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Effect of Saxagliptin on Oxidative and Apoptotic Biomarkers in Doxorubicin- Induced Cardiac Injury in Comparison with Telmisartan Treated Rats

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Abstract

One of the most effective drugs in the field of chemotherapy is doxorubicin. It has shown remarkable efficacy against multiple cancer targets. Despite the effectiveness of treatment, an important drawback is the cardiotoxicity caused by doxorubicin. This limitation has led oncologists to explore potential ways to prevent or reduce this toxic side effect. We investigate in this study whether saxagliptin and telmisartan have protective effects on heart tissue. We study their effects on oxidative stress and apoptotic indicators in particular. A total of 28 rats, 7 animals in each of four groups: First group(control group): seven rats in good health were given distilled water for fourteen days in a row before being sacrificed on the fifteenth day.Group 2 (positive group): Seven rats were given a 20 mg/kg intraperitoneal dose doxorubicin HCl as single dose. The rats were sacrificed after twenty-four hours. In third group, rats took 10 mg/kg saxagliptin orally for 14 days. They received a single dosage of 20 mg/kg Doxorubicin IP on day 15, after 24 hours, they were slaughtered .In Group 4, seven rats were given 10 mg/kg Telmisartan orally for 14 days in a row. Doxorubicin was administered intraperitoneally at a dosage of 20 mg/kg on the fifteenth day. The rats were sacrificed after a day. Glutathione (GSH), malondialdehyde (MDA), creatinine kinase (CK-mb), and caspase 3 levels were quantified in this investigation. The doxorubicin treated group had a significantly lower GSH level compared to the saxagliptin and telmisartan groups ($p<0.05$). Likewise, when contrasted with the doxorubicin-treated group, the saxagliptin and telmisartan groups exhibited a substantial decrease in MDA levels ($p<0.05$). The doxorubicin treated group had significantly higher CK-mb levels compared to the saxagliptin and telmisartan groups ($p<0.05$). Finally, when comparing the groups treated with doxorubicin to those treated with saxagliptin and telmisartan, there was a substantial drop in caspase 3 levels ($p<0.05$). It is clear from our in vivo enzymatic analysis that saxagliptin and telmisartan show promise as doxorubicin cardiotoxicity protectants. Further research into their effects on cardiac biomarkers and anti-inflammatory capabilities, as well as further prospective preventative measures, should be undertaken in a long-term study.

Keywords: Cardiotoxicity, Caspase 3, Malondialdehyde, Saxagliptin, Telmisartan.

Introduction

Streptomyces peucetius is the source of doxorubicin [(1)], an anthracycline antibiotic. It has a stellar reputation as a powerful chemotherapy drug for patients of all ages [(1)]. Breast, bladder, lung, and thyroid carcinomas, non-Hodgkin's lymphomas, and Hodgkin's disease are among the many malignancies that it is used to treat. Acute lymphoblastic leukaemia, lung cancer, paediatric leukaemia [(2)], Kaposi's sarcoma, and other metastatic malignancies are among the other conditions that it helps cure [(3)]. Despite its efficacy, its use is restricted due to a few side effects. A potentially fatal heart disease known as doxorubicin-induced cardiotoxicity (DIC) is one of these negative effects [(4)]. DIC can set in two weeks of finishing treatment, or it can happen soon after a single dose. Additionally, there is a late onset chronic type that can appear years or even decades after drug usage, and an early-onset chronic form that typically appears within a year of therapy.

Several processes contribute to doxorubicin's cardiotoxicity: oxidative stress, DNA and mitochondrial damage, iron overload, dysregulation of autophagy, necrosis, and apoptosis [(4)], and nitric oxide metabolism. Furthermore, it is thought to activate nuclear factor kappa-B (NF-κB), leading to the up-regulation of

