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Ameliorative Effects of Lutein Supplementation against Cardiotoxicity Induced by Daunorubicin and Ciprofloxacin in Rats

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Abstract

Daunorubicin clinical use has been limited by its cardiotoxicity. Iron-mediated oxidative stress in cardiomyocytes is the main mechanism of the anthracycline cardiotoxicity. Ciprofloxacin is a second-generation fluoroquinolone and most effective and used drugs. The molecular mechanism of the ciprofloxacin adverse effects provoked through the inhibition of the topoisomerase II in the mitochondria that cause mitochondrial DNA impairment of transcription and replication. Elevated levels of circulating cardiac troponins (Troponin T and I) are myocardial damage predictors. Lutein is an oxygenated carotenoid that derived from the diet in all mammalians including humans. It has anti-inflammatory effects, anti-genotoxic, improving cardiovascular diseases, reducing cancers risk, and improving cognitive functions. This study investigates the cardiotoxicity induced by ciprofloxacin in comparison with the cardiotoxicity of daunorubicin through the measurement of cardiac troponin I, interleukin 6, GSH peroxidase 4 and cleaved (caspase-3) levels in heart tissues; and to explore the protective effects of lutein against the ciprofloxacin and daunorubicin induce cardiotoxicity in the rat. Thirty adult Sprague- Dawley rats of both sexes divided to five groups of six rats each: Group I: given 10% dimethyl sulfoxide orally for 15 successive days. Group II: received Daunorubicin 20 mg/kg for last 3 days with cumulative dose (60 mg/kg) by IP injection. Group III: given for the last 5 days 500 mg/kg ciprofloxacin orally. Group IV: received oral dose of lutein (24mg/kg) daily for 15 consecutive days, and Daunorubicin by intraperitoneal injection. Group V: given lutein (24mg/kg) orally daily for 15 days, then given ciprofloxacin oral dose for last 5 days. Cardiotoxicity induced by ciprofloxacin and daunorubicin, associated by increasing levels of cardiac troponin I, interleukin 6, GSH peroxidase 4 and cleaved (caspase-3) levels in heart tissues. pretreated cardiotoxic rats with lutein (Group IV and Group V) was showed significant decline in the cardiac troponin I level, also reversed oxidative stress markers; rat Glutathione peroxidase 4 levels, to the control level. Suppression of the apoptotic and inflammatory markers, by measuring rat interleukin 6 levels and rat cleaved (caspase-3) levels respectively, in heart tissues.

Keywords: Cardiotoxicity, Cardiac troponin I, Daunorubicin, Ciprofloxacin and Lutein.

Introduction

Daunorubicin is one of the anthracycline anti-tumor agents that used widely for the management of acute myeloid leukemia (AML). but, the clinical usage of daunorubicin is limited due to its systemic toxicities, mainly the heart [(1)]. Decrease in cardiac function in AML patients by daunorubicin treatment with cytarabine combination determined by the dropping in the left ventricular ejection. Daunorubicin interfere with heart pumping activity and also may lower the blood cell production ability of the body. Thus, patients need transfusion of blood that may lead to bleeding complications and many of infections [(2)]. Several mechanisms for daunorubicin induction of cardiotoxicity had suggested. Anthracyclines results in dose-dependent cardiac toxicities [(3)]. Moreover, oxidative stress of the myocardia mediated by Iron is the well-described mechanism for the anthracycline cardiotoxicity [(4)].

Poisons for the topoisomerase, including the anthracyclines, stabilizing the intermediate that block the reaction of the catalytic enzyme resulting in DNA strand is cut and bond to the enzyme by covalent bond.

