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Research Article

Semaglutide Mitigates Doxorubicin-Induced Hepatic and Renal Damage: Functional, Anti-Inflammatory, and Histopathological Insights

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Abstract

Objective: This research was intended to elucidate the nephroprotective and hepatoprotective effects of semaglutide against doxorubicin-induced toxicity. ***Methods***: Thirty-five female rats were allocated and classified into 5 groups: Negative control: distilled water for the period of seven days. The next group of rats, known as the positive control, was treated with only distilled water in addition to only one dose of doxorubicin (12 mg/kg) on the 7th day. Low dose of semaglutide (SL), moderate dose of semaglutide (SM), and high dose of semaglutide (SH). All semaglutide groups received treatment for the duration of 7 days and a single dose of doxorubicin on the 7th day. On the 8th day, all the animals underwent euthanization, and samples of blood were collected for the purpose of measuring (Liver enzymes, ADH, urea, creatinine, hs-CRP, TNF-α, IL-10, and CBC. Liver and kidney tissues were submitted for histopathological analysis. ***Results***: Semaglutide groups significantly reduced serum creatinine and blood urea, with a maximum reduction observed in the SH group. The SH group significantly attenuated hs-CRP and TNF-α. All doses of semaglutide significantly elevated the level of IL-10 and ameliorated the granulocyte-to-lymphocyte and platelet-to-lymphocyte ratios compared to the positive control. The microscopical analysis by a histopathologic expert supports the biochemical results as well. ***Conclusions***: Semaglutide possesses hepatic and renoprotective effects via attenuating the biomarkers of liver and kidney damage along with anti-inflammatory activity, with the maximum effects offered by the highest dose of semaglutide.

Keywords: Anti-inflammatory activity, Doxorubicin, Hepatotoxicity, Nephrotoxicity, Semaglutide.

السيماجلوتايد يخفف من الأضرار الكبدية والكلوية الناتجة عن دوكسوروبيسين: رؤى وظيفية، مضادة للالتهاب، وتحليلات نسيجية

الخلاصة

الهدف: توضيح التأثيرات الواقية للكلى وحماية الكبد للسيماجلوتايد ضد السمية الناتجة عن دوكسوروبيسين. **الطرائق**: تم تخصيص وتصنيف خمسة وثلاثين جرذا أنثى إلى 5 مجموعات: الضابطة السلبية: ماء مقطر لمدة سبعة أيام. تمت معالجة المجموعة التالية من الفئران، المعروفة باسم المجموعة الضابطة الإيجابية، بالماء المقطر فقط بالإضافة إلى جرعة واحدة فقط من دوكسوروبيسين (12 ملغ/كغ) في اليوم السابع. جرعة منخفضة من السيماجلوتايد (SL)، جرعة متوسطة من السيماجلوتايد (SM)، وجرعة عالية من السيماجلوتايد (SH). تلقت جميع مجموعات السيماجلوتايد علاجا لمدة 7 أيام وجرعة واحدة من دوكسوروبيسين في اليوم السابع. في اليوم الثامن، خضعت جميع للقتل الرحيم، وجمعت عينات من الدم لغرض القياس (إنزيمات الكبد، ADH، اليوريا، الكرياتينين، IL-10، TNF-α، hs-CRP، وCBC). تم تقديم أنسجة الكبد والكلى للتحليل النسيجي المرضي. **النتائج**: مجموعات السيماجلوتايد خفضت بشكل ملحوظ الكرياتينين في المصل واليوريا الدموية، مع لوحظ أقصى انخفاض في مجموعة SH. قامت مجموعة SH بتخفيف كبير من hs-CRP وTNF-α. جميع جرعات السيماجلوتايد رفعت بشكل ملحوظ مستوى IL-10 وحسنت نسبة الخلايا الحبيبية إلى اللمفاوية والصفائح الدموية إلى الخلايا اللمفاوية مقارنة بالنتيجة الضابطة الإيجابية. يدعم التحليل المجهري الذي يجريه خبير نسيجي النتائج الكيميائية الحيوية أيضا. **الاستنتاجات**: يمتلك السيماغلوتايد تأثيرات حماية للكبد وحماية الرينولايتد من خلال تخفيف المؤشرات الحيوية لتلف الكبد والكلى إلى جانب النشاط المضاد للالتهابات، مع أقصى تأثير ممكن من أعلى جرعة من السيماجلوتايد.

