Protective Role of Quercetin in Preventing Thioacetamide Induced Heart and Lung Injury in Adult Male Albino Rat

Original Article

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ABSTRACT

Introduction: Thioacetamide is one of the organo-sulfur compound, their possible hazards are not fully studied. Overproduction of oxidant species is the main mechanism of Thioacetamide induced histological changes in many organs. Quercetin is a powerful antioxidant compound thereby may alleviate these effects.

Aim of the Study: To assess the histological changes induced by Thioacetamide on adult male albino rat heart and lung as well as the probable role of Quercetin in attenuating these changes.

Material and Methods: 24 adult male albino rats were divided into 3 equal groups: group I (Control group), group II Thioacetamide group at a dose of 50 mg/kg/day and group III received 50 mg/kg/day of thioacetamide and quercetin that was dissolved in distilled water. The rats were sacrificed after 28 days heart and lungs were harvested and fixed.

Sections from both the heart and lungs were stained by Harris Hematoxylin & Eosin and Masson Trichrome stain. Sections from the heart were additionally stained for PAS. Sections from the lung were subjected to immunohistochemical staining for CD68. All sections were examined under light microscope. Further statistically analyzed and interpreted.

Results: Thioacetamide administration result in more heart and lung injury score. Significant reduction in the injury score was found in Concomitant administration of quercetin with thioacetamide resulted in improvement in the structure of the lung and heart.

Conclusion: Thioacetamide administration had a negative impact on both heart and lungs. meanwhile, quercetin exerted a protective effect when it was administrated with Thioacetamide

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Key Words: Heart, lung, quercetin, rats, thioacetamide.

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INTRODUCTION

Thioacetamide (TAA) is an organo-sulfur compound with the chemical formula C2H5NS. Its particles are crystalline solid and water soluble. It serves as a source of sulfide ions in the synthesis of organic and inorganic compounds[1,2]. It can be inhaled or absorbed through the skin. It irritates the eyes, nose and throat[3-5].

Thioacetamide prove to affect many organs. Induces acute as well as chronic liver disease (fibrosis and cirrhosis) in an experimental animal model. Administration to rats is associated with elevated transaminase levels, metaboliceacidosis, and sometimes lead to hepatic encephalopathy, therefore replicating the initiation and progression of human liver disease in an experimentaluanimal model[6].

Thioacetamide considered as a highly toxic material[7], in turn, it can affect the structure and function of the cell[8].

Regardless what is the route of exposure, TAA is rapidly distributed in nearby tissues and is reported to be reproductive toxicant, genotoxic, and carcinogenic to rodents[9]. It has been reported that the liver, spleen, kidney, and erythrocytes also have significant binding ability to TAA[9]. Much research has been done to understand the morphologically and biochemically induced changes that occur in the liver of TAA-treated rats[10–13].

The effects of TAA are not limited to the liver, as significant structural and functional changes have been reported in the kidney,[14] thymus,[15] spleen,[16] and intestine[17].

Cardiac malfunction is considered as an important complication of cirrhosis of the liver , but the role of TAA in cardiac abnormalities is not well understood. It has been studied in animals after TAA-induced cirrhosis[18], but few studies have been conducted to determine TAA-induced heart and lung damage.

Quercetin is a flavonoid compound with strong antioxidant activity and preventive role in various diseases, has been extensively studied[19]. It is one of the most abundant flavonoids in vegetables, fruits, olive oil and tea[19].

It contains many phenolic hydroxyl groups and is a powerful oxygen-free radical scavenger and metal

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chelating agent[20]. Quercetin has been shown to show therapeutic potential for many diseases such as ischemic heart disease, liver fibrosis, atherosclerosis , renal damage, and chronic biliary atresia[20,21].

In this context, this study was designed and demonstrates TAA-induced cardiac and lung changes in experimental model and determines whether treatment with quercetin has beneficial effects.

AIM OF THE WORK

The aim of the current study was to examine the protective effects of quercetin against TAA-induced heart and lung injury.

