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The Protective Effects of Hidrosmin and Vitamin C Against Doxorubicin-Induced Sub-Acute Cardiac Toxicity in Rats

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Abstract

Doxorubicin is a chemotherapeutic agent belong to the anthracyclines that are used for the treatment of a wide variety of malignancies, however, it is correlated with serious cardiotoxicity, Hidrosmin is a synthetic flavonoid derived from hesperidin, diosmin which has pleiotropic effects including anti-ischemic, antihypertensive, anti-inflammatory, and antioxidant activities. Vitamin C is a water-soluble vitamin that may reduce the risks of cardiovascular disease, cancer, and stroke. Forty-five mature male rats their prime weight from 250-280 gm were divided into five groups; **Group 1:** Control group, in which rats were injected with normal saline of (1ml/kg) intraperitoneally every other day and orally administered (0.5 ml/kg) of dimethyl sulfoxide daily for fourteen days. **Group 2:** Rats in this group were injected intraperitoneally with doxorubicin (2.5 mg/kg), every other day and orally administered (0.5 ml/kg) of dimethyl sulfoxide daily for fourteen days. **Group 3:** Rats were administered orally hidrosmin daily at a dose (300 mg/kg/day) and injected intraperitoneally with doxorubicin (2.5 mg/kg) every other day for fourteen days. **Group 4:** Rats were administered orally vitamin C daily at a dose (100 mg/kg/day) and injected intraperitoneally with doxorubicin (2.5 mg/kg) every other day and (0.5 ml/kg) of dimethyl sulfoxide orally daily for fourteen days. **Group 5:** Rats were given orally a combination of hidrosmin at a dose (300 mg/kg/day) and vitamin C at a dose (100 mg/kg/day) daily and injected intraperitoneally with doxorubicin (2.5 mg/kg) every other day for fourteen days; on day fifteen animals sacrificed for measurement of troponin I, tumour necrosis factor-alpha, inducible nitric oxide synthase, and histopathological study; **Group 3** shows a significant reduction ($P< 0.05$) in troponin I, tumour necrosis factor-alpha, and inducible nitric oxide synthase compared to **Group 2**; moreover **Group 5** shows a highly significant reduction ($P< 0.001$) in troponin I, tumour necrosis factor-alpha, and inducible nitric oxide synthase compared to **Group 2** and **Group 3**; hidrosmin improves histopathological finding when compared with doxorubicin alone. Hidrosmin shows a cytoprotective effect against doxorubicin-induced cardiac toxicity through attenuation of the deleterious effects of reactive oxygen species furthermore combination of hidrosmin plus vitamin C produces a synergistic effect than using each alone.

Keywords: Cardiac toxicity, Doxorubicin, Hidrosmin, Rats, Vitamin C.

Introduction

Doxorubicin (DOX) is a chemotherapeutic agent belonging to the anthracyclines family that is used for the treatment of various types of malignancies including Hodgkin's disease, acute lymphoblastic leukaemia, breast cancer, and pediatric leukaemia [(1)]. Heart toxicity is considered one of the most common side effects associated with DOX which limits its use [(2)]. acute and chronic toxicity with DOX has been reported [(3)], dose-dependent and irreversible toxicity also may occur, and even more, cardiomyopathy may develop years after DOX cessation [(4)]. A series of studies have been focused on identifying the methods or drugs which may reduce such toxicity [(5)]. Numerous studies have been conducted to understand the molecular mechanism responsible for DOX-induced cardiac toxicity [(1)]. Overproduction of reactive oxygen species in the mitochondria may cause damage to DNA, lipids, and protein which could affect cardiac function and structure [(6)]. Other suggested mechanisms include sarcomere structure alterations, dysregulation of calcium homeostasis, modulation of gene expression, and TOP2β cleavage complexes in cardiomyocytes [(7, 8)].

Hidrosmin is a synthetic flavonoid derived from hesperidin, diosmin which has pleiotropic effects including anti-ischemic, antihypertensive, anti-inflammatory, and antioxidant activities in several experimental animal studies [(9)]. Hidrosmin is approved for the treatment of a patient suffering from chronic vascular insufficiencies with varicose of the inferior limbs due to its antioedematous

effects and reducing swelling and cramps by affecting on variety of inflammatory mediators like histamine, and bradykinin [10]. Moreover, numerous studies tried to explore the protective effects of hidrosmin against ROS overproduction, it was found that hidrosmin downregulated the expression of cytokine also modulated redox balance genes also it shows free radicals scavenging activity, however, its use may associated with headache and gastrointestinal symptoms like nausea, vomiting, and diarrhoea [11, 12, 13].

