue oxidative stress and antioxidant parameters.

Parameter	I: Control	II: DOX	III: SEM 3 + DOX	IV: SEM 7 + DOX	V: SEM 14 + DOX	VI: VRP + DOX
MDA/TBARS (nmol/mg protein)	2.84 ± 0.12 ***	5.96 ± 0.21	5.01 ± 0.18 **	4.22 ± 0.16 ***	3.38 ± 0.14 ***	3.21 ± 0.13 ***
GSH (µg/mg protein)	7.82 ± 0.31 ***	4.16 ± 0.22	4.92 ± 0.24 ns	5.74 ± 0.27 **	6.91 ± 0.29 ***	7.18 ± 0.30 ***
SOD (U/mg protein)	8.64 ± 0.34 ***	4.32 ± 0.25	5.21 ± 0.27 ns	6.18 ± 0.29 **	7.52 ± 0.32 ***	7.78 ± 0.33 ***
Catalase (U/mg protein)	6.92 ± 0.28 ***	3.48 ± 0.21	4.27 ± 0.23 ns	5.12 ± 0.25 **	6.18 ± 0.27 ***	6.42 ± 0.28 ***
TAC (µmol/g tissue)	1.86 ± 0.08 ***	0.94 ± 0.06	1.14 ± 0.06 ns	1.36 ± 0.07 **	1.67 ± 0.08 ***	1.72 ± 0.08 ***
Total protein (mg/g tissue)	82.5 ± 2.4 ***	61.8 ± 2.1	67.4 ± 2.2 ns	72.8 ± 2.3 *	78.1 ± 2.4 ***	79.6 ± 2.3 ***

Mean ± SEM, n = 6. Symbols denote Tukey comparison against Group II (DOX).

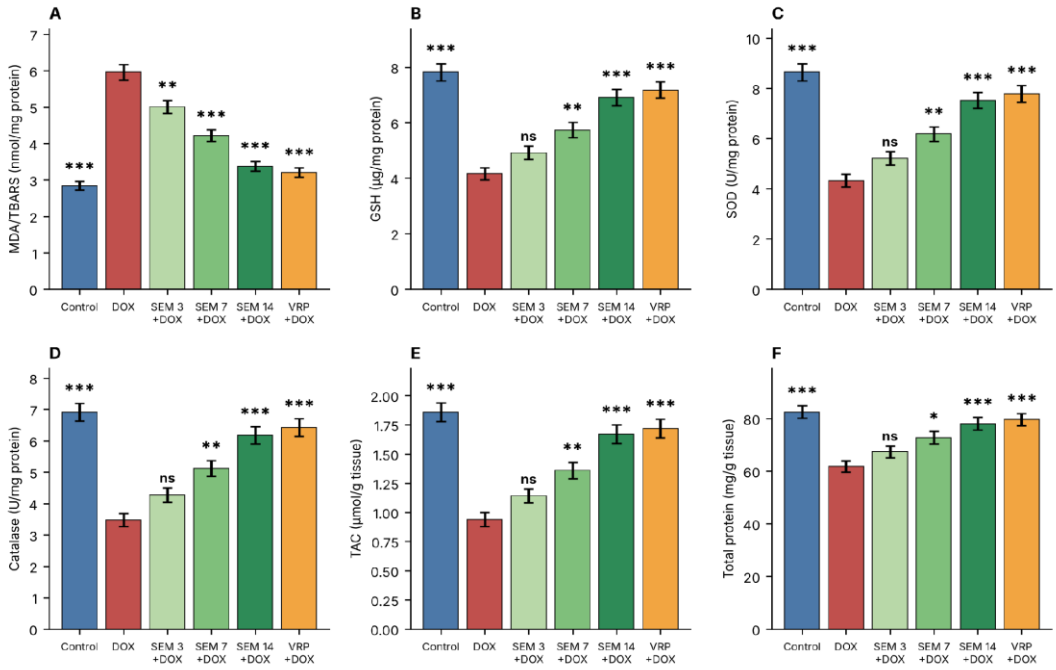


Figure 4. Cardiac tissue MDA/TBARS (A), GSH (B), SOD (C), catalase (D), TAC (E) and total protein (F). Statistics and abbreviations as in Figure 2.

3.6 Infarct size and histopathology

TTC staining showed that infarct size increased from 2.8 ± 0.6% of left ventricular area in controls to 32.6 ± 2.1% with doxorubicin (Table 5, Figure 5B, Figure 6). Semaglutide reduced infarct size dose-dependently to 27.4 ± 1.9%, 20.8 ± 1.7% and 13.6 ± 1.4% at 3, 7 and 14 mg/kg (verapamil 11.8 ± 1.3%). Light microscopy of control hearts showed normal architecture, whereas doxorubicin hearts showed marked myofibrillar disarray, cytoplasmic vacuolisation, inflammatory infiltration, interstitial oedema and necrosis (overall score 3.6). Injury scores decreased to 2.8, 2.0 and 1.0 with semaglutide 3, 7 and 14 mg/kg, and to 0.9 with verapamil (Table 5, Figures 5C and 7).

