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Ameliorative Effect of Lycopene against Cardiac Toxicity Induced By Tilmicosin in Male Albino Rats

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Abstract **Original Research Article**

Tilmicosin is amacrolide antibiotic known to induce cardiotoxic effect when administered at large doses. The present study was carried out to investigate whether Lycopene (LYC) would ameliorate the acute cardiotoxic effect of tilmicosin antibiotic in treated rats. Fifty male albino rats were used throughout the experiment. They were divided equally into five groups, as follows: Group (1) (control), injected s/c with isotonic saline solution, Group (2) administrated 0.2 cm olive oil oral by stomach tube daily and kept also as control and scarified after 15 days. Group (3) administrated 10 mg / kg of lycopene dissolved in olive oil and given by stomach tube daily and scarified after 15 days Group (4) administrated 60 mg / kg of tilmicosin single subcutaneous dose and scarified after 5 days. Group (5) (Prophylactic group) administrated 10 mg / kg of lycopene for 15 days then 60 mg / kg tilmicosin s/c and scarified after 5 days. The effects of tilmicosin were evaluated with respect to alterations in serum, lactate dehydrogenase (LDH), creatine kinase (CK) activities also measurement of total malondialdehyde (MDA), catalase activity (CAT) and glutathione content of the heart tissues and histopathological findings of the heart sections in tilmicosin-treated rats with or without Lycopene. On the other hand, pretreatment of rats with Lycopene revealed marked decrease in cardiac biochemical parameters toward the normal limits. It concluded that lycopene effectively combated oxidative damage and protected antioxidant defense status of the cell against tilmicosin cardiotoxicity.

Keywords: Cardiotoxicity, Antioxidant, Oxidative stress, Rats, Lycopene, Tilmicosin.

INTRODUCTION

Tilmicosin (TIL) is a long-acting macrolide antibiotic approved for the treatment of cattle with Bovine Respiratory Disease. However, overdose of TIL has been reported to induce cardiotoxicity [1]. Although, macrolide antibiotics are considered to be one of the safe anti-infective drugs, cardiotoxic effects of tilmicosin such as positive chronotropy, negative inotropy, acute heart failure and alteration in electrocardiogram have been reported in sheep, cattle, horses, goats and dogs[1-4]. Tilmicosin-induced cardiotoxicity is through increasing free radical production and decreasing antioxidant enzymes in heart [5, 6].

Oxidative stress, induced by reactive oxygen species (ROS), is associated with the incidence of numerous diseases [7]. In recent years, the antioxidant activity of crude drugs or a natural food diet has become central focus for research designed to prevent or ameliorate tissue injury. Antioxidants provide an effective means to combat the deleterious effects of ROS and are increasingly being considered as strategic chemopreventive agents in the management of human diseases. Lycopene is a potent antioxidant of the carotenoid family, and a naturally occurring pigment, that gives a characteristic red color to tomato, watermelon, pink grapefruit, orange and apricot [8]. This study was carried out to investigate the protective effect of lycopene against timicosin-induced cardiotoxicity in male albino rats.

MATERIALS AND METHODS

Tested substance

Tilmicosin (Tilmicosin phosphate injection), solution**.** Each 1mL contains 300 mg of tilmicosin, USP as tilmicosin phosphate in 25% propylene glycol, phosphoric acid as needed to adjust pH and water for injection**.**

Lycopen is red crystalline substance($C_{40}H_{56}$) that is the main pigment of certain fruits, as the tomato and.paprika, and is a precursor to c arotene in plant biosynthesis biosynthesis. It was obtained from DEBEIKY Pharmatheutical Company.