Vitamin C is a water-soluble vitamin [14], that plays an important role in different metabolic processes as being a cofactor for enzymes involved in the antioxidant mechanisms as being an electron donor in detoxifying oxidative stress [14], transcription, and regulation of gene expression, and also exerts beneficial effects in inflammation and for the immune system [15]. Coadministration of flavonoids with vitamin C may enhance the activity of vitamin C [16]. It was reported that a diet rich in vitamin C may reduce the risks of cardiovascular disease, cancer, and stroke [17].

The current study aims to assess the protective effects of hidrosis and/or vitamin C versus doxorubicin-induced sub-acute cardiac toxicity.

Materials and Methods

Forty-five mature male rats (to exclude the influence of gender differences on the inflammatory and oxidative biomarkers [18]) their prime weight from 250-280 gm were bought from the College of Pharmacy Dhi Qar University and were kept under control conditions at the Animal House of the College of Pharmacy Basrah University. The rats received regular pellets and unrestricted access to the water source throughout the study.

Drugs

Two hundred milligrams of DOX vials were purchased from Pfizer in the U.S. and administered intraperitoneally. Hidrosmin (200 mg capsule) was purchased from FEAS pharma company, Bulgaria, (hidrosmin selected because it has fewer adverse effects and also has an antioxidant activity which may antagonise the oxidative damage induced by doxorubicin [19, 20]) dissolved in 4 ml of dimethyl sulfoxide (DMSO), and given by oral gavage and dose selected based on human therapeutic dose and previous studies [21, 22, 11]. A vitamin C tablet (500 mg) was provided by a healthy care company, Australia which dissolved in 15 ml of normal saline (NS) to prepare a stock solution and was given by oral gavage [23].

Study design

Rats in the present study were split into 5 groups each one containing nine as follows:

Group 1: Control group, in which rats were injected with NS of (1ml/kg) intraperitoneally (IP) every other day and orally administered (0.5 ml/kg) of DMSO daily for fourteen days. **Group 2:** Rats in this group were injected IP with DOX (2.5 mg/kg) [24], every other day and orally administered (0.5 ml/kg) of DMSO daily for fourteen days. **Group 3:** Rats were administered orally hidrosmin daily at a dose (300 mg/kg/day) [19] and injected IP with DOX (2.5 mg/kg) every other day for fourteen days. **Group 4:** Rats were administered vitamin C daily at a dose (of 100 mg/kg/day)[25] and injected intraperitoneally with DOX (2.5 mg/kg) every other day and (0.5 ml/kg) of DMSO daily orally for fourteen days. **Group 5:** Rats were given orally a combination of hidrosmin at a dose (300 mg/kg/day) and vitamin C at a dose (100 mg/kg/day) daily by oral gavage and injected intraperitoneally with DOX (2.5 mg/kg) every other day for fourteen days.

At day fifteen, rats were anaesthetized by using chloroform and sacrificed. Intracardiac puncture to achieve 5 ±1 mL of blood, which was then collected in gel-activated tubes for serum collection for measuring troponin I using rat ELISA kit purchased from Mybiosource company, USA, inducible nitric oxide synthase (iNOS), using rat ELISA kit purchase from Mybiosource company, USA, tumour necrosis factor-alpha (TNFα) using rat ELISA kit purchase from Elabscience company, USA, and heart-extracted for histopathological examination.

Histopathological examination

The heart of each animal was extracted and then after was washed with phosphate-buffered saline and then stored in a 10% formalin solution before histopathological study according to the method of Junqueira [26].

Statistical analysis

Statistical analysis was performed by using a Statistical Package for the Social Sciences (SPSS) version 26. Data were presented as mean ± SD. A one-way analysis of variance was used to examine the statistical significance of the differences between the experimental groups (ANOVA). In which P-values below 0.05 were recognized as statistically significant differences.

Results

In Table 1, and Figure 1 rats injected IP with (2.5 mg/kg) every other day for 14 days **Group 2** shows a highly significant increase (P< 0.001) in serum troponin I level compared with **Group 1**. Mean±SD of the serum levels of troponin I for (**Group 2** and **Group 1**) was found to be respectively, 1900.77 ± 0.83^{b} and 40.88 ± 0.78^{a}. Meanwhile, **Group 3** shows a highly significant decrease (P<0.001) in serum troponin I compared with **Group 2**. Mean±SD of the serum levels of troponin I for (**Group 3** and **Group 2**) was found to be respectively, 1299.88 ± 0.78^{c}, and 1900.77 ± 0.83^{b}. In addition to that

Group 4 shows a highly significant decrease (P<0.001) in serum troponin I compared to **Group 2**. Mean±SD of the serum level of troponin I for (**Group 4** and **Group 2**) was found to be respectively, 700.88 ± 0.78[d], and 1900.77 ± 0.83[b]. A better result will be achieved in **Group 5** shows a highly significant decrease (P<0.001) in serum troponin I compared with **Group 2**. Mean±SD of the serum levels of troponin I for (**Group 5** and **Group 2**) was found to be respectively, 294 ± 0.86[e], and 1900.77 ± 0.83[b].