Table 5. Myocardial infarct size and histopathological injury scores.

Parameter	I: Control	II: DOX	III: SEM 3 + DOX	IV: SEM 7 + DOX	V: SEM 14 + DOX	VI: VRP + DOX
Infarct size (% LV area)	2.8 ± 0.6 ***	32.6 ± 2.1	27.4 ± 1.9 ns	20.8 ± 1.7 ***	13.6 ± 1.4 ***	11.8 ± 1.3 ***
Myofibrillar disarray	0	4	3	2	1	1
Vacuolisation	0	4	3	2	1	1
Inflammatory infiltration	0	3	3	2	1	1
Interstitial oedema	0	3	2	2	1	1
Necrosis	0	4	3	2	1	1
Overall injury score (0–4)	0.0	3.6	2.8	2.0	1.0	0.9

Infarct size: mean ± SEM, n = 6, Tukey comparison against Group II. Histological scores are semi-quantitative (0 = absent, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe).

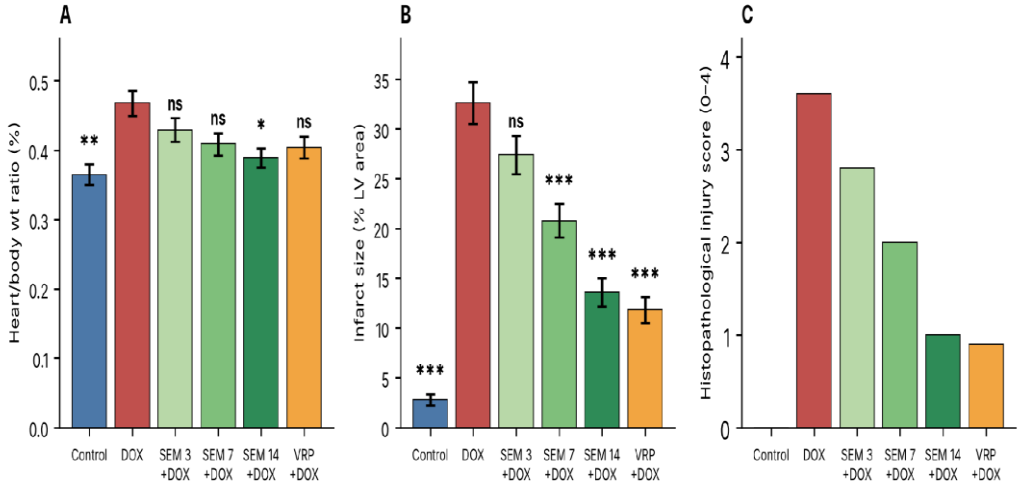


Figure 5. Heart-to-body weight ratio (A), myocardial infarct size (B) and overall histopathological injury score (C). Statistics and abbreviations as in Figure 2.



Figure 6. Representative TTC-stained transverse heart sections. [Panels A–H: assign each panel to its group; the thesis shows eight panels for six groups.]

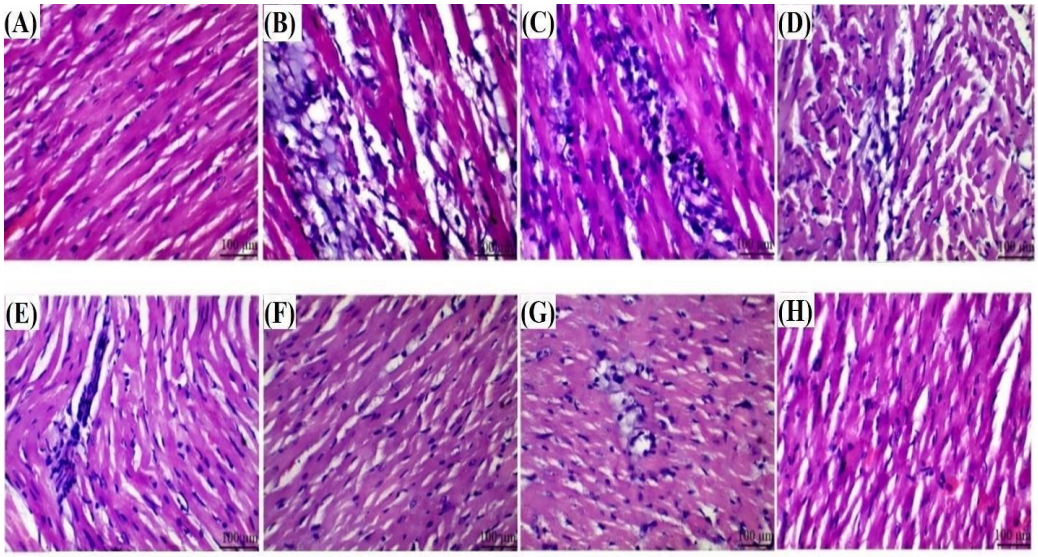


Figure 7. Representative H&E-stained myocardial sections (scale bar 100 µm). [Panels A–H: assign each panel to its group.]