proinflammatory cytokines such tumor necrosis factor (TNF-α) [5]. Where all these mechanisms are interconnected at the molecular level [5]. Given the diverse applications, there is a need to explore drugs that can provide benefits such as supporting the long-term use of doxorubicin in cancer survivors, acting as cardioprotective agent, and reducing the occurrence of doxorubicin cardiotoxicity [1]. One of the medications is Saxagliptin, which is a potent and competitive dipeptidyl peptidase-4 (DPP-4) inhibitor, that affects certain hormones involved in regulating blood sugar levels [6]. It is commonly prescribed as a treatment for type 2 diabetes. They work by increasing insulin secretion through the elevation of a certain hormone level and indirectly by inhibiting an enzyme responsible for breaking down other hormones [7]. Since DDP4 has a pleiotropic effect ,it does caused an interconnected mechanisms that makes cardiac tissue more prone to the Doxorubicin induced cardiotoxicity, by affecting inflammatory pathways through degradation of IL-1,GLP-1,CXCL10,exacerbate oxidative stress by the production of reactive oxygen species, favouring apoptosis through degradation of GLP-1 which normally has protective effect and increase the activation of caspase, also through modulation of PI3K-Akt pathway where DDP4 inhibit this cascade which makes cardiac tissue more susceptible to apoptosis and decrease the ability of tissue repair, affecting endothelial function by enhancing the degradation of peptides like **BRP-1** (brain natriuretic peptide) causing reduction in blood flow and decrease oxygen and nutrient supply to cardiac tissue what makes more prone to ischemia thus cardiac damage, promote fibrosis through the activation of fibroplast which leads to alteration in cardiac function [7]. Additional peptides that are cleaved by DPP-4 have direct impacts on cells in the heart and blood vessels. Consequently, DPP4 inhibition has beneficial cardiovascular effects that are unaffected by GLP-1[8], where there is different peptides which are substrates of DPP4 enzyme including; atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), stromal cell-derived factor-1α (SDF-1α), and substance P [7,8]. SDF-1α a chemokine that improve cardiac perfusion which in turn improve the recovery after myocardial in fraction, substance p has a protective effect against cardiac damage by regulating blood pressure, prevention of fibrosis and apoptosis, also DDP4 encourage clot formation by inhibiting fibrin polymerization [7,8]. Conditions like obesity, inflammation, oxidative stress, and apoptosis are associated with elevated DPP-4 activity. It is well-established that DPP4 inhibitors have cardiovascular effects, mostly via the GLP-1 receptor (GLP-1R). Furthermore, there have been separate anti-inflammatory and antifibrotic benefits shown by DPP4 inhibitors. One prominent example of this is saxagliptin (SAX) and metabolites [9].

Because of this, DPP4 inhibitors can protect mitochondrial function, and alleviate pro oxidant production [10]. Another medicine used in this research is telmisartan, which is a class of medicine belonging to angiotensin II type1 (AT1) receptor blockers and is used to treat hypertension [11]. They function as a partial peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist [12], preventing the interaction of ang-II with AT-1R and blocking intracellular signaling pathways from this receptor [12]. The efficacy, safety, and many benefits of this family of drugs are well-known, and they include a decreased risk of cardiovascular disease [13].

The capacity of telmisartan to inhibit lipid peroxidation and protect against GSH depletion may explain how it protects against toxicities caused by Dox. probably due to its lipophilic and its antioxidant structure [13], the aim of this study is to investigate more about saxagliptin ability to act as cardioprotective agent against doxorubicin induced cardiac toxicity when compare it to telmisartan and whether both of them could be consider as adjuctive treatment.

Materials and Methods

Materials

The drugs utilized in this study include Doxorubicin, which was obtained from Khan delwal Laboratories (KLAB) in Mumbai, India, saxagliptin, sourced from Mucklin in China, and telmisartan, also obtained from Mucklin in China. Both saxagliptin and telmisartan should be stored at room temperature, while doxorubicin should be stored at cool condition and after dissolving with distelled water, the solution should be used immediately.

Animal conditioning

In this experiment a group of 28 rats were used, including both males and females, with weights ranging from 150 to 220 grams, kept in controlled environment in polypropylene cages. At a temperature of 22 ± 2 °C, the rats were kept in a normal light/dark cycle and were fed commercial pellets, also make sure the water was always available.

Experimental design

1. Group 1 (represent as negative control): all seven healthy rats received distilled water for 14 consecutive days, on day 15 they received Doxorubicin IP as single dose (20 mg/kg), and sacrificed after 24 hrs.

2. Group 2 (represented as positive control): seven rats received doxorubicin HCl (20 mg/kg)

intraperitoneally as single dose [14]. Then the rats were sacrificed after 24 hrs.

3. Group 3: the rats received saxagliptin (10 mg/kg/day) [9] orally for 14 consecutive days, on day 15 they received Doxorubicin IP as single dose (20 mg/kg), and sacrificed after 24 hrs.

4. Group 4: seven rats received Telmisartan (10 mg/kg/day) [15] orally for 14 consecutive days, on day 15 they received Doxorubicin IP as a single dose (20 mg/kg) [16], and sacrificed after 24 hrs.