Table 1. Effects of Hidrosmin and Vitamin C on Serum Troponin I Level

Treated Groups	**Mean Troponin I level pg/ml ±SD**
Group 1 (IP NS 1 ml/kg) every other day and oral 0.5ml/kg of DMSO daily for 14 days	40.88 ± 0.78[a]
Group 2 DOX IP (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	1900.77 ± 0.83[b]
Group 3 hidrosmin (300 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	1299.88 ± 0.78[c]
Group 4 vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	700.88 ± 0.78[d]
Group 5 hidrosmin (300 mg/kg/day) plus vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	294 ± 0.86[e]

Each data is expressed as mean ± standard deviation (SD). Values in small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of rats in each group= 9.

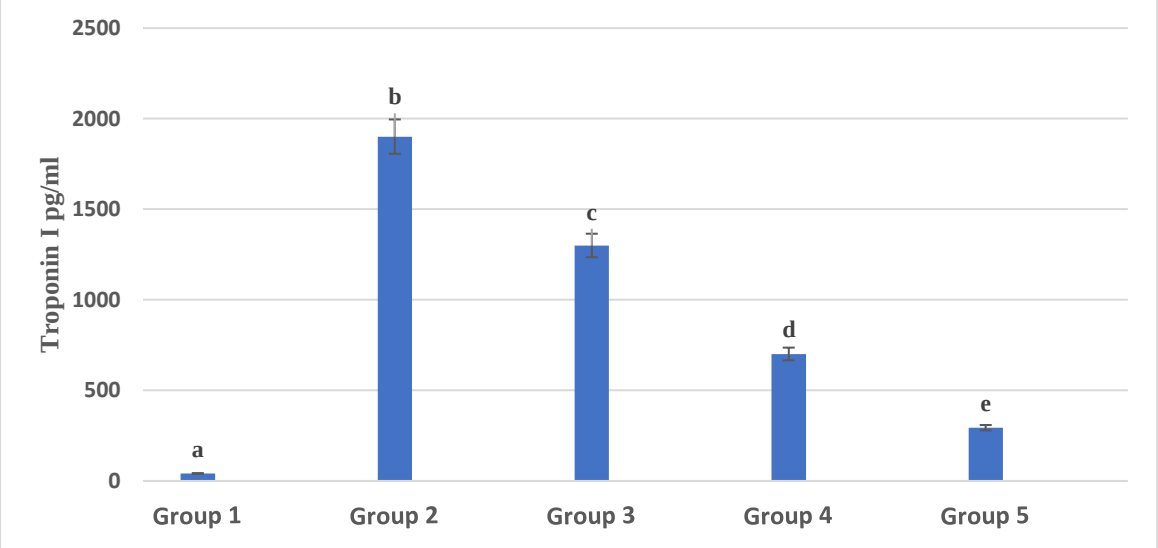

Figure 1. Effects of Hidrosmin and Vitamin C on Serum Troponin I Level

Each value represents mean ± standard deviation (SD). Values expressed in different small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of animals in each group=9

Furthermore, in Table 2 and Figure 2, rats IP injected with (2.5 mg/kg) every other day for 14 days, **Group 2** shows a highly significant increase (P< 0.001) in serum TNF-α level compared with **Group 1**. Mean±SD of the serum levels of TNF-α for (**Group 2** and **Group 1**) was found to be respectively, 4706.88 ± 0.92[b] and 97 ± 0.86[a]. Meanwhile, **Group 3** showed a highly significant decrease (P<0.001) in serum TNF-α compared with **Group 2**. Mean±SD of the serum levels of TNF-α for (**Group 3** and **Group 2**) was found to be respectively, 3002.33 ± 0.70[c], and 4706.88 ± 0.92[b]. Furthermore, **Group 4** shows a highly significant decrease (P<0.001) in serum TNF-α compared to **Group 2**. Mean±SD of the serum level of TNF-α for (**Group 4** and **Group 2**) was found to be respectively, 1574.44 ± 0.88[d], and 4706.88 ± 0.92[b]. A better result will be achieved in **Group 5** showing a highly significant decrease (P<0.001) in serum TNF-α compared with **Group 2**. Mean±SD of the serum levels of TNF-α for (**Group 5** and **Group 2**) was found to be respectively, 852.88 ± 0.78[e], and 4706.88 ± 0.92[b].