As the DNA is broken, the intermediate reaction called DNA-Top2 cleavage complex (Top2cc) [5], Topoisomerase II– anthracycline–DNA cleavage complex triggers death of the cell. In addition, tumor cells overexpressed the Top2a, anthracyclines target the Top2b that expressed in the cardiomyocytes [6]. The derivation of the fluoroquinolones carboxylic acid is Ciprofloxacin, which is a second generation and most effective and useful drugs [7]. Inhibiting of the topoisomerase II (DNA-gyrase) and also the topoisomerase IV enzymes is the mechanism of ciprofloxacin action, since these enzymes are essential for DNA transcription in the bacteria and their recombination, repair, replication, and strand supercoiling repair [8]. Molecular mechanisms mentioned by researchers for the adverse effects of ciprofloxacin to be through the inhibition of mitochondrial topoisomerase II (DNA-gyrase) that may lead to the dysfunction of mitochondrial DNA replication and transcription, which affect the cellular differentiation and proliferation [9]. Lutein has a high antioxidant activity; in addition to decrease the risk of age-related disorder [10]. Lutein is an oxygenated carotenoid (a xanthophyll), which is non-synthesized in all mammalians including humans, that they deriving it from diet [11]. Studies showed that the intake of lutein supplementation or from the diet in high concentration, has beneficial effects on some eye diseases, also preventing the age-related macular degeneration (AMD) [10, 11], which is a pathologic change in the macula retinal layers and their vasculature that resulted in the loss of the central vision [12], also cataract [10]. Several studies recently, suggested the anti-inflammatory effects of lutein [11, 13], and also capable to improve cognitive functions [14], even decreasing the risk of malignancies [10], cardiovascular disease improved by lutein supplement [15] and many else systemic conditions [16]. Also, it has been mentioned that lutein has anti-genotoxic properties, attenuation the suppression in immunity by using the mouse models due to radiation by ultraviolet [17]. This study investigates the cardiotoxicity induced by ciprofloxacin in comparing to the cardiotoxicity of daunorubicin through the measurement of cardiac troponin I, interleukin 6, GSH peroxidase 4 and cleaved (caspase-3) levels in heart tissues; and to explore the lutein protective effect against the ciprofloxacin and daunorubicin induction of cardiotoxicity in the rat models.

Materials and Methods

Chemicals and kits: Rat Highly sensitive Cardiac Troponin I (Hs-cTnI), Rat Glutathione Peroxidase 4 (GPX4), Rat Interleukin 6(IL-6) and Rat cleaved (caspase-3) ELISA KIT ware from the SUNLONG BIOTECH CO., LTD., company in China. Drug: Daunorubicin 10mg/5ml vials from the Fresenius Kabi company in India; The pure ciprofloxacin powders from the Shaanxi Yuantai Biological Technology Co., Ltd. Company in China; the pure powder of lutein was from the Xi`an, Rongsheng, Biotechnology Co., Ltd. company in China.

Animals

Thirty Sprague- Dawley adult rats of both sexes, each weighing (160- 210) gm taken from the Animals House, College of Pharmacy /University of Baghdad, under conventional and controlled laboratory conditions. Experimental rats housed in cages, under temperature of about (25°C), relative humidity and natural cycle of the light/dark. Standard tap water and laboratory rodent chow supplied in *ad libitum*. The animals adapted one-week period prior of the experiment. The animals divided into five groups of six rats for each group:

- **GroupI (Control):** rats given orally daily dose of 10% dimethyl sulfoxide (4 ml/kg) for 15 successive days.
- **GroupII (Daunorubicin-treated):** given oral daily dose of 10% dimethyl sulfoxide (4 ml/kg) for 15 successive days, then received Daunorubicin 20mg/kg for last 3 days (with a cumulative dose of 60mg/kg) by Intra-peritoneal (IP) injection.
- **GroupIII (Ciprofloxacin-treated):** given oral daily dose of 10% dimethyl sulfoxide (4 ml/kg) for 15 days, and then received 500 mg/kg ciprofloxacin oral dose for the last 5 days [8].
- **GroupIV (24mg lutein /kg/day+ Daunorubicin):** given lutein oral daily dose of (24mg/kg, dissolved in 10% dimethyl sulfoxide) for 15 consecutive days, and subsequently received Daunorubicin 20mg/kg for last 3 days (with a cumulative dose of 60mg/kg) by intraperitoneal injection (IP).
- **GroupV (24mg lutein /kg/day+ Ciprofloxacin):** given lutein oral daily dose (24mg/kg, dissolved in 10% dimethyl sulfoxide) for 15 successive days, and subsequently received 500mg/ kg of ciprofloxacin dose orally for last 5 days.