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INTRODUCTION

Doxorubicin (DOX) belongs to the anthracycline cytotoxic drug class; it has been applied clinically for the treatment and decreasing the progression of different types of cancer, such as blood cancer, breast cancer, pulmonary cancer, etc. Moreover, long-term use of DOX is limited by its serious adverse effects, such as renal and hepatic toxicity [1]. DOX induces hepatotoxicity via disruption of the normal ratio of reactive oxygen species (ROS) to antioxidants. In fact, the generation of free radicals by this anticancer is considered the main mechanism of hepatotoxicity. In addition to that, it attenuates the activity and level of antioxidant enzymes such as superoxide dismutase, glutathione, and glutathione peroxidase. Moreover, such toxicity is characterized by augmentation of liver enzymes such as ALT and AST [2]. As mentioned beforehand, DOX causes multiple organ toxicity. Similar to hepatotoxicity, the generation of ROS has been proposed to be responsible for the toxic effect of DOX on kidneys [3]. Semaglutide is an antidiabetic drug, which mitigates blood glucose via stimulating glucagon-like peptide 1 receptor (GLP-1R). Fortunately, its available as an oral and subcutaneous formulation [4]. Semaglutide possesses multiple clinical benefits, including decrement

of blood sugar, weight loss, lowering of blood pressure, and cardioprotection [5]. Reis-Barbosa *et al*. documented hepatoprotective effects of semaglutide in a study conducted on obese mice via suppression of the mTOR pathway and stimulation of insulin signaling together with the AMPK pathway [6]. Furthermore, another animal study demonstrated the nephroprotective effect of semaglutide. The author stated that semaglutide improved the albuminuria and attenuated the severity of glomerulosclerosis [7]. Nowadays, several strategies are applied by researchers and scientists to prevent and decrease the adverse effects associated with cytotoxic agents, including DOX. Accordingly, this animal study was designed to determine the hepato-protective and reno-protective effect of different doses of semaglutide against DOX-induced hepatic and renal toxicity.

METHODS

Experimental procedures

Thirty-five female albino Wistar rats weighing 220–250 grams were enrolled in the current study and housed in the University of Sulaimani's animal house in plastic enclosures with sufficient ventilation, with a humidity of 55 ± 5% and a temperature of 25 ± 2°C, over a 12-hour dark-light cycle for two weeks for acclimatization before starting the experiment. The University of Sulaimani's Ethical Committee authorized experimental procedures (PH86-23). It complied with the 1998 Canadian Council for Animal Care (CCAC) Guidelines for Animal Experimentation. The rats had unrestricted access to water and were fed a regular laboratory diet. Spontaneously, the rats were classified into five different groups, with each group consisting of seven rats: NC, control group (negative); rats were administered only distilled water subcutaneously (SC) for a period of seven days. PC, or positive control; rats were administered distilled water subcutaneously for seven days duration, in addition to only one dose of doxorubicin (12 mg/kg) by intraperitoneal route on the 7th day. Semaglutide in low dosage (SL) group; rats were administered 0.06 mg/kg subcutaneously for seven days duration, in addition to only one dose of doxorubicin (12 mg/kg) by intraperitoneal route on the 7th day. Semaglutide in moderate dosage (SM) group; rats were administered 0.12 mg/kg subcutaneously for seven days duration, in addition to only one dose of doxorubicin (12 mg/kg) by intraperitoneal route on the 7th day. Semaglutide in the high-dosage (SH) group: rats were administered 0.24 mg/kg subcutaneously for seven days duration, in addition to only one dose of doxorubicin (12 mg/kg) by the intraperitoneal route on the 7th day. According to the previous findings, the doses and the route of administration of semaglutide [8] and doxorubicin [9] were determined. On day 8 after 24 hours of the administration of doxorubicin, all the animals were euthanized, and cardiac puncture was applied for the gathering of blood samples and transferred for evaluation of biochemical and inflammatory markers (ALT, AST, ADH, urea, creatinine, hs-CRP, TNF-α, IL-10, and CBC), and liver and kidney tissues were sent for histopathological examination.

Histopathology evaluation

Successively, after the animals were sacrificed within an inhalation chamber by using a chloroform overdose, samples of the heart, liver, and kidney were taken for histological analysis as part of the postmortem examination. In short, tissue samples were put into tissue cassettes and left to cure for at least 48 hours using a 10% formaldehyde solution. After that, the samples will be passed through a succession of ethanol alcohols that get thinner as they dehydrate, and they will then be cleaned with xylene. The sample will then be both blocked and embedded using molten paraffin utilizing an automated embedder for wax at a temperature of between 60 and 70 degrees Celsius. Using a rotary microtome, tissue samples that had been paraffinized were sectioned to a degree of thickness of 4 µm and then placed onto a slide made of glass. Next, tissue slides underwent deparaffinization, were washed for 30 minutes with xylene solution, and were left to dry. Afterwards, the fixed parts were covered, slid, and inspected by an anonymous pathologist after Harris's hematoxylin and eosin had been used to stain and wash with a number of xylene solutions.