Preparation of heart tissue homogenate

The rats were meticulously anaesthetised with diethyl ether prior to the sacrification. After that, they were dismembered compassionate for their head. After that, the cardiac tissues were extracted and set aside for analysis [13].A pre-cooled PBS solution (pH=7.4, 4℃) was used to eliminate any remaining blood after the heart was quickly extracted and cleaned. After that, delicately cleaned it off with filter paper and cut it into small pieces. In a tube, 0.4 g of chopped tissue and 3.6 ml of PBS (pH=7.4, 4℃) were mixed to create the tissue homogenate for every rat [13]. A Dyna-Passion® WT130 homogeniser, made in Selangor, Malaysia, by Success Technic Industries, will be used to carry out the homogenisation procedure. Homogenisation will last for one minute at 4℃ using set 3. The samples were maintained on ice during the entire process. After the suspension went through a freeze-thaw cycle, where it was centrifuged in refrigerated centrifuge (HERMLE Labortechnik GmbH, Germany) at 10,000 rpm for 10 minutes at 4℃. The supernatant that resulted was quickly collected and kept at -20℃ until analysis day [13] .To evaluate different levels (GSH, MDA, CASP 3, CK-mb), and then ELISA technique was performed according to USCN® kit instructions and the instrument used was Human Reader HS®.

Statistical analysis

Mean ± Standard deviation (SD) was used to present the study's outcomes. The statistical package for the social sciences, version 24, was used to assess data increments and analyses. To compare the groups' means, a t-test was performed, and significant differences were indicated by (P values<0.05).

Results

The Effect of saxagliptin and telmisartan on CK-mb level

A significant increase in CK-mb levels was seen in group 2 (positive control) compared to group 1 (negative control) ($p<0.05$), according to the data analysis in Table 1. Conversely, when compared to Group 2, a significant reduction in CK-mb levels was observed after administering saxagliptin (10 mg/kg) and telmisartan (10 mg/kg) to Group 4.

Table 1. The Effect of Saxagliptin and Telmisartan on CK-mb level

GROUPS		CK- mb (nmol/mg protein)
I.	Negative control group	3.22±**0.3770**
II.	DOX group	59.13±**1.160***
III.	Saxagliptin 10mg/Kg + DOX 20mg/Kg	2.49±**0.308**#
IV.	Telmisartan 10mg/Kg + DOX 20mg/Kg	4.15±**0.174**#

*Notably different when compared to group I (the negative control) (P<0.05). Data are presented as Mean±STD, with n=7.

#Compared to group II (the positive control), there was a significant difference (P<0.05).

Effect for saxagliptin and telmisartan on the level of GSH

The data analysis in Table 2 shows that there was a statistically significant drop in GSH levels in group 2, the positive control, as compared to group 1, the negative control ($p<0.05$).

Alternatively, following administration of telmisartan and saxagliptin, the GSH levels of group 4 (10 mg/kg) were noticeably greater than those of group 2 ($p<0.05$).

Table2. Effect of saxagliptin and telmisartan on the level of GSH

GROUPS		GSH (nmol/mg protein)
I.	Negative control group	68.42±**2.113**
II.	DOX group	19.21±**3.276***
III.	Saxagliptin 10mg/Kg + DOX 20mg/Kg	48.14±**3.864**#
IV.	Telmisartan 10mg/Kg + DOX 20mg/Kg	47.22±**1.743**#

*Notably different when compared to group I (the negative control) (P<0.05). Data are presented as Mean±STD, with n=7.

#Compared to group II (the positive control), there was a significant difference (P<0.05).

Effect of saxagliptin and telmisartan on MDA level

Group 2, acting as the positive control, had significantly higher MDA levels than group 1, acting as the negative control, according to the findings in Table 3 ($p<0.05$). After receiving saxagliptin (10 mg/kg) and telmisartan (10 mg/kg), groups 3 and 4 showed a substantial decrease in malondialdehyde (MDA) levels compared to group 2.

Table3. Effect of saxagliptin and telmisartan on MDA level

GROUPS		MDA (nmol/mg protein)
I.	Negative control group	1.85±**0.302**
II.	DOX group	119.82±**1.655***
III.	Saxagliptin 10mg/Kg + DOX 20mg/Kg	29.23±**3.529**#
IV.	Telmisartan 10mg/Kg + DOX 20mg/Kg	2.44±**0.522**#

*Notably different when compared to group I (the negative control) ($P<0.05$). Data are presented as Mean±STD, with n=7. #Compared to group II (the positive control), there was a significant difference ($P<0.05$).