Table 2, Effects of Hidrosmin and Vitamin C on Serum TNF-α Level

Treated Groups	**Mean TNF-α level pg/ml ±SD**
Group 1 (IP NS 1 ml/kg) every other day and oral 0.5ml/kg of DMSO daily for 14 days	97 ± 0.86^{a}
Group 2 DOX IP (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	4706.88 ± 0.92^{b}
Group 3 hidrosmin (300 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	3002.33 ± 0.70^{c}
Group 4 vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	1574.44 ± 0.88^{d}
Group 5 hidrosmin (300 mg/kg/day) plus vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	852.88 ± 0.78^{e}

Each data is expressed as mean ± standard deviation (SD). Values in small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of rats in each group= 9

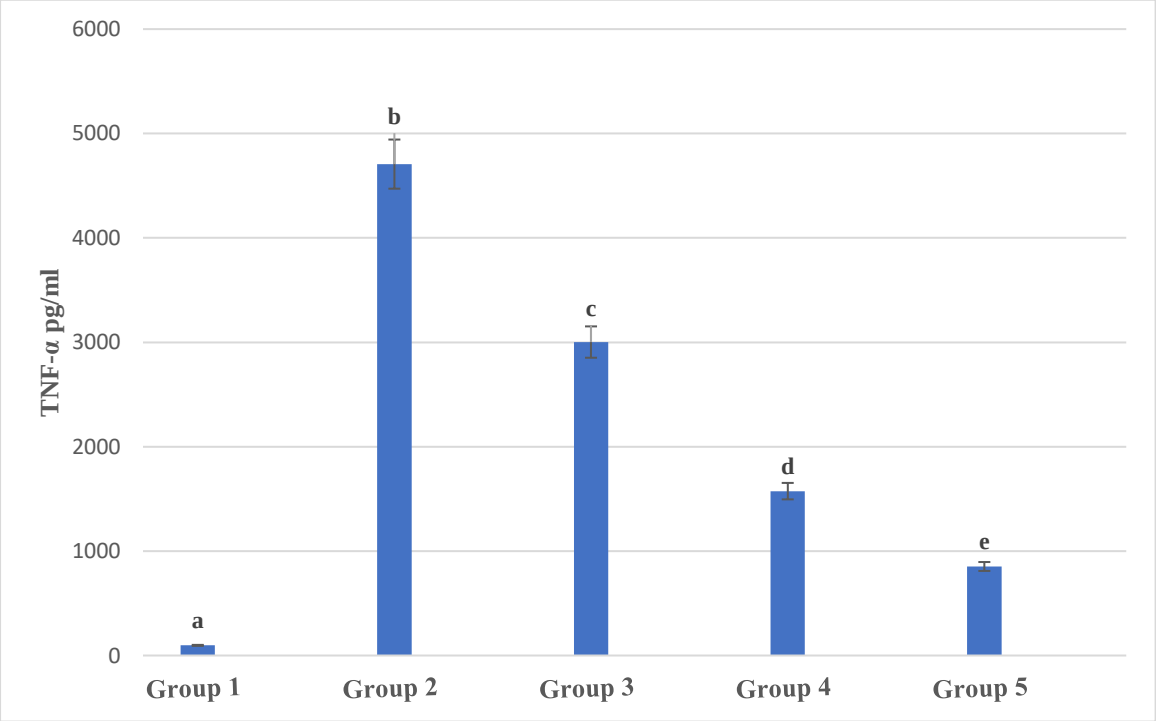

Figure 2. Effects of Hidrosmin and Vitamin C on Serum TNF-α Level

Each value represents mean ± standard deviation (SD). Values expressed in different small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of animals in each group=9