Scoring of lesions semi-quantitatively

Generally speaking, in relation to liver sections, congestion of blood vessels was measured in µm and determined statistically as a mean percentage area, whereas vacuolar degenerations were quantified as the mean percentage of 10 randomly selected microscopic fields' cell counts. In the meantime, in segments of the kidney, assessment of kidney tubular vacuolar degeneration using a semi-quantitative method was measured in the same manner as in liver sections. Additionally, using a high-power magnification (1000X), inflammatory cells inside the hepatic tissue were counted in ten randomly selected areas. After that, a percentage was computed for the mean average and compared statistically. Additionally, vascular congestions were quantified in micrometers. Conversely, certain degenerative alterations were evaluated in the liver and kidney sections, measured in µm squares, and presented as a mean percentage after statistical analysis. On the other hand, inflammatory and degenerative cells at high power magnification (1000X) were tallied in 10 randomly chosen fields, after which, by using statistical methods, the mean average is expressed as a percentage. The lesion grading and scoring method (a score between 0 and 10% indicates the absence of lesions, a score between 10 and 25% indicates mild lesions, a score between 25 and 50% indicates moderate lesions, a score between 50 and 75% represents severe lesions, and a score between 75 and 100% indicates the presence of critical lesions) was applied to display the average % of all calculated values.

Statistical analysis

To carry out the statistical analysis, GraphPad Prism 7 was utilized. The mean ± standard deviation (S.D.) was implemented to express the measured parameter values. To compare the statistics between the various groupings, one-way analysis of variance (ANOVA) and Bonferroni multiple comparison tests were conducted. Using a *p*-value of less than 0.05 to determine if the results were statistically significant (lesions).

RESULTS

In this study, the levels of AST and LDH were significantly higher in the DOX-injected group compared to the NC group ($p< 0.01$), with non-significant elevation of ALT level ($p> 0.05$). Different doses of semaglutide reduced the level of these enzymes in a non-significant manner ($p> 0.05$) (Figure 1 A-C).

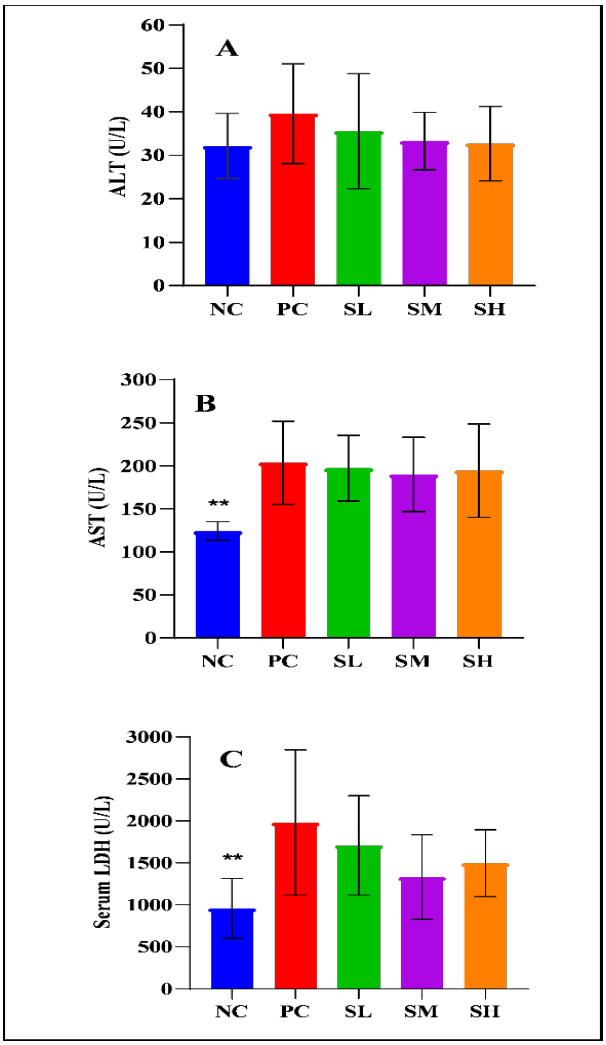

Figure 1: Impact of various doses of semaglutide on liver function tests. Data were expressed as mean ± S.D (n= 7 female rats in each group); Data * significantly different compared to positive control group (ANOVA and *post hoc* test (* $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$).