After the end of the treatment by about 24 hours, rats euthanized by the use of diethyl ether, rats' heart tissues were excised quickly and then putted in a chilled pH 7.4 phosphate buffer solution (PBS) at 4^0C, then by using filter paper blotted and weighed in-order to the tissue homogenates preparation (10%) we added 1gm of heart tissue pH 7.4 PBS (9ml), then by using of tissue homogenizer the tissue homogenized for 1 minute at 4 ^{0}C. The freshly prepared tissues homogenates kept frozen unless immediately worked for the measuring of rat cardiac troponin I (Hs-cTnI), rat Glutathione Peroxidase 4 (GPX4), rat Interleukin 6(IL-6) and rat cleaved (caspase-3) levels in heart tissue homogenates [11].

Statistical Analysis

Data values expressed as mean ± standard deviation (mean± SD); and the analysis was done by the utilization of the Statistical Package Social Sciences (SPSS) computerized program of version 23. Statistically significant determined among different groups by the one-way analysis of variance (one way-ANOVA) when the P value is less than the 0.05 (P<0.05).

Results and Discussions

Cardiotoxicity induced by daunorubicin and ciprofloxacin (GroupII and GroupIII respectively), associated by significant elevation of cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues homogenate (P<0.05) (Figure. 1) and significant (P<0.05) decreasing in the GSH peroxidase 4 (GPX-4) levels in heart tissues homogenate (P<0.05) (Figure. 2) each compared to the control group.

Cardiotoxicity induced by daunorubicin (GroupII), associated by significant elevation of cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues homogenate (P<0.05) (Figure. 1) each compared to the cardiotoxicity induced by ciprofloxacin (GroupIII) rats. However, there was non-significant differences in the GSH peroxidase 4 (GPX-4) levels in heart tissues homogenate (P<0.05) (Figure. 2) each between GroupII and GroupIII rats.Administration of lutein (24mg/kg) in association with daunorubicin and ciprofloxacin (Groups IV and V respectively) resulted in significant reduction in cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues homogenate (P<0.05) (Figure. 1); moreover, significant elevation in the GSH peroxidase 4 (GPX-4) levels in heart tissues homogenate (P<0.05) (Figure. 2) each compared to GroupII and GroupIII rats respectively. Administration of lutein (24mg/kg) in association with daunorubicin (Groups IV) resulted in non-significant differences in cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues homogenate (P<0.05) (Figure. 1); moreover, non-significant differences in the GSH peroxidase 4 (GPX-4) levels in heart tissues homogenate (P<0.05) (Figure. 2) each compared to administration of lutein (24mg/kg) in association with ciprofloxacin (Group V) rats. Troponin is striated muscle protein complex that regulating their contraction [18]. A variety of substrates may cause elevation the levels of the circulating cardiac troponins, as the left ventricular hypertrophy and myocarditis, which are precursors of heart failure that may be asymptomatic [6, 19]. The elevation of the cardiac troponin is a sign for the myocardial tissue damage rather than myocardial infarction [15, 20]. Troponin I and T expressed in the heart, while in the skeletal muscle expressed the troponin C type [21, 22]. The intercalate DNA and inhibition of topoisomerase II is mainly responsible for the anti-cancer activities of daunorubicin in the fast-proliferating tumor. Anthracyclines are poisons to the topoisomerase II block the reaction of the catalyzing enzyme and stabilizing an intermediate and the DNA is broken which may lead eventually to cell apoptosis when the DNA cuts become irreversible [23]. It is well established that the capacity of different chemotherapeutic drugs to induce apoptosis is correlated with their anticancer efficacy [24].