3.7 Statistical summary and dose–response

One-way ANOVA showed a significant treatment effect for every parameter (Table 6). Across serum, tissue and structural endpoints, the response to semaglutide increased progressively from 3 to 14 mg/kg, and Group V was not significantly different from Group VI (verapamil) for any endpoint (Tukey, all $p > 0.05$).

Table 6. One-way ANOVA summary (df 5, 30).

Parameter	F	p	Group V vs VI
LDH	52.7	<0.0001	ns
CK-MB	30.8	<0.0001	ns
cTn-T	16.2	<0.0001	ns
TNF-α	54.6	<0.0001	ns
IL-6	50.9	<0.0001	ns
IL-10	22.4	<0.0001	ns
Total protein	12.0	<0.0001	ns
MDA/TBARS	56.5	<0.0001	ns
GSH	26.9	<0.0001	ns
SOD	30.1	<0.0001	ns
Catalase	27.8	<0.0001	ns
TAC	25.1	<0.0001	ns
Heart/body wt ratio	4.8	0.0023	ns
Infarct size	48.1	<0.0001	ns

F and p values were recalculated from the reported group means and SEM (n = 6) and should be replaced by the output of the statistical software run on the raw data.

4. Discussion

This study shows that semaglutide protects the rat heart against doxorubicin in a dose-dependent manner across serum, biochemical, structural and histological endpoints, with the highest dose approaching the effect of verapamil.

The model behaved as expected. Doxorubicin raised LDH, CK-MB and cTn-T, increased lipid peroxidation, depleted GSH, SOD, catalase and TAC, shifted cytokines towards a pro-inflammatory profile, produced a large TTC-negative area and caused severe myocardial damage on histology. These changes match the established mechanism, in which redox cycling, mitochondrial injury and inflammation overwhelm the limited antioxidant reserve of cardiac tissue.

Protection by semaglutide increased with dose. The 3 mg/kg dose reduced MDA and LDH but had limited effects on CK-MB, cTn-T, GSH, SOD, catalase, TAC and infarct size, whereas 7 mg/kg gave significant improvement in most endpoints and 14 mg/kg gave the largest effect without a plateau in the range tested. The heart-to-body weight ratio needs careful interpretation: absolute heart weight changed little between groups, so the higher ratio with doxorubicin mainly reflects loss of body weight, not true cardiac hypertrophy, and the partial recovery of body weight with semaglutide contributes to the lower ratio.

Semaglutide 14 mg/kg was statistically indistinguishable from verapamil for every endpoint, with verapamil numerically slightly better for cytokines and antioxidant enzymes. The literature on verapamil with doxorubicin is mixed: it preserved ATP and limited calcium disturbance in doxorubicin-exposed adult cardiomyocytes [10], but increased doxorubicin-induced suppression of muscle gene expression in cultured neonatal myocytes [11]. A mechanistically distinct agent that matches verapamil in whole animals is therefore of interest.

The pattern of changes is consistent with antioxidant and anti-inflammatory mechanisms. Semaglutide restored endogenous antioxidant defences and lowered MDA, suppressed TNF-α and IL-6, and raised IL-10, which fits earlier reports that GLP-1 receptor agonists limit doxorubicin injury through mitochondrial and SIRT1-related pathways [7,8]. The docking results offer a possible molecular link, with the strongest predicted binding to NF-κB and Bcl-2 and weaker binding to Bax and NRF2. They are predictions only, since blind docking of a large peptide does not account for flexibility, the receptor-mediated route of action or pharmacokinetics, and they do not demonstrate inhibition or activation of these proteins. Combined in silico and in vivo designs have been used for other cardioprotective agents in doxorubicin-treated rats [12].

4.1 Limitations

Only male rats were used, treatment was short compared with clinical anthracycline exposure, and there was no follow-up after treatment ended. Antitumour efficacy of doxorubicin was not measured, so it is not known whether semaglutide protects the heart without reducing the anticancer effect. Protein expression of NF-κB, Bax, Bcl-2 and NRF2 was not measured, so the docking-based mechanism remains unconfirmed. Semaglutide is a peptide with a long half-life and a different pharmacokinetic profile from small molecules [13], and the doses used here need to be related to clinical regimens in later work. Histological scores were semi-quantitative.

5. Conclusion

Semaglutide at 3, 7 and 14 mg/kg attenuated doxorubicin-induced cardiotoxicity in Wistar rats in a dose-dependent manner. It reduced cardiac injury markers, inflammatory cytokines, lipid peroxidation, infarct size and histological damage, and restored antioxidant defences, with the 14 mg/kg dose comparable to verapamil. Docking suggested favourable interactions with NF-κB, Bcl-2, Bax and NRF2. These findings support further study of semaglutide as a cardioprotective adjunct to anthracycline chemotherapy, including its effect on antitumour efficacy, protein-level mechanistic confirmation and chronic low-dose regimens.

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Disclosure of conflict of interest:

There is no conflict of interest.

Author contribution:

Pavithra .R had principal responsibility for the conception, design of the study and drafting of manuscript

Santhosh Kumar.G was responsible for the revision of the manuscript for important intellectual content Dr. J. Karthi, Dr. S. Swarnalatha contributed towards reviewing of the literature. All authors agreed on the final version of manuscript.

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