Serum creatinine was significantly increased by the positive control in comparison to the NC group ($p< 0.001$). Significant decrement of serum creatinine was determined with both SL and SM groups ($p< 0.001$) and a maximum reduction was observed in the SH group ($p< 0.0001$) relative to the positive control. Blood urea was also elevated in the PC group when estimated against NC ($p< 0.001$), while all three groups of varying semaglutide doses showed a significant diminution in comparison with the positive control ($p< 0.001$) (Figure 2A and B).

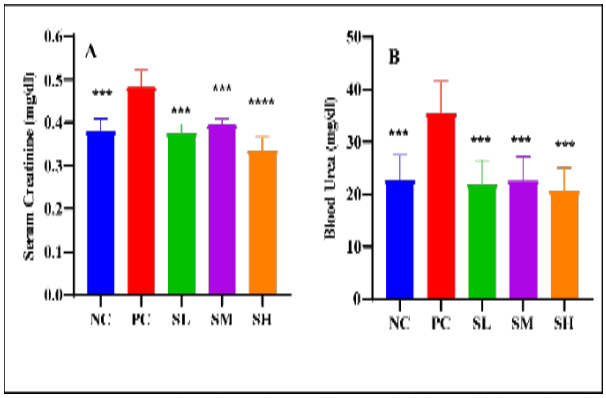

Figure 2: Impact of various doses of semaglutide on kidney function tests. Data were expressed as mean ± S.D (n= 7 female rats in each group); * significantly different compared to positive control (ANOVA and *post hoc test*; * $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$).

Table 1 represents the impact of various doses of semaglutide on the hematological markers. No significant changes were determined in the levels of WBC, RBC, HGB, and HCT in each treatment group ($p> 0.05$). Meanwhile, platelet levels significantly increased in DOX-treated rats in comparison to the NC group ($p< 0.05$).

Table 1: Impact of different doses of semaglutide on hematological markers (n=7 in each group)

Parameters	NC	PC	SL	SM	SH
WBC	9.9±2.5	8.2±1.9	8.4±1.8	8.5±2	7±1.8
RBC	7.8±0.6	7.7±0.4	8±0.7	7.6±0.3	7.4±0.4
HGB (g/dL)	15.2±0.9	15±0.8	15.3±0.88	14.9±0.47	14.6±0.45
HCT	45±3.1	44.5±2.6	45±3.4	43±1.9	42±1.5
PLT	70±144	875±91*	776±69.9	791±203	741±118

Values are presented as mean ±STD; n: number of animals. * Significantly differences compared with the negative control group (paired t-test, $p<0.05$). NC: negative control: PC: positive control; SL: low dose of semaglutide; SM: medium dose of semaglutide; SH: high dose of semaglutide; WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; PLT: platelets.

Doxorubicin administration resulted in a significant elevation of both hs-CRP and TNF-α when estimated against the NC group ($p< 0.05$), and the use of different doses of semaglutide resulted in a decrement of hs-CRP and TNF-α levels; however, only the SH group reached a significant level ($p< 0.05$) in comparison with the PC group (Figures 3A and B). IL-10 level declined significantly in the PC group in contrast to the NC group ($p< 0.05$), and semaglutide groups have significantly elevated serum levels of IL-10 in comparison with the PC group ($p< 0.001$) (Figure 3C). For the ratio of granulocyte to lymphocyte and platelets to lymphocyte, DOX increased the ratio significantly in comparison with the negative control ($p< 0.05$). Furthermore, groups of SL, SM, and SH ameliorated the ratios; however, they were not significant ($p> 0.05$) (Figure 3D and E).