Experimental design

Fifty male albino rats (western strain) were divided in to 5 groups each of 10 rats. Group I rat in this was administrated 0.5 ml saline s/c and kept as control and scarified after 5 days. Group II rats were administrated 0.2 cm olive oil oral by stomach tube daily and kept also as control and scarified after 15 day. Group III rats were received therapeutic dose of lycopene (10 mg / kg) dissolved in olive oil and given by stomach tube daily and scarified after 15 days [9-12]. Group IV rats were injected 60 mg / kg of tilmicosin single dose s/c and scarified after 5 days. The therapeutic dose is 10mg/kg (Equivalent to 1ml / 30 kg) given as a single subcutaneous injection [13-17] and Group V (Prophylactic group**)** administrated 10 mg / kg of lycopene for 15 days than 60 mg / kg tilmicosin s/c and scarified after 5 days. All rats are kept under observation all over the experimental period.

Sampling

Blood samples were collected by puncture of retro orbital plexus from each rat in each group at of experiment. Blood collected in clean dry centrifuge tubes, allowed to stand for one hour at room temperature till clotted and centrifuged at 3000rpm for fifteen minutes, for serum separation, and then kept in -20^{C} for biochemical analysis.

Heart tissue divided to two parts one (1 g) of each rat in each group was collected in labeled Eppendorf tubes at the end of the experiment. The heart samples were washed by physiological saline and kept in plastic bag separately then stored at -80 °C for determination of oxidative cascade. Other part of heart tissue was collected and fixed in 10% formol saline for histopathological studies.

Biochemical analysis

CK and LDH were measured by using special diagnostic Kits for according to *Lee TH & Goldman L.* [18].

Detection of oxidative cascades

Oxidative status was done by determination of the activity of CAT, GSH and MDA levels by using special diagnostic kits obtained from Bio diagnostic company Egypt according to Aebi, H. [19], Beutler, *et al*. [20] and Satoh [21] respectively.

Histopathological examination

Autopsy samples were taken from heart in different group of rat. Samples fixed in formalin solution 20%. Washing was done under tape water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene embedded in paraffin at 56 degree in hot air oven for twenty four hours. Paraffin bees wax tissue blocks were prepared for sectioning at 4 microns thickness by slide microtome. The obtained tissue sections were collected on glass slides, deparaffined and stained by hematoxyline and eosin stains for histopathological examinations using light microscope *Banchroft et al.* [22]

Statistical analysis

The data were analyzed for obtaining mean, standard deviation (SD) and statistical comparisons between means of different groups. The statistical analyses were done by one way ANOVA and DUNCAN test using SPSS program version 11.P value < 0.05 was assumed for statistical significance.

RESULTS

Regarding to serum enzyme biomarkers were investigated; as presented in Table (1), Animals treated with tilmicosin showed significant increase in the serum levels of CK and LDH compared to normal control group and LYC-only treated group ($P<0.05$) . LYC only did not differ from the control group. Meanwhile, pretreatment with LYC in the LYC+Tilmicosin (prophylactic) group significantly reduced the serum levels of CK and LDH as compared to tilmicosin treated group ($P<0.05$).

Regarding to oxidative indices were represented in Table (2), Animals treated with tilmicosin showed significant increase in the levels of MDA, and CAT compared to normal control group and LYC-only treated group ($P<0.05$) while tilmicosin only depressed activities of glutathione peroxidase compared to control group. Meanwhile, pretreatment with LYC in the LYC+TIL (prophylactic) group significantly reduced the serum levels of MDA, and CAT as compared to tilmicosin treated group ($P<0.05$). LYC only did not only differ from the control group but it increases the activity of glutathion also which provides powerful antioxidant protection to body systems.

Regarding to the histopathological findings of heart in control groups showed no histopathological alterations and the normal histological structure of the myocardial muscle bundles were recorded in control saline group (Photo.1) and in control oil (Photo.2). Concerning to the histopathological changes of heart in the lycopene treated rat, there were no histopathological alterations as recorded in (Photo.3). Heart of tilmicosin administrated rats showed oedema was detected in the pericardium while the underlying myocardium showed degenerative change (Photo.4). There was congestion in the subpericardium as well as the myocardium blood vessels (Photo. 5& 6). Focal Zenkers necrosis was detected in the myocardium (Photo.7) while the endocardium showed oedema with inflammatory cells infiltration (Photo. 8). Heart of prophylactic group: Focal Zenkers necrosis was detected in some few myocardial bundles (Photo.9).