MATERIALS AND METHODS

Animals

Twenty four adult male Albino rats 7–9 weeks old; 180–200 g body weight purchased from the animal house, Alexandria University, Egypt. Animals were placed in the laboratory for a week under the laboratory conditions.

Materials

Both thioacetamide (TAA) and quercetin were purchased from Sigma-Aldrich Corp., St. Louis, MO, USA

Experiment design

Rats were allocated into 3 groups; **Group I** (Control, n=8): Rats in this group received distilled water by gavage and intraperitoneal injection of normal saline (NaCl 0.9%), 5 days/week for 28 days. **Group II** (Thioacetamide (TAA) group, n=8); rats received TAA dissolved in NaCl 0.9% given intraperitoneally in a dose of 50 mg/kg/day, 5 days/week for 28 days, this dose and duration causes low grade injury as described by Murad *et al*.[22] **Group III** (TAA-quercetin treated group, n=8); rats in this group received TAA as in group II and quercetin that was dissolved in distilled water and given daily.

Methods

The heart and both lungs were harvested and fixed in 10% neutral buffered formalin. Sections were then dehydrated by ascending grades of ethanol (70%, 90% and 100%). Xylene was used as a clearing agent then both soft and hard paraffin were consecutively used for embedding. Five –micron-thick sections were obtained, dewaxed in xylene then rehydrated using descending grades of ethanol (100%, 90% and 70%). Sections from both the heart and lungs were stained by Harris Hematoxylin & Eosin (H&E) and Masson Trichrome stain. Sections from the heart were additionally stained for PAS. Sections from the lung were subjected to immunohistochemical staining for CD68 (Clone KP-1, ready to use, mouse monoclonal antibody, DAKO, USA), performed by DAKO Autostainer. All sections were examined under light microscope (Olympus CX23).

In the lungs, interstitial inflammation was scored as follows: absent (score 0), mild (score 1), moderate (score 2), severe (score 3). Fibrosis was assessed by trichrome stain and was scored as follows: absent (score 0), mild (score 1), moderate (score 2), dense (including fibro cellular lesion) (score 3). A total lung injury score was obtained by adding the inflammation score and fibrosis score[23].

In the heart, the following features were assessed and scored: features of reversible injury including pale cytoplasm with vacuolization (1 point), increased eosinophilia (1 point), cytoplasmic fragmentation (1 point), cellular swelling and rounding (1 point), features of irreversible injury including: nuclear pyknosis (2 points), membrane disintegration (2 points). Fibrosis was assessed by trichrome stain and was scored as follows: absent (score 0), mild (score 1), moderate (score 2), dense (score 3). All these parameters were added to give a total injury score[24].

Ethical considerations

Study procedures were reviewed and approved by AFM research ethics committee.

RESULTS

Lung

All eight rats in group I (Table 1) showed a preserved architecture with neither notable increase in interstitial inflammatory cells nor fibrosis, with a total lung injury score of 0 (Figs.1A, 2A). In group II (Table 1), 2/8 rats (25%) showed preserved lung architecture. A moderate interstitial inflammatory infiltrate was noted (score 2) with no fibrosis (score 0). The total lung injury score was 2 in both rats. In group II, In 6/8 rats, (75%) a dense interstitial inflammatory infiltrate mainly composed of lymphocytes and plasma cells showing temporal homogeneity (score 3). Moderate interstitial fibrosis (score 2), was seen in 2/8 rats (25%), while dense interstitial fibrosis and fibrocellular lesions (score 3) in the form of aggregates of lymphocytes and fibroblasts with few poorly formed giant cells were found in 4/8 rats (50%). These fibrocellular lesions showed striking similarity to fibrosing non-caseating granuloma, but were only focally positive for CD68. (Figure 2D). The total lung injury score was 2 in 2/8 rats (25%), 5 in 2/8 rats (25%) and 6 in 4/8 rats (50%) (Figs. 1B,1C,1D,1E,2B,2C,2D,2E). All eight rats in group III (table 1)showed preserved lung architecture with mild interstitial inflammation (Score 1) (Fig.1F). No fibrosis is observed (Score 0), with a total injury score of 1 (Fig.2F).