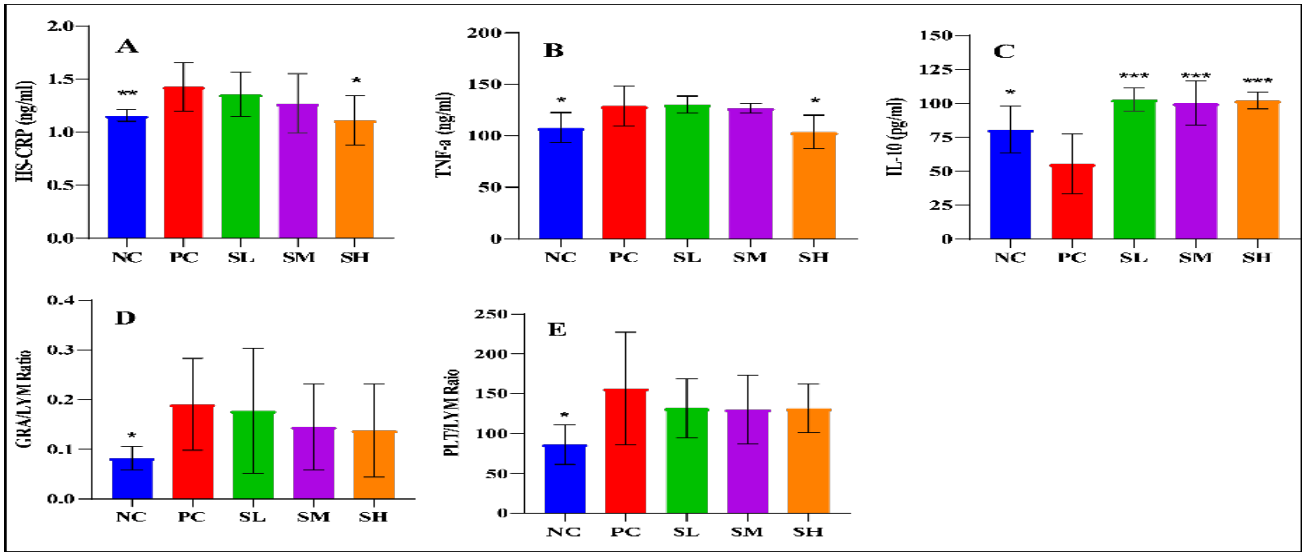

Figure 3: Impacts of various doses of semaglutide on inflammatory biomarkers. Data were expressed as mean ± S.D (n= 7 animals in each group); * significantly different compared to positive control (ANOVA and *post hoc* test;* $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$).

The semiquantitative evaluation of liver sections is presented in Table 2. It reveals a dose-related, significant decrease ($p< 0.05$) in the proportion of cellular hydropic, degradation of vacuoles, and even number of inflammatory cells in the SEM-treated groups, as they drop to a moderate score when compared to the positive control group. Semaglutide therapy often results in a considerable reduction in the overall severity of the lesion.

Table 2: Semi-quantitative assay of liver sections (n=7 in each group)

Groups	Hydropic Degeneration* (%)**	Vascular Congestion * (%)**	Inflammatory Cells* (%)**	Lesion Scoring (0 -100%)	Lesion Grading
(G1) NC†	4.89^{A}#	3.47^{A}	5.63^{A}#	0-10	No lesion
(G2) PC	89.57^{E}	78.21^{E}	76.44^{E}	75-100	Critical
(G3) SL	81.52^{E}	75.23^{E}	76.91^{E}	75-100	Critical
(G4) SM	69.45^{D}	59.71^{D}	58.11^{D}	50-75	Severe
(G5) SH	49.53^{C}	51.93^{C}	41.76^{C}	25-50	Moderate

Notes: *Hepatocytes hydropic, degradation of vacuoles and inflammatory cells were estimated in (%) of cell numbers within the section. Area of blood vessels congestion estimated in mean percentage of (µm). **Each value represents a mean percentage (n=7). #Statistical comparison among groups: Mean values with different capital letters have significant differences at ($P < 0.05$). †G1: Control negative group (CNG), Distilled water; G2: Control positive group, Doxorubicin (DOX) 12 mg/kg; G3: DOX 12 mg/kg with Semaglutide (SEM) group 0.06 mg/kg; G4: DOX 12 mg/kg with Semaglutide (SEM) group 0.12 mg/kg; G5: DOX 12 mg/kg with Semaglutide (SEM) 0.24 mg/kg of body weight.

Additionally, when comparing the SEM group to the PC group, the morphometric examination of the histopathological lesions reveals a significant reduction in the severity of the lesions ($p< 0.05$) (Figure 4). The semiquantitative evaluation of kidney sections is presented in Table 3, where a significant decrease ($p< 0.05$) in the proportion of renal tubules with hydropic degeneration, cellular swelling, and vascular congestion with all doses of SEM in comparison with the PC group is shown. Furthermore, when comparing the SL and SM groups to the PC group, morphometric examination of the histopathological lesions shows a significant reduction ($p< 0.05$) in the severity of the lesions. In general, histopathological results of kidney sections demonstrate significant alleviation in lesion severity in a dose-dependent manner (Figure 5).