Moreover, Table 3, and Figure 3 show that rats IP injected with (2.5 mg/kg) every other day for 14 days **Group 2** shows a highly significant increase (*P*< 0.001) in serum iNOS level compared with **Group 1**. Mean±SD of the serum levels of iNOS for (**Group 2** and **Group 1**) was found to be respectively, 17.9 ± 0.86^{b} and 2.11 ± 0.07^{a}. Meanwhile, **Group 3** showed a highly significant decrease (*P*<0.001) in serum iNOS compared with **Group 2**. Mean±SD of the serum levels of iNOS for (**Group 3** and **Group 2**) was found to be respectively, 13.12 ± 0.08^{c},

and 17.9 ± 0.86[b]. Furthermore, **Group 4** shows a highly significant decrease (P<0.001) in serum iNOS compared to **Group 2**. Mean±SD of the serum level of iNOS for (**Group 4** and **Group 2**) was found to be respectively, 8.08 ± 0.09[d], and 17.9 ± 0.86[b]. A better result will be achieved in **Group 5** showing a highly significant decrease (P<0.001) in serum iNOS compared with **Group 2**. Mean±SD of the serum levels of iNOS for (**Group 5** and **Group 2**) was found to be respectively, 5.13 ± 0.07[e], and 17.9 ± 0.86[b].

Table 3.Effects of Hidrosmin and Vitamin C on Serum iNOS Level

Treated Groups	**Mean iNOS level ng/ml ±SD**
Group 1 (IP NS 1 ml/kg) every other day and oral 0.5ml/kg of DMSO daily for 14 days	2.11 ± 0.07[a]
Group 2 DOX IP (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	17.9 ± 0.86[b]
Group 3 hidrosmin (300 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	13.12 ± 0.08[c]
Group 4 vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day and oral 0.5 ml/kg of DMSO daily for 14 days	8.08 ± 0.09[d]
Group 5 hidrosmin (300 mg/kg/day) plus vitamin C (100 mg/kg/day) plus DOX (2.5 mg/kg) every other day for 14 days	5.13 ± 0.07[e]

Each data is expressed as mean ± standard deviation (SD). Values in small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of rats in each group= 9

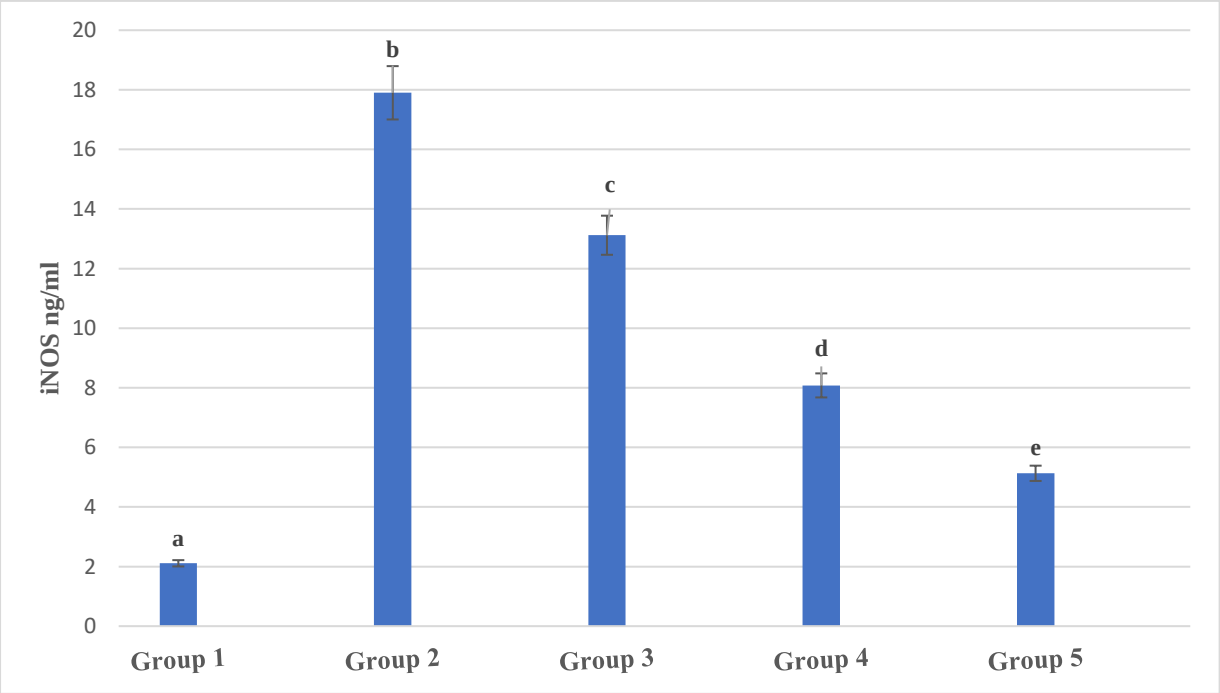

Figure 3. Effects of Hidrosmin and Vitamin C on Serum iNOS Level

Each value represents mean ± standard deviation (SD). Values expressed in different small letters (a, b, c, d, and e) are significantly different (P<0.05). Number of animals in each group=9