Using statistical tests[25] and as showed in Table 1 this difference in total lung injury score of the three groups was statistically significant at $p \leq 0.05$

Heart

All eight rats in group I (Table 2) showed normal cardiomyocytes in both right and left ventricles. No fibrosis was detected. The total heart injury score was 0 in all eight rats (Figs. 3A, 4A). In group II (Table 2) 2/8 rats (25%) showed pale cytoplasm with focal vacuolization (score 1), while 6/8 rats (75%) showed increased eosinophilia (score 1), cytoplasmic fragmentation

(score 1), swelling and rounding up of the cardiomyocytes (score 1), membrane disintegration (score 2) with pyknotic nuclei (score 2). Mild fibrosis (score 1) was detected in 2/8 rats (25%) (Figs.3B,3C,3D,4B,4C), while 6/8 rats (75%) showed no fibrosis (score 0). The total heart injury score was 1 in 2/8 rats (25%), 7 in 4/8 rats (50%) and 8 in 2/8 rats (25%). All rats in group III (table 2) showed increased eosinophilia (score 1) (Figs. 3E,3F). No fibrosis was detected (score 0). The total heart injury score was 1 (Fig. 4D).

As showed in Table 2 this difference in total heart injury score of the three groups was statistically significant at $p \leq 0.05$