Effect of saxagliptin and telmisartan on caspase-3 level

The data analysis in Table 4 shows that there was a significant difference in caspase-3 levels between Group 2, the positive control, and Group 1, the negative control ($p<0.05$).Treatment of group 4 with saxagliptin and telmisartan (10 mg/kg) resulted in a significant reduction in caspase-3 levels, in contrast to group 2.

Table4. Effect of saxagliptin and telmisartan on caspase-3 level

GROUPS		Caspase (nmol/mg protein)
I.	Negative control group	3.16±**0.343**
II.	DOX group	6.14±**0.095***
III.	Saxagliptin 10mg/Kg + DOX 20mg/Kg	3.68±**0.158**#
IV.	Telmisartan 10mg/Kg + DOX 20mg/Kg	1.10±**0.198**#

*Notably different when compared to group I (the negative control) ($P<0.05$). Data are presented as Mean±STD, with n=7. #Compared to group II (the positive control), there was a significant difference ($P<0.05$).

Discussion

The potential for doxorubicin to cause cardiac damage has long been a source of concern for oncologists, who fear that the medicine may have limited clinical utility. It appears that Doxorubicin-induced cardiotoxicity is caused by various mechanisms [14,17]. The doxorubicin-induced cardiotoxicity has been linked to ROS (superoxide anions (O_2^-), hydrogen peroxideH2O2) which are released by redox cycle, which could lead to the production of highly reactive hydroxyl radicals (OH) through Fenton reaction) [18], inflammation, oxidative stress, and cell death in multiple investigations [17,18]. Heart tissue is especially vulnerable to oxidative damage due to its rapid oxygen consumption rate, high mitochondrial density/volume, and low levels of antioxidant enzymes [16]. Protecting cardiac tissue from doxorubicin-induced oxidative stress is another benefit of antioxidant therapy multiplication by fourteen. Some signs of oxidative stress were seen in the effects of DOX on glutathione levels, lipid peroxidation, and antioxidant enzyme activity [18]. Due to DXR-induced oxidative stress, the intrinsic mitochondria-dependent apoptotic pathway becomes active in cardiomyocytes. The process leads to myofibril degeneration and mitochondrial dysfunction. Abnormal conduction and elevated serum creatine kinase isoenzyme-MB (CK-MB) are hallmarks of DXR-induced cardiotoxicity [18], DOX-induced apoptotic tissue damage [18], and DOX-induced myocardial damage [19], and there is some evidence to suggest that cellular apoptosis, or programmed cell death, plays a significant role in the pathophysiology of such conditions [19].

Acute cardiotoxicity, as measured by CK-MB, an indicator of cardiac damage; an oxidative stress response, as shown by increased MDA levels and a significant decrease in GSH, an enzyme that scavenges free radicals; and an increase in caspase 3, one of the main mechanisms responsible for cardiomyocyte loss in failing hearts, are all confirmed by this study. A single intra-peritoneal dose of doxorubicin (20 mg/kg) is also required. By reducing levels of the cardiac biomarker CK-MB and the apoptotic marker CASPASE 3, this study showed that saxagliptin and telmisartan, when taken before therapy, reduce doxorubicin-induced cardiotoxicity, reduced malondialdehyde levels and increased glutathione (GSH) levels are additional outcomes of these medicines' antioxidant activities [20-23].

Effect of saxagliptin and telmisartan pre treatment on cardiac biomarkers (CK-MB)

A statistically significant increase in CK-MB levels was observed in this study when compared to the control group. This is an earlier study that also found that doxorubicin had an effect

on this marker, suggesting that doxorubicin-induced cardiotoxicity is the cause of the decrease in cardiac function [18].

One possible method by which saxagliptin protects the heart is by blocking the AGE-RAGE pathway. Advanced Glycation End Products, or AGEs, can modify the structure and function of cardiac tissue directly and interact with the RAGE receptor to produce indirect damage. Evidence is mounting that AGEs and RAGE can upset the oxidative process balance, which in turn activates the NF-κB signalling pathway and causes inflammation [20].

Improvements in systolic and diastolic functions, along with an elevation in neurohormonal indicators as serum ANG 1-7, may constitute the cardioprotective impact of telmisartan. Telmisartan also reverse inflammatory events and oxidative stress signalling by modulating the expression of ACE2/ANG 1-7/Mas receptors which in turn prevent further damage to the cardiac tissue, which in turn reduces myocardial remodeling also improving systolic and diastolic pressure which is crucial for patient who suffers from cardiac diseases as heart failure [20].