Table-1: Shows: Effects of tilmicosin and lycopene on levels of serum CK and LHD of male albino rats

	CK (U/L)	LDH(U/L)
Control saline	191.36±11.63	679.4±21.44
Control oil	189.48±10.9	475.2±39.59
Lycopene	183.3±9.43	544.5±54.27
Tilmicosin	273.56±27.27	1426.6±16.72
Prophylactic	163.12±9.78	201.48±21.17

* P < 0.05 significantly different from control values.

Table-2: shows: Effects of tilmicosin and lycopene on MDA, CAT and GSH concentrations in heart tissues of male albino rats

	MDA(nmol/gm)	CAT(U/gm)	GSH(mg/dl)
Control saline	51.33±1.51	15.67±2.11	32.30±1.92
Control oil	46.13±2.49	15.38±1.19	30.14±0.92
Lycopene	38.52±6.36	10.07±0.87	41.19±1.96
Tilmicosin	101.46±11.76	43.44±9.01	25.49±2.01
Prophylactic	68.11±10.08	32.43±9.23	58.32±11.59

*Results with different superscripts within the same row are significantly different ($p < 0.05$) MDA; malondialdehyde, CAT; catalas activity and GSH; reduced glutathione.

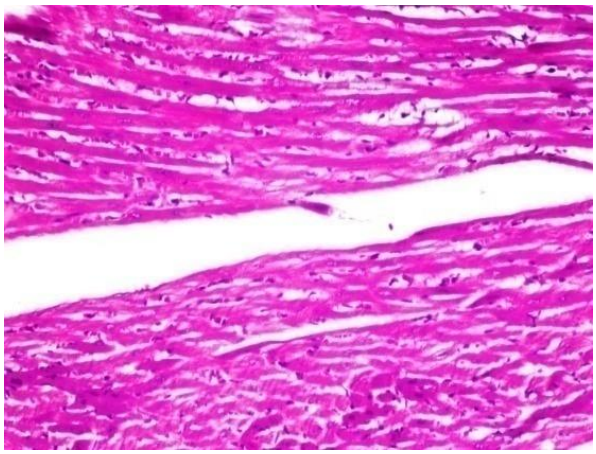

Photo-1: Heart of rat in control group showing normal histological structure of the myocardial bundles

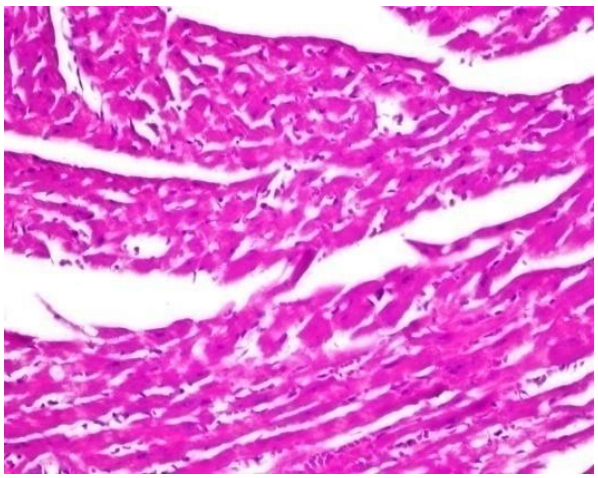

Photo-2: Heart of rat in control group showing normal histological structure of the myocardial bundles