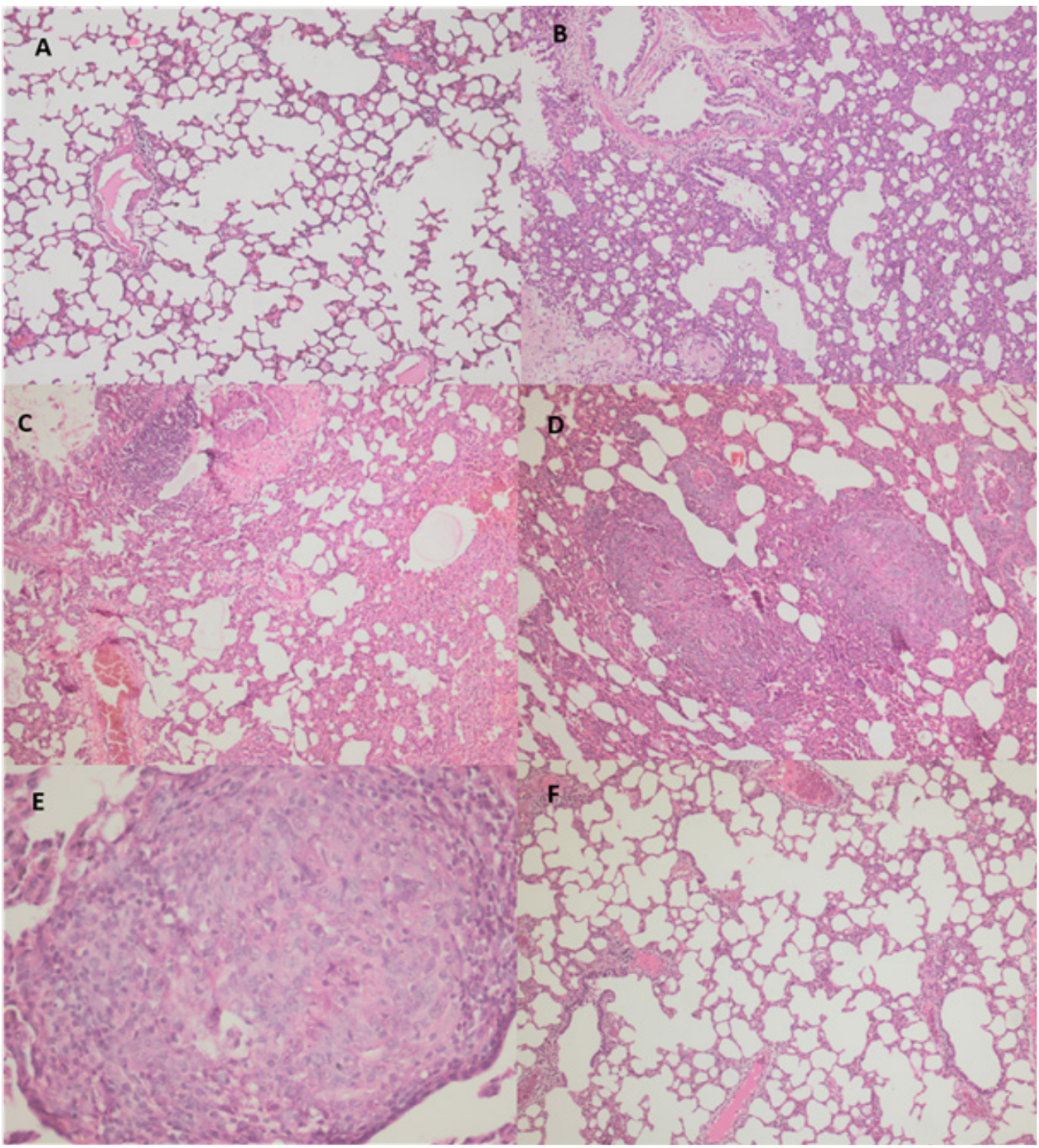

Fig. 1: Inflammation score in lung: A: Preserved architecture with no interstitial inflammation (score =0) in group I (H&Ex40). B: Moderate interstitial inflammation (score 2) in group II. C: Dense interstitial inflammation (score 3) in group II. D: Fibrocellular lesions detected in group II. (x100). E: Higher magnification of fibrocellular lesions showing fibroblasts, lymphocytes and poorly formed giant cells (H&Ex400). F: Mild interstitial inflammation (score 1) detected in group III. (H&Ex100).