Effect of saxagliptin and telmisartan on malondialdehyde (MDA)

This study indicated that the MDA level was considerably greater in the group that received dox as compared to the control group. This confirms what a prior study had found: that DOX-induced cardiotoxicity is mainly caused by elevated levels of cardiac oxidative stress. The accumulation of dioxin-like compounds (DOCs) in cardiac mitochondria has been found to enhance ROS generation, which in turn can cause lipid oxidation[18].

However, when contrasted with the DOX group, the saxagliptin and telmisartan groups showed a substantial reduction in MDA levels. Peroxidation of endogenous lipids can cause necrosis and injury to the heart muscles [20,21]. Therefore, this reduction is vital for protecting cells. Malondialdehyde (MDA), quantified as thiobarbituric acid reactive substance (TBARS), is one byproduct of lipid peroxidation. The fact that saxagliptin can inhibit lipid peroxidation is supported by the fact that it dramatically reduces TBARS levels [19]. Furthermore, saxagliptin protects against free radicals by increasing the activity of key defense enzymes including catalase and superoxide dismutase [19,22]. By successfully lowering the inflammatory alterations associated with Dox-induced cardiotoxicity, the group treated with telmisartan demonstrates a considerable improvement in reducing heart injury. In particular, telmisartan and other AT1 receptor blockers can prevent the cardiotoxic oxidative stress that is caused by Dox [21].

Effect of saxagliptin and telmisartan on GSH

Doxorubicin is believed to mainly induce cardiotoxicity by generating reactive free radicals. Doxorubicin exacerbates cardiac damage since the heart naturally has fewer antioxidant enzymes such as glutathione (GSH), superoxide dismutase (SOD), and catalase [22,23]. Furthermore, the doxorubicin group's GSH levels were significantly lower than the control groups, according to this study. The GSH level increased significantly in the saxagliptin group as compared to the doxorubicin group. This is in line with earlier studies showing that saxagliptin lowers MDA levels and raises levels of antioxidant enzymes (CAT and GSH) [22]. It also implies that saxagliptin has antioxidant characteristics. The telmisartan group seems to have been protected from DXR-induced cardiotoxicity. This is thought to be occurring due to the telmisartan mechanism, an AT1 receptor antagonist, that reduces GSH depletion by blocking DXR's ability to interact with cell membranes and cause oxidative damage [23].

Effect of saxagliptin and telmisartan on the level of caspase-3

The elevation of cardiac apoptosis is suggested by the rise in caspase 3, which is seen in the dox-treated group. This is doxorubicin-induced cardiotoxicity. One extremely poisonous metabolite is the semiquinone, which is derived from DXR. It can combine with oxygen molecules to set off a cascade of reactions that produce hydrogen peroxide, superoxide anion radicals, and hydroxyl radicals, all of which are known as reactive oxygen species (ROS). Damage to mitochondria and cell membranes, two crucial components of cells, can be caused by these radicals, leading to cell death in cardiomyocytes [18]. Caspase 3 levels were found to be significantly lower in the group that received saxagliptin. This confirms what other research has shown: that saxagliptin helps keep mitochondrial architecture intact, myofibrils organised, and Z lines in a regular pattern [19]. Its capacity to scavenge free radicals is the reason behind this protection. Learn the intriguing processes by which saxagliptin exerts its antioxidant and anti-apoptotic effects [19,24]. There was a statistically significant drop in caspase 3 levels in the telmisartan group when contrasted with the DOX group. Consistent with earlier research showing that telmisartan can decrease caspase-3 levels, this validates the anti-apoptotic action of telmisartan. Telmisartan accomplishes this by increasing PPAR-gamma expression and decreasing the expression of several other factors, including nuclear factor kappa-B, interleukin-6, TNF-alpha, iNOS, and caspase-3[24,25].

Conclusion

Based on the data excluded by this study, it appears that both saxagliptin and telmisartan show promising results where they can be used in conjunction with doxorubicin. Both of these drugs have properties that can potentially reduce the cardiotoxicity of doxorubicin, such as their anti-oxidant, anti-apoptotic, and cardio-protective effects.

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Conflicts of Interest

The authors have no conflict of interest.

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Ethics Statements

The research has the approval from the scientific and ethical committees of the College of Pharmacy University of Baghdad. Approval Number: RECAUBCP21122023W in 21-12-2023 .