Histopathology of rats' heart tissue

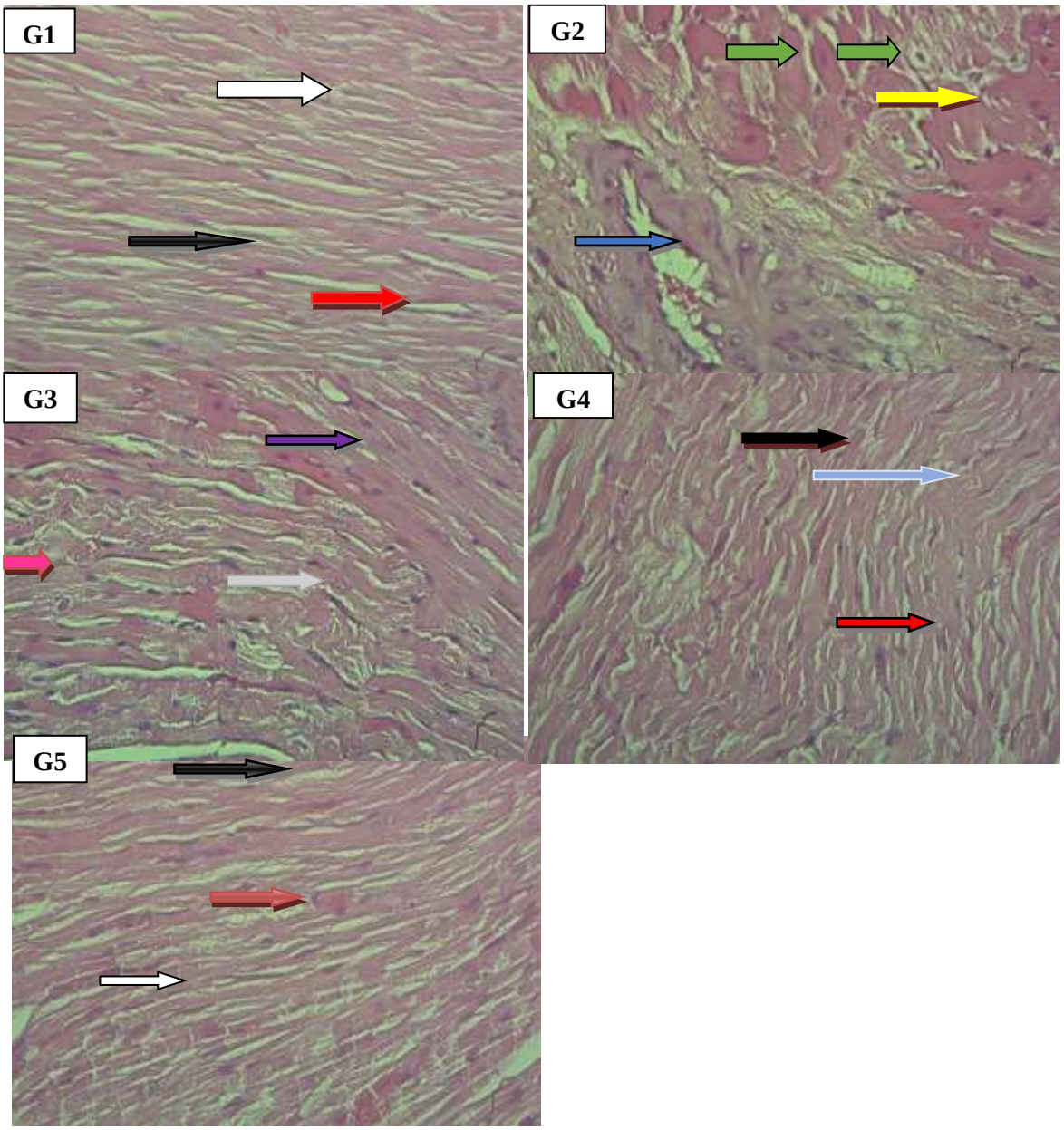

Figure 4 Photomicrograph of the heart section of the rat in different studied groups

(**G1**) Which represents Group 1, normal cardiac muscle in a longitudinal section of a syncytium of myocardial fibers (red arrow) with centrally located nuclei (black arrow), faint dark pink intercalated discs (white arrow). (**G2**) Which represents Group 2, a characteristic microscopic feature is the Aschoff nodules (blue arrow) pancarditis with missive degeneration of myocytes (yellow arrow) as well as vacuolation of myocardial muscle cells (green arrow). (**G3**) Which represents Group 3, myocyte damage occurs (grey arrow), myocardium fibers are thickness (purple arrow), and vacuolation of nuclei (pink arrow). (**G4**) Which represents Group 4, normal syncytium of myocardial fibers respectively (red arrow), with centrally located nuclei (black arrow), with fewer myocardium fibers are thickness compared with Group 3(light blue arrow). (**G5**) This represents Group 5, the normal architecture structure of myocardium components (syncytium red arrow, nuclei black arrow, intercalated discs white arrow respectively may be noticed compared with (Groups 2, 3, and 4)? **H&E:40X**.