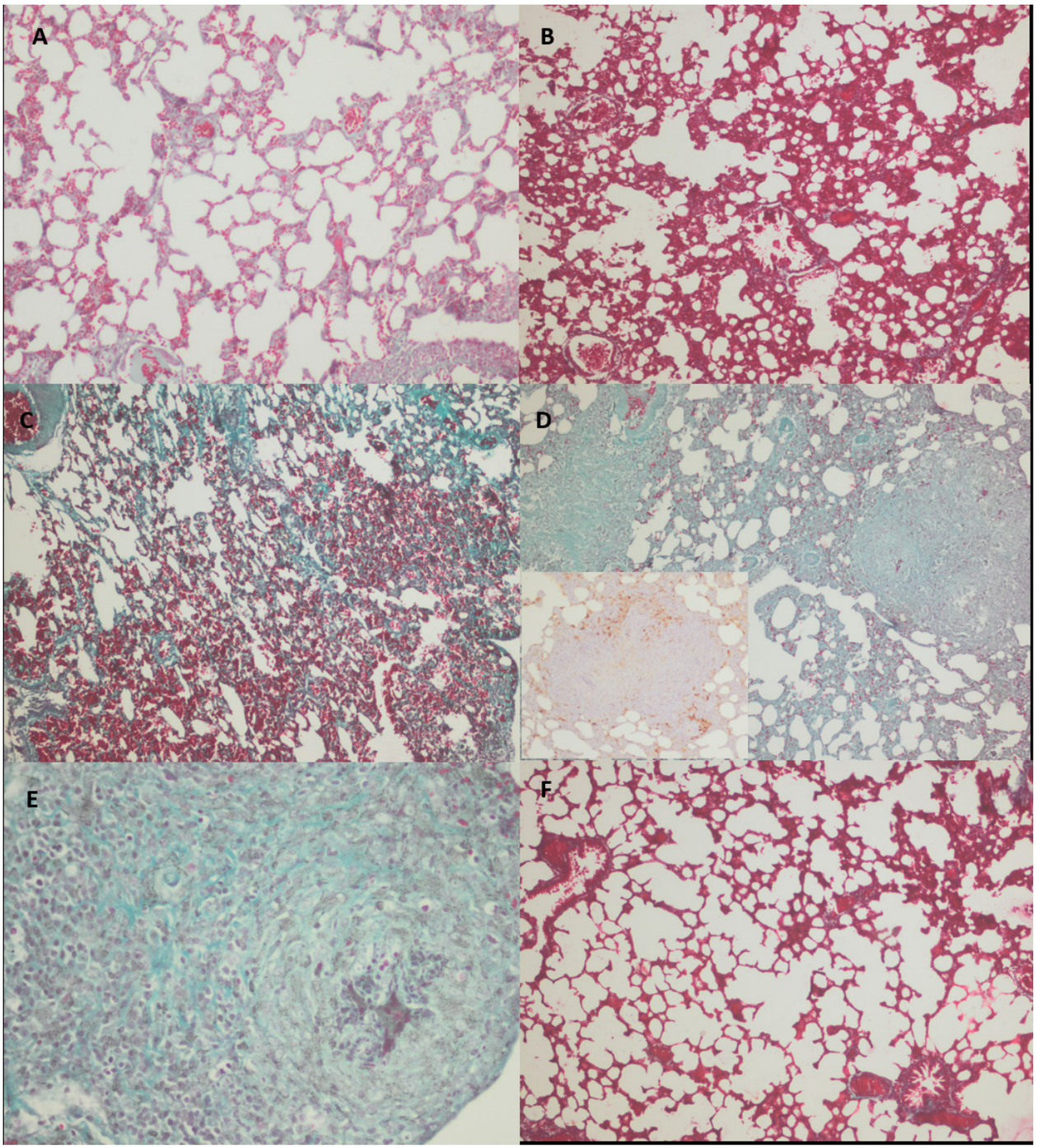

Fig. 2: Fibrosis score in lung: A: Preserved architecture with no fibrosis (score 0) in group I. B: Preserved architecture with no fibrosis (score 0) in group II. C: Moderate fibrosis (score 2) in group II. D: Dense fibrosis with fibrocellular lesions (score 3) in group II. Inset: The fibrocellular lesions are only focally positive for CD68. (IHCx200) E: Higher magnification of fibrocellular lesions showing fibroblasts, lymphocytes and poorly formed giant cells (Trichrome x400). F: Preserved architecture with no fibrosis (score 0) in group III. (Trichrome x100).