Author Contribution

The first author did the practical work and result analysis. The second author supervised the whole work.

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تأثير الساكساجليبتين على المؤشرات الحيوية المؤكسدة وموت الخلايا المبرمج في إصابة القلب الناجمة عن الدوكسوروبيسين مقارنة بالجرذان المعالجة بالتيلميسارتان

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[٢]فرع الادوية والسموم ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق.

الخلاصة

يعتبر الدوكسوروبيسين واحد من بين أقوى الأدوية وأكثرها فعالية في مجال العلاج الكيميائي بسبب فعاليته على العديد من أهداف السرطان, لكن على الرغم من فعاليته، إلا أن أحد الآثار الجانبية الهامة التي يسببها الدوكسوروبيسين هو تسمم عضلة القلب. وهذا التاثير جعل اطباء الاورام يستكشفون طرقا محتملة لمنع او تقليل هذا التاثير , في هذه الدراسة يتم الاستكشاف عن امكانيه وجود تاثير وقائي لكل من الساكساجليبتين والتيلميسارتان على أنسجة القلب , ودراسه تاثيرهم على علامات موت الخلايا المبرمج والأكسدة بشكل اخص.مجمل عدد الجرذان هو ثمان وعشرون تقسم إلى أربع مجموعات، كل مجموعة بها ٧من الجرذان : المجموعة الاولى (مجموعه التحكم): جميع الفئران السبعة السليمة تلقت الماء المقطر لمدة ١٤ يومًا متتالية وتم التضحية بها في اليوم ١٥. المجموعة ٢ (تمثل السيطرة الإيجابية): تلقت ٧ فئران دوكسوروبيسين (٢٠ ملغم / كغم) داخل الصفاق كجرعة وحيدة. ثم تم التضحية بالفئران بعد ٢٤ ساعة. المجموعة ٣: تلقت الفئران ساكساجليبتين (١٠ ملجم/كجم/يوم) عن طريق الفم لمدة ١٤ يومًا متتاليًا، وفي اليوم ١٥ تلقت دوكسوروبيسين داخل الصفاق كجرعة وحيدة (٢٠ ملجم/كجم)، وتم التضحية به بعد ٢٤ ساعة. المجموعة ٤: تلقت ٧ فئران تيلميسارتان (١٠ ملغم / كغم / يوم) عن طريق الفم لمدة ١٤ يومًا متتاليًا، في اليوم ١٥ تلقوا دوكسوروبيسين داخل الصفاق كجرعة وحيدة (٢٠ ملغم / كغم)، وتم التضحية بهم بعد ٢٤ ساعة.تم قياس كل من الغلوتاثيون والمالونداليديهايد والكاينيز والكاسبيز ٣ في هذه الدراسه,اظهرت المجموعه المعالجه بلدوكسوروبيسين انخفاضا ملحوظا بمستوى الغلوتاثيون عند مقارنته بكل من مجموعتي السكساجلبتين والتيلميسارتان ($P<0.05$), ومثل ذلك بالنسبه للمالونداياالادهليد عند مقارنه المجموعه المعالجه بلدوكسوروبيسين بمجموعتي السكساجلبتين والتيلميسارتان لوحظ انخفاضا ملحوظا ($P<0.05$),واظهرت المجموعه المعالجه بلدوكسوروبيسين زياده ملحوظه بمستوى الكرياتينين كاينيز عند مقارنتها بكل من مجوعتي السكساجلبتين والتيلميسارتان ($P<0.05$) , واخيرا بلنسبه للكاسبيز ٣عند مقارنه المجموعه المعالجه بالدوكسوروبيسين بكلا المجموعتي المعالجتين بالسكساجلبتين والتيلميسارتان لوحظ انخفاضا واضحا بمستوى الكاسبيز ٣ ($P<0.05$). يتضح من الدراسة الأنزيمية على الجسم الحي أن كلا من ساكساجليبتين والتيلميسارتان يظهران تأثيرًا وقائيًا واعدًا ضد تسمم القلب بالدوكسوروبيسين, يوصى بالعمل على ابحاث اضافيه عن تاثيرهما على المؤشرات الحيوية للقلب و مضادات للالتهابات و أيضًا بالدراسة على المدى الطويل للبحث عن أي حماية ممكنة إضافية.

الكلمات المفتاحية: سمية القلب، كاسباس ٣، مالوندالديهايد، سكساكلبتين، تلميسارتان.