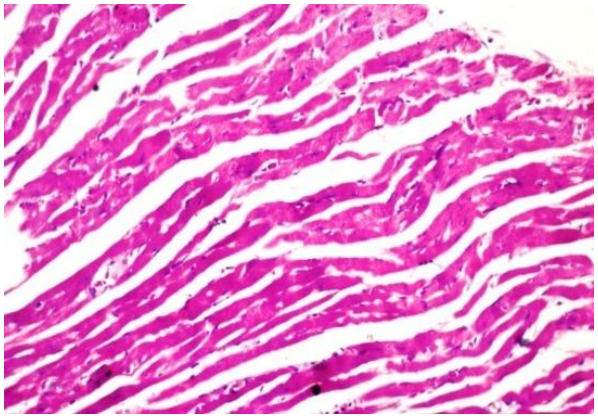

Photo-3: Heart of rat in lycopene group showing normal histological structure

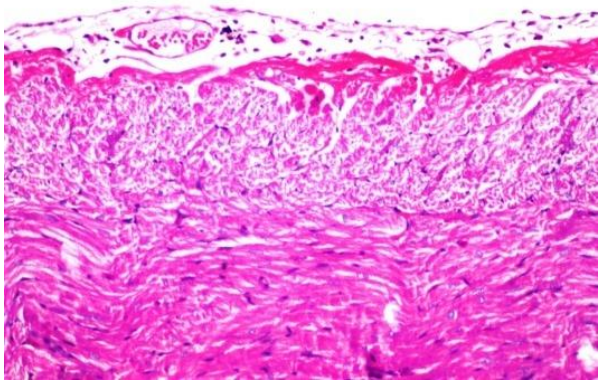

Photo-4: Heart of tilmicosin group showing oedema in pericardium with degeneration in underlining myocardium

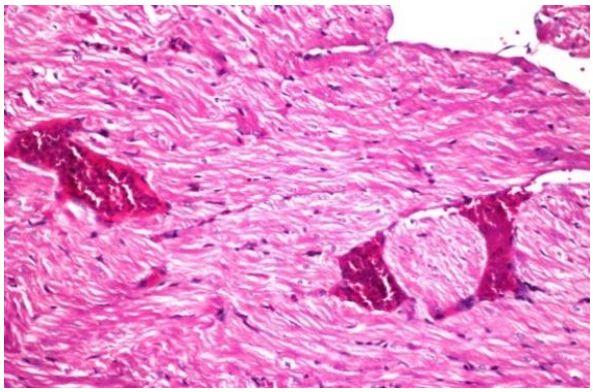

Photo-5: Heart of tilmicosin group showing congestion in subpericardium blood vessels

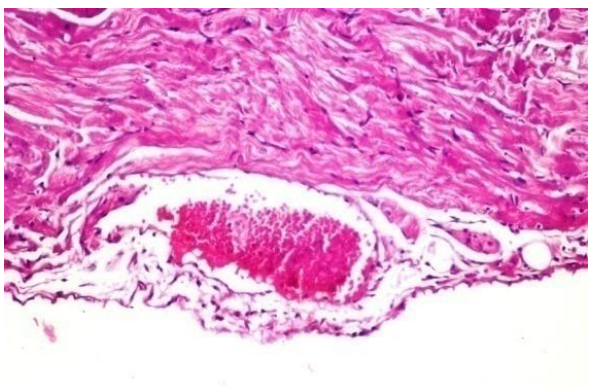

Photo-6: Heart of tilmicosin group showing congestion in myocardial blood vessels.