DISCUSSION

Organ toxicities are the main drawbacks of cancer chemotherapy. Doxorubicin is a very effective cytotoxic agent used worldwide for the management of different types of cancer. However, its use is associated with several organ toxicities, including heart, liver, and kidney [1]. The goal of this study is to find out how different doses of semaglutide protect the liver and kidneys from damage caused by DOX. In this study, DOX caused hepatotoxicity, which was shown by a rise in AST and LDH levels that was statistically significant but not in ALT levels. This finding was in parallel to the previous study conducted by Zhao *et al*. [10]. In line with a previous study on rodents [11] the findings of the current study elucidate that different doses of semaglutide mitigated serum levels of ALT, LDH, and AST; such findings could indicate the protective effect of semaglutide against DOX-induced hepatotoxicity. Furthermore, renal degeneration induced by DOX clearly observed as the significant elevation of creatinine and blood urea nitrogen. It has been documented that DOX causes damage in different organs, including the kidney [12]. One of the well-known mechanisms of DOX-induced toxicity is initiating oxidative damage in multiple organs via the generation of free radicals and lipid peroxidation.

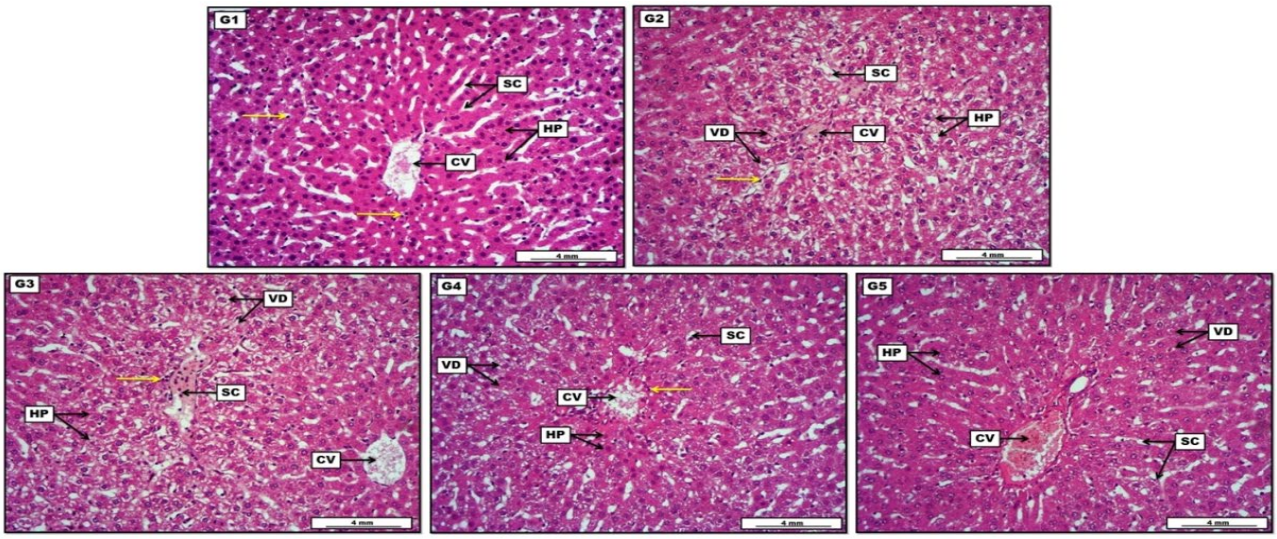

Figure 4: Microscopic photograph of Liver from groups; **(G1):** treated with D.W, liver sections demonstrate no prominent morphological changes, indicated by classically organized radiated hepatocytes (HP) around the normally appeared central vein (CV) with distinctive sinusoidal capillaries (SC), with low grade infiltration of sinusoidal Kupffer cells (yellow arrow). **(G2):** Received DW for 7 days then injected with a single dose of Doxorubicin, show significant vacuolar degeneration (VD) within most of hepatocytes (HP) in the given section. Central vein appears congested and significantly narrowed beside significant narrowing of the sinusoidal capillaries (SC), together with mild infiltration of inflammatory cells along the margin of sinusoidal capillaries (yellow arrows). **(G3):** Group 3 (low dose) received 0.06 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, display significant vacuolar degeneration (VD) with many other hepatocytes (HP) show moderate cellular degeneration. Some of the sinusoidal capillaries (SC) are significantly dilated with clear perivascular coughing of inflammatory cells (yellow arrows), central vein (CV) appeared normal. **(G4):** Group 4 (moderate dose) received 0.12 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, express moderate degree of vacuolar degeneration (VD) together with other hepatocytes (HP) display normal architectural structure. Sinusoidal capillaries (SC) slightly narrowed, with perivascular coughing of inflammatory cells (yellow arrow) around the mildly congested central vein (CV). **(G5):** Group 5 (high dose) received 0.24 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, show moderate granular hydropic degeneration (VD), together with other hepatocytes in the given section with typical arrangement and no clear morphological lesions. Sinusoidal capillaries (SC) seem normally adjusted together with significant vascular congestion in the central vein (CV). H&E. Scale bar: 4 mm.