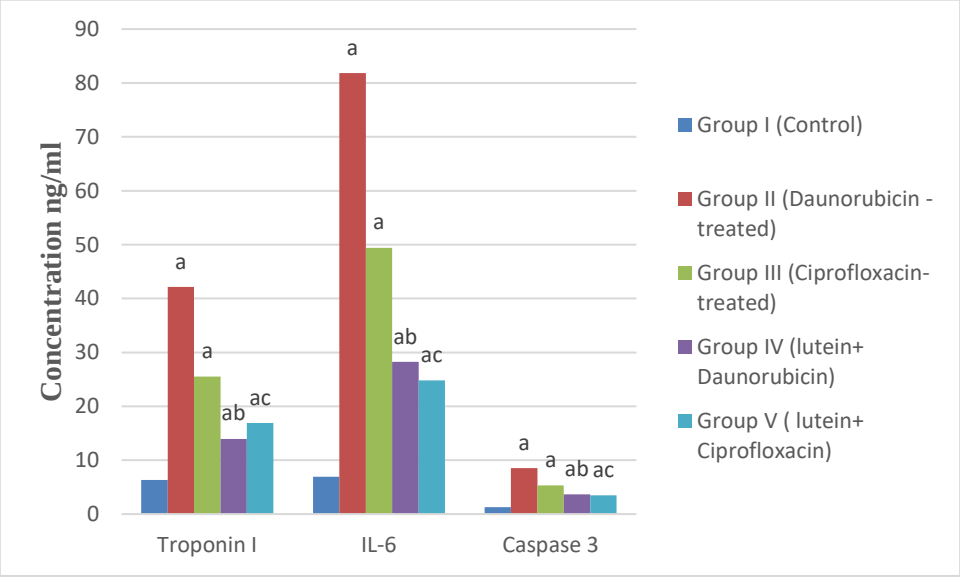

Figure 1. Effects of lutein (24mg) on daunorubicin and ciprofloxacin induced elevation in (Troponin I, IL-6 and Caspase 3). Data expressed by Mean±SD, n =6.Values symbolled with small letters (a) are significant (P< 0.05) comparing to control.Values symbolled with small letters (b, c) are significant (P< 0.05) comparing to daunorubicin and ciprofloxacin, respectively.

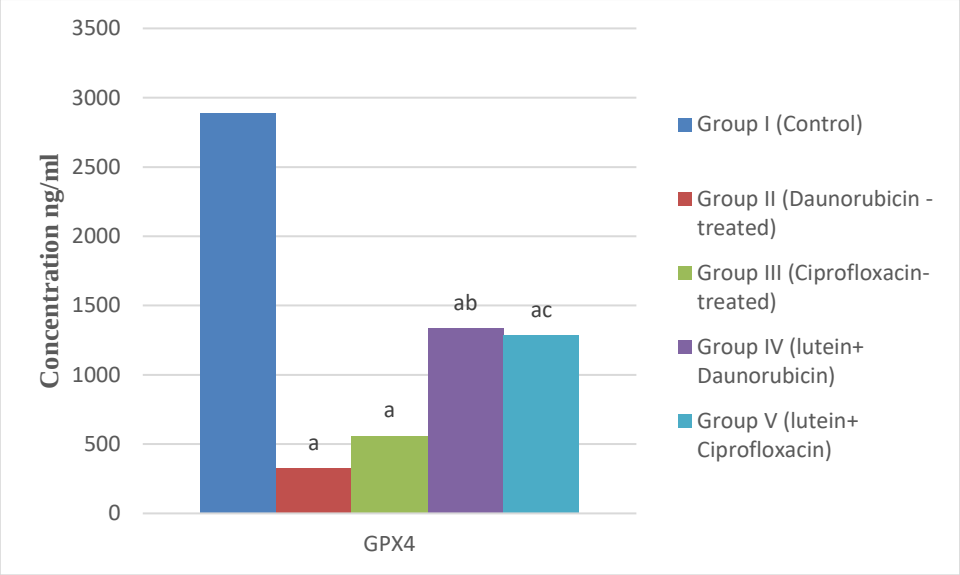

Figure 2. Effects of lutein (24mg) on daunorubicin and ciprofloxacin induced reduction in GSH peroxidase-4 (GPX 4) levels.

Data expressed by Mean±SD, n =6.
Values symbolled with small letters (a) are significant (P< 0.05) comparing to control.
Values symbolled with small letters (b, c) are significant (P< 0.05) comparing to daunorubicin and ciprofloxacin, respectively.

However, daunorubicin causes cumulative and dose-dependent cardiotoxicity, The present study confirms that daunorubicin caused cardiotoxicities, as showed by the significant (P<0.05) elevations in cardiac troponin I and cleaved (caspase-3) levels (Figure 1) in heart tissue homogenates. The reactive oxygen species production in the mitochondria of the heart cells often mentioned as cardiac toxicity molecular bases of daunorubicin [25]. The current study confirms that as showed by the significant (P<0.05) reduction in GPX 4 (Figure 2) levels in heart tissue homogenate. Cytostatic effects of anthracyclines established by several studies that can lead to apoptosis of the cells and to other death programs types including the immunogenic deaths [5] The antitumor activity of anthracycline may contribute to the induction of the IFN responses in addition to the stimulation of the immune system [26]. The current study confirms that, as was showed by the significant (P<0.05) elevations in interleukin 6 (Figure 1) in heart tissue homogenate.