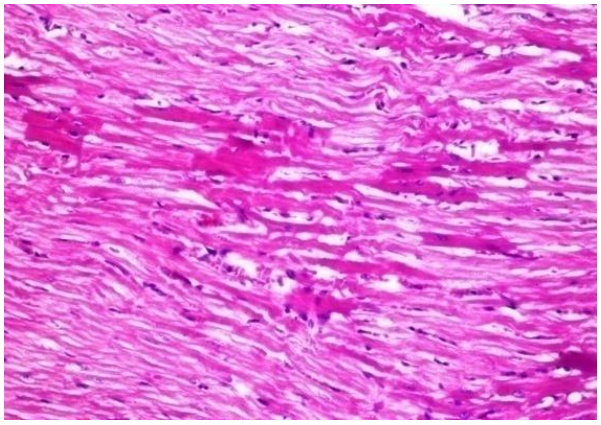

Photo-7: Heart of tilmicosin group showing Focal zenkers necrosis in myocardium

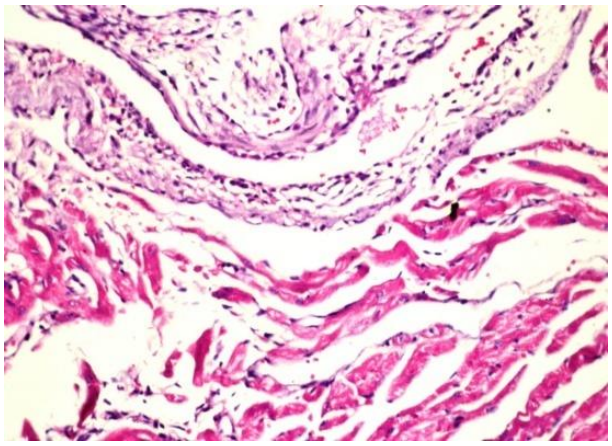

Photo-8: Heart of tilmicosin group showing oedema with inflammatory cells infiltration in endocardium

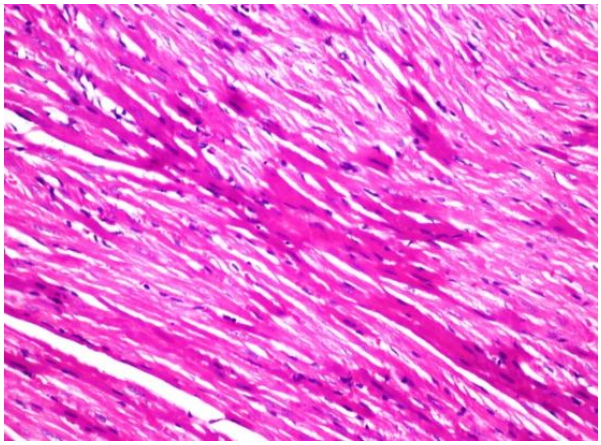

Photo-9: Heart of prophylactic group showed Focal Zenkers necrosis was detected in some few myocardial bundles

DISCUSSION

Cardiotoxicity represents one of the most serious side effects associated with new drug development. Tilmicosin has been prepared by chemical modification of desmycosin and used for the treatment of respiratory tract infections. The heart is the target organ of acute tilmicosin toxicity [23]. Tilmicosin is used for treatment of respiratory diseases in cattle, and other studies suggest that it may be used in swine [34], sheep [25], goat [26], rabbit [27] and turkey [28].

Serum LDH and CK enzymes activities have been used as markers of myocardial oxidative stress, usually associated with ischemic or toxic myocardial injury, and reflect the extent of damage in its musculature [29, 30]. Intriguingly, the significant alterations of these enzymes could be also indicating cardiac intoxication. Tilmicosin administration markedly elevated serum activities of LDH, and CK. Interestingly, pre-administration of LYC in tilmicosin treated group markedly reduced the activities of the cardiac enzymes to the normal levels.

In the present study, tilmicosin cause increased cardiac MDA and CAT levels, this accepted as an indicator of lipid peroxidation [31, 32]. Reduced GSH concentration of rat treated with tilmicosin alone in the organs could increase the burden on the cellular oxidant state since GSH is an important part of antioxidant defense system which plays an important role in preventing harmful effects of free radicals by scavenging hydroxyradicals and singlet oxygen [33]. Similar to our results [5], reported that tilmicosin decreased glutathione peroxidase levels in the heart tissue of mice treated with tilmicosin[34].