Table 3: Semi-quantitative assay of kidney sections (n=7 in each group)

Groups	Hydropic Degeneration* (%)**	Cellular Swelling* (%)**	Vascular Congestion * (%)**	Lesion Scoring (0 -100%)	Lesion Grading
(G1) NC†	6.89^{A}#	8.24^{A}	4.97^{A}	0-10	No lesion
(G2) PC	91.63^{E}	89.72^{E}	77.35^{E}	75-100	critical
(G3) SL	74.52^{D}	72.81^{D}	65.42^{D}	50-75	Severe
(G4) SM	63.81^{D}	62.49^{D}	56.28^{D}	50-75	Severe
(G5) SH	42.79^{C}	41.85^{C}	38.55^{C}	25-50	Moderate

Notes: *Kidney tubules hydropic degradation and Cellular swelling were estimated in (%) of cell numbers. The area of blood vessels congestion is estimated in (µm). **Each value represents a mean percentage (n=7). #Statistical comparison among groups: Mean values with different capital letters have significant differences at ($P < 0.05$). †G1: Negative control group (CNG), Distilled water; G2: Positive control group, Doxorubicin (DOX) 12 mg/kg; G3: DOX 12 mg/kg with Semaglutide (SL) group 0.06 mg/kg; G4: DOX 12 mg/kg with Semaglutide (SM) group 0.12 mg/kg; G5: DOX 12 mg/kg with Semaglutide (SH) 0.24 mg/kg of body weight.

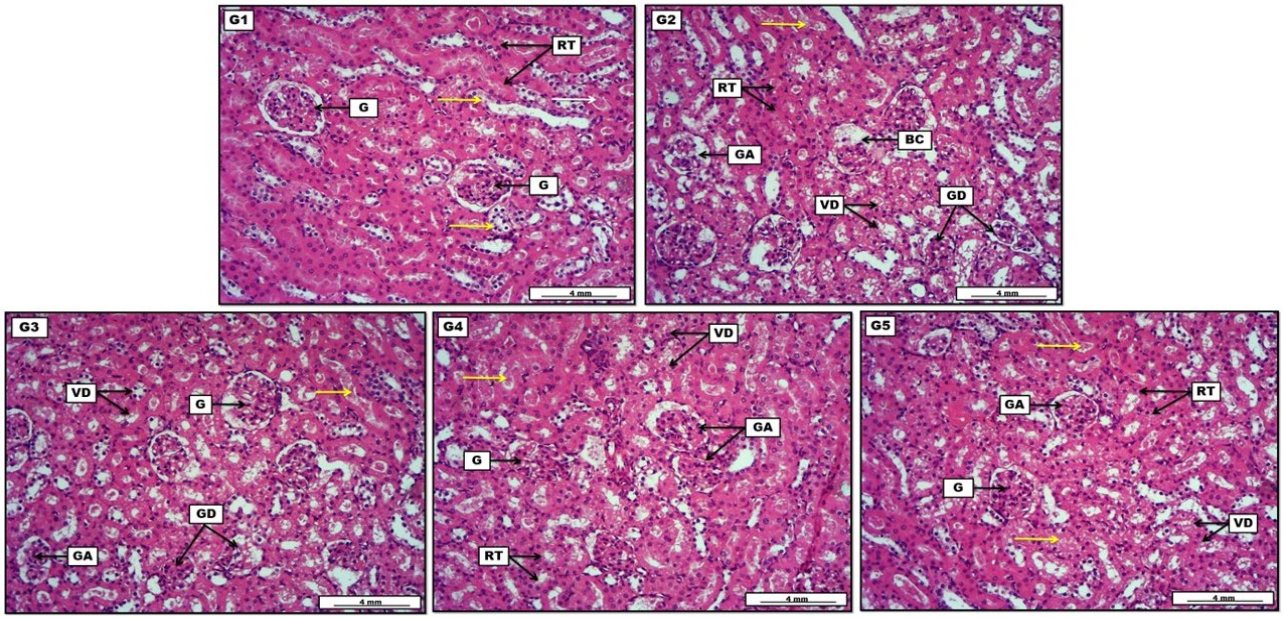

Figure 5: Microscopic photograph of kidney from groups; **(G1):** Received D.W, reveal no severe morphological changes, manifested by distinctive glomerular structure (G), together with no significant lesions in the renal tubules (RT) but for mild cellular swelling (yellow arrows). Moreover, some hyaline casts within the renal tubular lumina (white arrow) were observed. **(G2):** Received DW for 7 days then injected with a single dose of Doxorubicin, demonstrate significant glomerular degeneration and atrophy (GA and GD) evident by severe widening of the Bowman's space, in addition to, many renal tubular epithelia (RT) reveal significant vacuolar and cellular degenerations (VD) together