Fluoroquinolones including the ciprofloxacin inhibit the DNA gyrase, which hydrolyzing topoisomerase II, the adenosine triphosphate enzyme for keeping the state of bacterial chromosomes supercoiling during replicating and the forms of non-replicating, in addition the fluoroquinolones have inhibition effect on the topoisomerase IV [27].

Ciprofloxacin adverse reactions, especially in CNS, occurs due to formation of the free radicals; where, this evidenced or was supported by the fact of that ciprofloxacin can cause major alterations of the glutathione redox status both in the rat tissues in the brain and the liver [8]. The current study confirms that as showed by the significant (P<0.05) reduction in GPX-4 (Figure 2) levels in heart tissue homogenate.

Moreover, the mitochondrial toxicity of ciprofloxacin can be due to the oxidative stress (OS) reactions, inhibition of topoisomerases, altered calcium homeostasis and photosensitization [28]. ciprofloxacin caused Bone marrow (BM) toxicities, as was showed by the reduction in total WBCs counts, and total RBCs counts and inducing apoptosis through the elevation of the mitochondrial pro-apoptotic protein (Bax) that resulting in the releasing of cytochrome c and other proteins from opening in the outer membrane of the mitochondria, this release leading to activation of (caspase-9) that eventually resulting in (caspase-3) activation and apoptosis [8, 29], in addition to elevation of inflammatory mediators [11]. The current study confirms that the ciprofloxacin can cause cardiotoxicities, as was showed by the significant (P<0.05) elevations in cardiac troponin I as well as the significant elevations in interleukin 6 and elevation in (caspase-3) level in heart tissue homogenate (Figure 1); Thus, (caspase-3) or (caspase-7) activation sets amplification of upstream apoptotic events by off explosive feedback, which is apoptotic signaling key feature that is essential for apoptotic cell death efficiency [30].

The current study is considered the first that compared the induction of cardiotoxicities between daunorubicin and ciprofloxacin, that the current study showed that daunorubicin induce cardiotoxicities more significant than ciprofloxacin as showed by the significant ($P<0.05$) increasing of cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues (Figure. 1) each compared to that induced by ciprofloxacin. However, there was non-significant ($P<0.05$) differences in the GSH peroxidase 4 levels in heart tissues (Figure. 2) each between daunorubicin and ciprofloxacin. Thus, we did not have a chance to compare the results of this study with other reports concerning this respect.

The anti-inflammatory and the antioxidant action that led to neuro-protectant activity [31] of lutein was studied extensively in various disease models like ischemia/reperfusion injury, uveitis, light induced retinopathy and diabetic retinopathy. Furthermore, the antiapoptotic properties of lutein has been reported [11]. The current study showed that lutein (24mg/kg/day) attenuates daunorubicin and ciprofloxacin cardiac toxicities by producing significant ($P<0.05$) reduction in cardiac troponin I, interleukin 6, and cleaved (caspase-3) levels in heart tissues (Figure. 1); while, produced significant ($P<0.05$) elevation in the GSH peroxidase 4 levels in heart tissues (Figure.2).

Conclusion

The current study showed that daunorubicin induce cardiotoxicities more significant than ciprofloxacin, However, there was non-significant ($P<0.05$) differences in oxidative stress markers (Glutathione peroxidase 4) between daunorubicin and ciprofloxacin. In addition, several markers of the cardiotoxicity caused by both ciprofloxacin and daunorubicin was reversed by the pretreatment with lutein including the cardiac troponin I level, oxidative stress markers (Glutathione peroxidase 4), apoptotic (cleaved caspase-3), and inflammatory (IL-6) markers.

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Conflicts of Interest

There is no conflict of interest regarding the publication of my manuscript.

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Ethics Statements

The Research was approved by the Ethical Committee of the Department of Pharmacology and Toxicology, College of Pharmacy/University of Baghdad before the start of the study.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Alaa R. Khudhair, Nada N. Al-Shawi and Israa Radhi Khudhair; data collection: Mohammed Abdulameer Oleiwi; analysis and interpretation of results: Alaa R. Khudhair, Nada N. Al-Shawi, Mohammed Abdulameer Oleiwi and Israa Radhi Khudhair; draft manuscript preparation: Alaa R. Khudhair, Nada N. Al-Shawi and Israa Radhi Khudhair. All authors reviewed the results and approved the final version of the manuscript.