An observed increase in tissue GSH content in lycopene pretreated rats suggests that it prevent the tissue depletion of GSH. This could be due to the ability of lycopene to protect the ‘‘SH’’ groups from oxidative damage through inhibition of lipid peroxidation [10].

Tilmicosin treatment caused marked degeneration and necrosis of cardiac muscle fibers [35] in tilmicosin-treated rats. It is noteworthy that myocardial dissolution, necrosis and monocytes infiltrations as well as myofibrils and mitochondrial alterations were correlated well involved in myocardial oxidative stress associated with isoproterenol cardiotoxicity [36]**.** Whereas lycopene tilmicosin treated group, demonstrated minimal degree of myofibrils loss. Antioxidants demonstrated beneficial effects against drugs-induced cardiotoxicity in mice and rats [37, 36, 30].

Supplementation of lycopene could increase the levels of reduced glutathione in plasma and organs, elevating the glutathione peroxidase activity as well [38, 40]. Therefore, pretreatment of LYC might be alleviating the tilmicosin cardiotoxic effect through enhancing the antioxidant protection. Due to its highly lipophilic nature, lycopene exerts its maximal antioxidant activity at the level of cellular membranes and interacts with lipid components [7]. Through protecting membranes from lipid peroxidation, it counteracts tumour initiation.

Conclusion

Tilmicosin induced myocardial damage indicated by increase of LDH, CK, biomarkers as well as we may suggest that a single dose of tilmicosin at 60 mg/kg induces oxidative stress in the heart tissues. Myocardial tissue necrosis and myocytolysis. LYC exhibited significant protective effects toward tilmicosin-induced cardiotoxicity in rats.

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التأثير الوقائى لليكوبين مقابل تاثير التلميكوزين السام للقلب فى ذكور الفئران البيضاء

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قسم الطب الشرعى والسموم. كلية الطب البيطرى. جامعة بنها

ملخص التجربة:

الهدف من هذه الدراسة هو متابعة تاثير الليكوبين والتلميكوزين على قلوب الفئران البيضاء عن طريق قياس معدل انزيمات القلب وتاثير التلميكوزين السام عليه وقياس معدل الاكسدة فى انسجة القلب و التغييرات الهستوباثولوجية على القب.

فى مجموعة CK و LDHتلاحظ زيادة معدلانزيمات القلب الفئران المعاجة بالتلميكوزين فقط مقارنة بالمجموعة الضابطة على العكس فى المجموعة المعالجة بالليكوبين فلا يوجد تغير فى معدل انزيمات القلب , و فى المجموعة اللتى اعطيت الليكوبين كوقاية لمدة 15 يوما ثم حقنها بالتلميكوزين فنجد ان معدل زيادة الانزيمات الخاصة بالقلب لهذه المجموعة زياده طفيفة عن المجموعة الضابطة ولكنها ايضا اقل من الزيادة فى المجموعة المعالجة بالتلميكوزين فقط.

فى هذه الدراسة نجد ايضا زيادة فى دلالات اكسدة فى القلب فى المجموعة التى GSH و CAT و MDAوتكسيرالخلايا حقنت بالتلميكوزين عن المجموعة الضابطة , على عكس ذالك المجموعة التى اعطيت الليكوبين نجد ان الليكوبين ليس فقط دلالات الكسدة مثل المجموعة الضابطه ولكنها اقل منا مما يدل على ان الليكوبين يعتبر مضاد للاكسده قوى والذى يعزز ذلك المجموعة الوقائيه فنجد ان اقل من مجموعة التلميكوزين فقط من حيث وجود دلالات لتاكسد خلايا القب.

بالنسبة للتغيرات الهستوباثولوجية فى القلب فقد تلاحظ وجود تغيرات بصورة ملحوظة فى المجموعة المعالجة بالتلميكوزين فقط عن المجموعة الضابطة وكانت المجموعه المعالجة بالليكوبين مثل المجموعة الضابطة, اما فى المجموعة الوقائية فكانت التغيرات طفيفة.