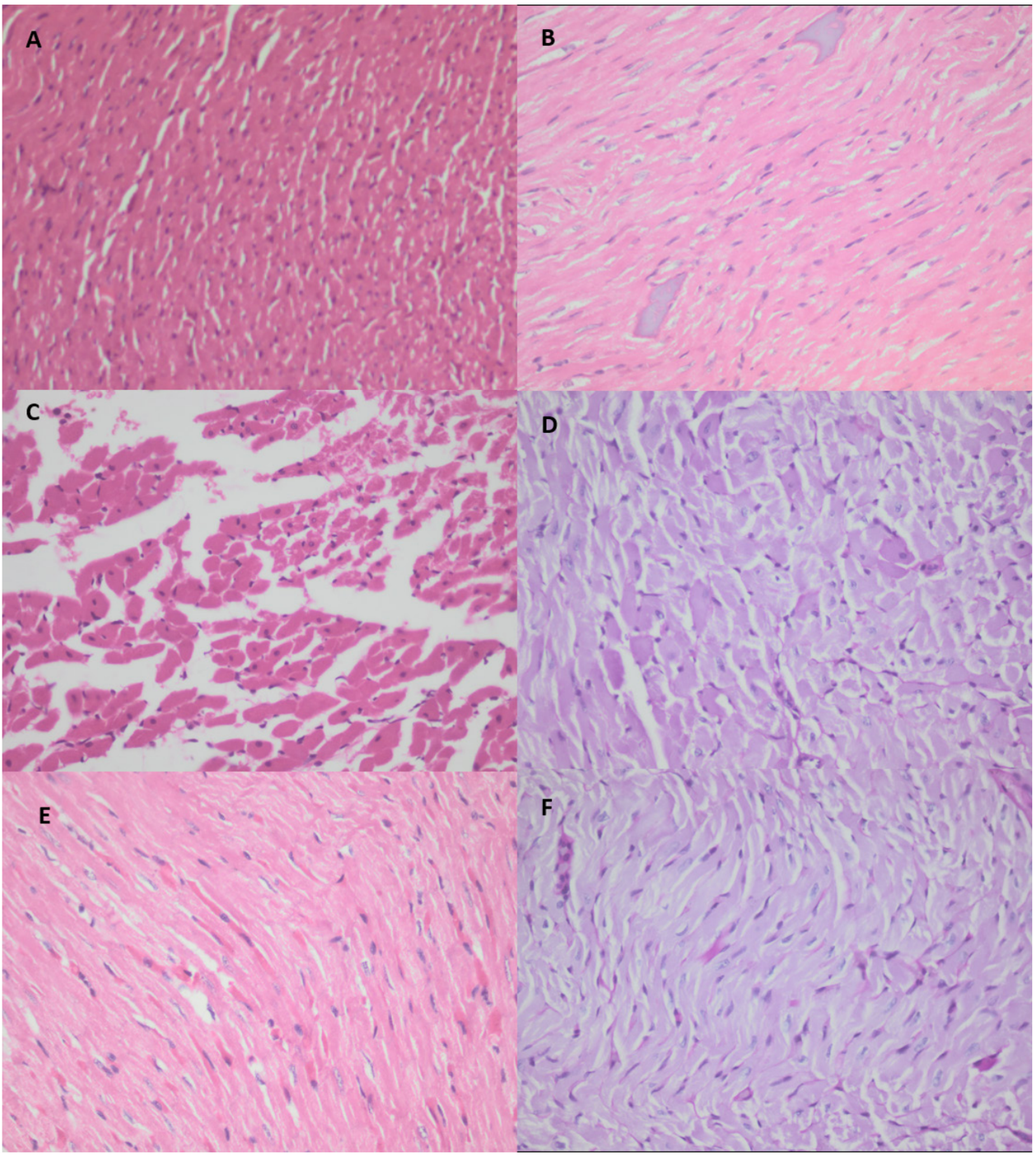

Fig. 3: Patterns of injury in cardiomyocytes. A: Group Ia showing normal cardiomyocytes.(H&Ex100) B: Group II showing pale cytoplasm with fragmentation and vacuolization. (H&Ex400) C &D: Group II showing rounded cardiomyocytes with loss of cellular cohesion increased eosinophilia and pyknotic nuclei with karyolysis. (H&Ex100 and PASx400 respectively) E &F: Group III showing increased eosinophilia. (H&E and PAS x400 respectively).