Discussion

In the present study, DOX caused a significant elevation in the serum troponin I, TNF-α, and iNOS as shown in group 2, these effects could be explained by selective inhibition of troponin, myosin light-chain 2, cardiac muscle gene expression for α-actin, and creatine kinase [27]. This may lead to loss of myofibrillar associated with DOX-induced cardiotoxicity [28, 29]. DOX also cause calcium overload that leads to damage of

myocyte and myocardial adrenergic function disruption, the release of proinflammatory cytokines including TNF-α, interleukins as well as the release of vasoactive amines [30]. Moreover, it has been suggested that DOX-induced sub-acute cardiac toxicity may be caused by free radical overproduction that causes DNA damage [31]. Furthermore, DOX chelate metal iron catalyses the generation of free radicals [32]. DOX also have a quinone structure, which can be reduced by NADPH-dependent processes to form a semiquinone free radical, which starts a chain reaction that produces superoxide and hydroxide radicals [33, 34]. In addition to that cardiac tissue, toxicity is exacerbated by low detoxification mechanism and antioxidant enzyme levels as well as due to direct blood supply that reaches the heart [35]. whereas rats treated with hidrosmin plus DOX (group 3) showed a significant decrease in serum levels of troponin I, TNF-α, and iNOS this could be referred to the cytoprotective, anti-oxidant activity of hidrosmin which coincides with previous studies that showed that the use of hidrosmin display a reduction in the serum level of iNOS and increase in serum concentration of superoxide dismutase, catalase [36], further studies showed that hidrosmin administration results in up-regulation in the transcription of NRF2 activation pathway as well **as** NF-κB inhibition which control and regulate the generation of ROS [37]. Another study showed that pretreatment with hidrosmin ameliorates the phosphorylation of H2A.X histone which is used as a marker of DNA damage results from ROS generation [38]. Moreover, rats treated with **vitamin** C (group 4) resulted in a **highly** significant reduction in serum levels of troponin I, TNF-α, and iNOS when compared with (group 2**)** moreover rats treated with a combination of hidrosmin plus vitamin C (group 5) results in a highly significant decrease in serum levels of troponin I, TNF-α, and iNOS when compared with (group 2), also produce better effects than the use of hidrosmin and vitamin C alone (group 3, group 4) respectively, these effects may produce from the antioxidant activity of both hidrosmin and vitamin C which can attenuate the deleterious effects of ROS on the heart which coincide Luna J *et al*. (2021) and Xi S *et al*. (2019) [19, 39].

In addition to that, the histopathological study in Figure 4 revealed that rats treated with DOX show a microscopic feature of the Aschoff nodules, pancarditis with missive degeneration of myocytes with vacuolation of myocardial muscle cells in group 2 when compared with the normal architecture of microscopic findings in group 1, furthermore microscopic findings in group 3 and 4 shows Myocyte damage, myocardium fibers are thickness and vacuolation of nuclei which represent group 3. Furthermore, normal syncytium of myocardial fibers, with fewer myocardium fibers are thickness, with centrally located nuclei in group 5 when compared with group 2, these findings coincide with Jiménez-C *et al*. (2021) and Corcostegui R *et al*. (1998) which confirms the cytoprotective effects of hidrosmin which may be explained through its antioxidant activity [19, 21].

Conclusion

Hidrosmin shows a cytoprotective effect against DOX-induced sub-acute cardiac toxicity through attenuation of the deleterious effects of reactive oxygen species furthermore combination of hidrosmin plus vitamin C produces a synergistic effect than using each alone.

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Conflicts of Interest

No conflict of interest was announced by the authors.

Funding

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Ethical Clearance

In Iraq, the Research Ethical Committee oversees scientific research with ethical approval from the ministries of the environment, health, higher education, and scientific research.

Author Contribution

The authors confirm the contribution to the paper as follows: study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation: Waleed K. Ghanim; histopathological study: Muhsin S. G. Al-Moziel. All authors reviewed the results and confirmed the final version of the manuscript.