with the presence of eosinophilic hyaline cast within the lumen of renal tubules. **(G3):** Group 3 (low dose) received 0.06 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, show significant glomerular degeneration and atrophy (GA and GD) together with significant vacuolar degeneration (VD). Presence of acidophilic hyaline cast within the tubular lumina (yellow arrow), some glomeruli (G) display mild dilation in their urinary spaces. **(G4):** Group 4 (median dose) received 0.12 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, illustrate moderate glomerular atrophy (GA) evident by mild spreading in the Bowman's capsule. Renal tubular epithelia (RT) show significant vacuolar degeneration (VD), together with the presence of hyaline cast (yellow arrow). **(G5):** Group 5 (high dose) received 0.24 mg/kg of Semaglutide for 7 days then injected with a single dose of Doxorubicin, demonstrate moderate degradation of vacuoles (VD) within the lining epithelial cells of renal tubules (RT). Some glomeruli (G) reveal mild to moderate glomerular atrophy (GA), in addition to the presence of acidophilic proteinaceous hyaline cast within the tubular lumen (yellow arrows). H&E. Scale bar: 4 mm.

Elevation of oxidative status leads to abnormality and disruption of glomerular permeability; such an effect ends with an increment of serum BUN and creatinine [13]. Additionally, a high level of BUN and creatinine is considered a hallmark of renal dysfunction [14]. Several clinical studies reported nephron-protective effects of GLP-1 analogues such as liraglutide in type 2 diabetes mellitus (T2DM) with cardiovascular comorbidity. Fortunately, this is the first study on the protective effect of different doses of semaglutide against DOX-induced liver and kidney damage. In the current study, semaglutide significantly reduced serum levels of creatinine and BUN, with the highest dose having the greatest impact. Although the exact renoprotective effect shown by semaglutide is still unclear, it could be attributed to the suppression of inflammation and free radical scavenging activities [15,16]. In the present study, the use of DOX did not produce any hematological changes except for elevating platelet count. Thrombocytopenia and bleeding are common in late-stage kidney disease and liver cirrhosis [17], and studies showed that DOX is associated with thrombocytopenia secondary to myelosuppression [18]. In addition to that, Kim *et al.* disclosed that DOX decreases platelet level via elevation of free radical synthesis and attenuation of antioxidant enzymes [19], and this was in contrast to the result of the current study. In addition, different doses of semaglutide exerted no effect on the hematological markers. Furthermore, regarding the effect of DOX on the inflammatory biomarkers, DOX is associated with a significant increase of hs-CRP and TNF-α along with significant mitigation of anti-inflammatory interleukin (IL-10). Fortunately, high-dose semaglutide attenuated serum levels of hs-CRP and TNF alpha. Likewise, all doses of semaglutide increased the serum level of IL-10 in a significant manner. Such a finding shows the anti-inflammatory effect of GLP-1 analogue against DOX-induced inflammation. Moreover, elevation of the granulocyte/lymphocyte ratio is an independent indicator for progression of tumor growth and metastasis [20]. Differently, the platelet/lymphocyte ratio represents inflammation in several diseases, such as myocardial injury [21]. Moreover, DOX elevated the ratio of granulocyte to lymphocyte and platelets to lymphocyte in a significant manner; this could be an indicator of inflammation. Semaglutide at different doses showed a non-significant amelioration of the ratios. Similarly, previous studies elucidated the inflammatory suppressing effects of semaglutide in patients with type 2 diabetes mellitus via attenuating inflammatory biomarkers [22] and other studies conducted in diabetic patients using semaglutide revealed anti-inflammatory effects through attenuating hs-CRP and IL-6 [23,24]. Semaglutide has also been shown to exert an anti-inflammatory effect by ameliorating lipopolysaccharide-induced acute lung injury through blocking of the NF-κB signaling pathway [25]. Moreover, the histopathological analysis also supported the biochemical outcomes, where a remarkable decline in vascular congestion along with attenuation of inflammation and lesion scoring was observed with the high dose of semaglutide in both hepatic and renal tissues.

Conclusion

Semaglutide showed hepatoprotective and renoprotective effects via attenuating the biomarkers related to liver and kidney functions as well as ameliorating the inflammatory markers such as hs-CRP and TNF alpha together with elevating the anti-inflammatory cytokine IL-10. The histopathological findings greatly support the biochemical findings suggesting semaglutide a potential medicine to be evaluated in clinical studies.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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