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التأثيرات التحسينية لمكملات اللوتين ضد تسمم القلب الناجم عن الداونوروبيسين و السيبروفلوكساسين في الجرذان

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الخلاصة

يعد الاستخدام السريري للداونوروبيسين محدودًا بسبب سميته القلبية. إن الإجهاد التأكسدي بوساطة الحديد في الخلايا العضلية القلبية هي الآلية الرئيسية لتسمم القلب بالأنثراسيكلين. سيبروفلوكساسين هو الجيل الثاني من الفلوروكينولونات وأكثر الأدوية فعالية واستخداماً. التاثيرات الجزيئية الضارة للسيبروفلوكساسين من خلال تثبيط التوبويزوميراز II في الميتوكوندريا الذي يسبب ضعف الحمض النووي للميتوكوندريا في النسخ والتكرار. تعد المستويات المرتفعة من التروبونينات القلبية المنتشرة(التروبونين I وT) مؤشرات على تحطم عضلة القلب. اللوتين هو كاروتينويد مؤكسج مشتق من النظام الغذائي لجميع الثدييات بما في ذلك البشر. له تأثيرات مضادة للالتهابات، ومضاد للسموم الجينية، ويحسن أمراض القلب والأوعية الدموية، ويقلل من خطر الإصابة بالسرطان، ويحسن الوظائف الإدراكية. تبحث هذه الدراسة السمية القلبية الناجمة عن السيبروفلوكساسين ومقارنتها مع السمية القلبية للداونوروبيسين من خلال قياس مستويات التروبونين القلبي I، الإنترلوكين ٦، الجلوتاثيون البيروكسيديز 4 ومستويات الكاسبيز ٣ المشقوق في أنسجة القلب؛ واستكشاف التأثيرات الوقائية المحتملة للوتين ضد تسمم القلب الناتج عن السيبروفلوكساسين والداونوروبيسين في الجرذان. ثلاثون جرذان سبراغ داولي البالغة من كلا الجنسين قسمت إلى خمس مجموعات مكونة من ستة جرذان: المجموعة I: تلقت ١٠٪ ثنائي ميثيل سلفوكسيد عن طريق الفم لمدة ١٥ يومًا متتاليًا. المجموعة II: تلقت داونوروبيسين ٢٠ ملغم/كغم لآخر ٣ أيام بجرعة تراكمية ٦٠ ملغم/كغم) عن طريق الحقن IP. المجموعة III: تناولت جرعة سيبروفلوكساسين عن طريق الفم بجرعة ٥٠٠ ملغم/كغم خلال الخمسة أيام الماضية. المجموعة IV: تم إعطاؤها جرعة فموية من اللوتين (٢٤ ملغم/كغم) يومياً لمدة ١٥ يوماً متتالية، وجرعة داونوروبيسين عن طريق الحقن داخل الصفاق. المجموعة V: تلقت جرعة من اللوتين عن طريق الفم (٢٤ ملغم/كغم) يومياً لمدة ١٥ يوماً متتالية، ثم تلقت جرعة سيبروفلوكساسين عن طريق الفم خلال آخر ٥ أيام. السمية القلبية الناجمة عن سيبروفلوكساسين وداونوروبيسين، المرتبطة بزيادة مستويات تروبونين القلب I، إنترلوكين ٦، GSH بيروكسيديز ٤ ومستويات كاسبيز ٣ المشقوق في أنسجة القلب. أظهرت الفئران المسممة للقلب المعالجة باللوتين (المجموعة V والمجموعة IV) انخفاضًا كبيرًا في مستوى التروبونين القلبي I، كما عكست علامات الإجهاد التأكسدي؛ الجلوتاثيون بيروكسيديز ٤ مستويات، إلى مستوى السيطرة. قمع علامات موت الخلايا المبرمج والالتهابات، عن طريق قياس مستويات إنترلوكين ٦ ومستويات كاسبيز ٣ المشقوقة على التوالي، في أنسجة القلب.

الكلمات المفتاحية: السمية القلبية، التروبونين القلبي I، داونوروبيسين ، سيبروفلوكساسين وليوتين.