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التأثيرات الوقائية للهيدروسمين وفيتامين ج ضد تسمم القلب شبه الحاد الناتج عن الدوكسوروبيسين في الجرذان

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الخلاصة

الدوكسوروبيسين هو عامل علاج كيميائي ينتمي إلى مجموعة الأنثراسيكلين التي تستخدم لعلاج مجموعة واسعة من الأورام الخبيثة، ومع ذلك، فإنه يرتبط بتسمم القلب الخطير، وهيدروسمين هو فلافونويد اصطناعي مشتق من الهسبيريدين، والديوسمين الذي له تأثيرات متعددة التأثيرات بما في ذلك مضاد الإقفار، الأنشطة الخافضة للضغط والمضادة للالتهابات ومضادات الأكسدة. فيتامين ج هو فيتامين قابل للذوبان في الماء وقد يقلل من مخاطر الإصابة بأمراض القلب والأوعية الدموية والسرطان والسكتة الدماغية. تم تقسيم خمسة وأربعين جرذ اً ذكراً ناضجاً تتراوح أوزانهم الأساسية بين ٢٥٠-٢٨٠ جرام إلى خمس مجموعات؛ **المجموعة ١**: المجموعة الضابطة، حيث تم حقن الجرذان بمحلول ملحي عادي (١ مل / كجم) داخل الصفاق كل يومين وتم إعطاؤها عن طريق الفم (٠,٥ مل / كجم) من ثنائي ميثيل سلفوكسيد يوميًا لمدة أربعة عشر يومًا. **المجموعة ٢**: تم حقن الجرذان في هذه المجموعة داخل الصفاق باستخدام دوكسوروبيسين (٢,٥ ملجم / كجم)، كل يومين وتم إعطاؤها عن طريق الفم (٠,٥ مل / كجم) من ثنائي ميثيل سلفوكسيد يوميًا لمدة أربعة عشر يومًا. **المجموعة ٣**: تم إعطاء الجرذان هيدروسمين عن طريق الفم يوميًا بجرعة (٣٠٠ مجم/كجم/يوم) للفئران وحقنها داخل الصفاق باستخدام دوكسوروبيسين (٢,٥ مجم/كجم) كل يومين لمدة أربعة عشر يومًا. **المجموعة ٤**: تم إعطاء الجرذان فيتامين ج عن طريق الفم يوميًا بجرعة (١٠٠ مجم / كجم / يوم) وتم حقنها داخل الصفاق باستخدام دوكسوروبيسين (٢,٥ مجم / كجم) كل يومين و (٠,٥ مل / كجم) من ثنائي ميثيل سلفوكسيد عن طريق الفم يوميًا لمدة أربعة عشر يومًا. **المجموعة ٥**: أعطيت الجرذان عن طريق الفم مزيجًا من الهيدروسمين بجرعة (٣٠٠ مجم / كجم / يوم) وفيتامين ج بجرعة (١٠٠ مجم / كجم / يوم) يوميًا وتم حقنها داخل الصفاق باستخدام دوكسوروبيسين (٢,٥ مجم / كجم) كل يومين لمدة أربعة عشر يوما؛ في اليوم الخامس عشر، تم التضحية بالحيوانات لقياس التروبونين الأول، وعامل نخر الورم ألفا، وسينسيز أكسيد النيتريك المحفز، ودراسة الأنسجة المرضية؛ تُظهر **المجموعة ٣** انخفاضًا كبيرًا ($P<0.05$) في التروبونين I، وعامل نخر الورم ألفا، وسينسيز أكسيد النيتريك المحفز مقارنةً **بالمجموعة ٢**؛ علاوة على ذلك، تُظهر **المجموعة ٥** انخفاضًا كبيرًا للغاية ($P<0.001$) في التروبونين I، وعامل نخر الورم ألفا، وسينسيز أكسيد النيتريك المحفز مقارنةً **بالمجموعة ٢** و**المجموعة ٣**؛ يحسن الهيدروسمين النتائج النسيجية المرضية عند مقارنته بالدوكسوروبيسين وحده. يُظهر هيدروسمين تأثيرًا وقائيًا للخلايا ضد تسمم القلب الناجم عن الدوكسوروبيسين من خلال تخفيف التأثيرات الضارة لأنواع الأكسجين التفاعلية، علاوة على ذلك، فإن مزيج الهيدروسمين مع فيتامين ج ينتج تأثيرًا تآزريًا من استخدام كل منهما بمفرده.

الكلمات المفتاحية: سمية القلب،دوكسوروبسين، هيدروسمين، الجرذان ، فيتامين ج.