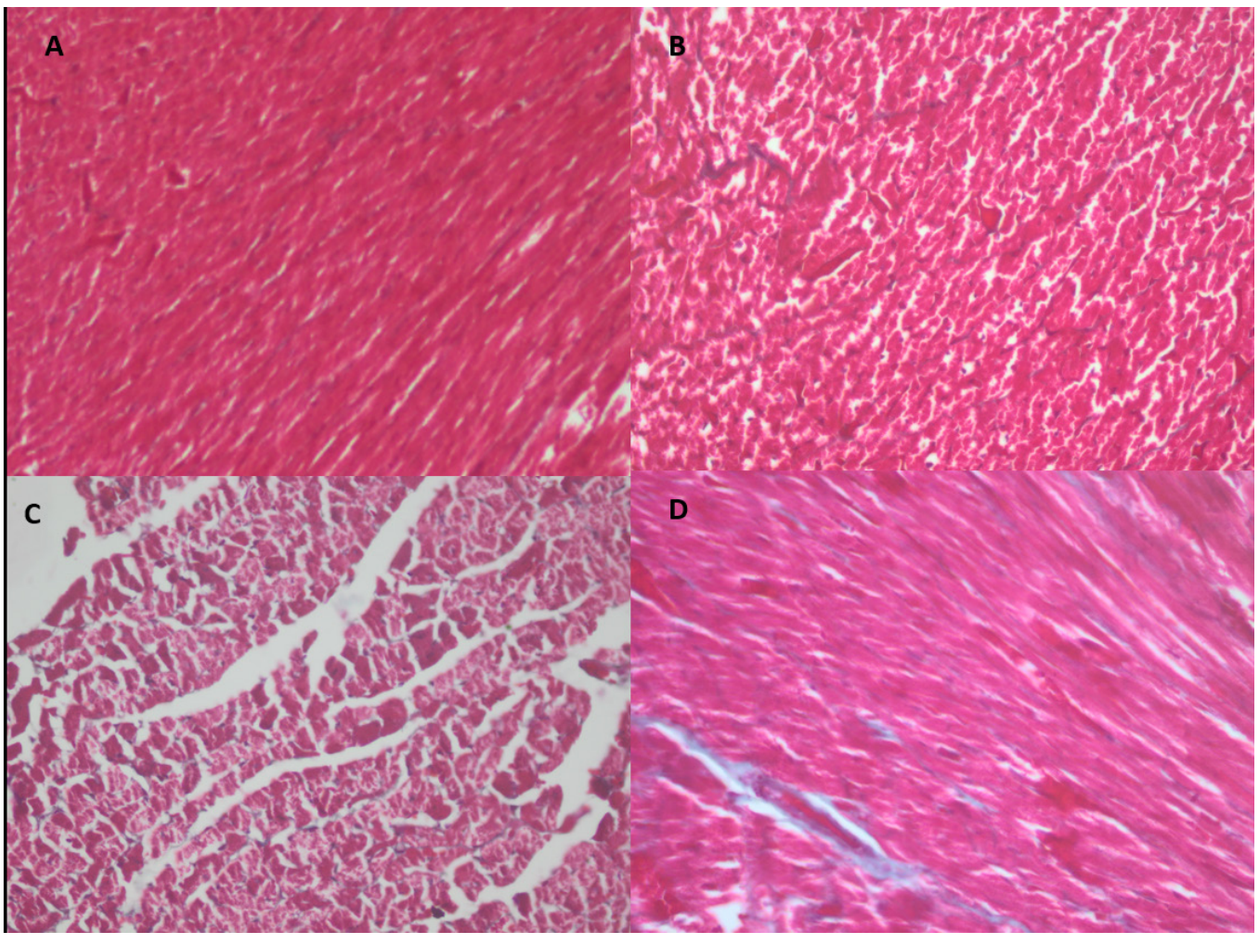

Fig. 4: A: Group I showing normal cardiomyocytes with no fibrosis. B; Group II showing fragmented cytoplasm with intact cell membrane and no fibrosis. C: Group II showing fragmnented cytoplasm with focally disintegrated membranes, increased eosinophilia and mild fibrosis. D: Group III showing increased eosinophilia with no fibrosis. (Trichrome x400).

Table 1: Total lung injury score in different groups

	I (n=8)	II (n=8)	III (n=8)	$\chi 2$	MC_p
Inflammation score					
0	8 (100%)	0	0		
1	0	0	8 (100%)	37.871*	<0.001*
2	0	2 (25%)	0		
3	0	6 (75%)	0		
Fibrosis score					
0	8	2 (25%)	8 (100%)		
1	0	0	0	12.612*	0.001*
2	0	2 (25%)	0		
3	0	4 (50%)	0		

$\chi 2$: Chi square test MC: Monte Carlo *p*: *p value* for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Table 2: Heart injury score of the different groups

	Group I	Group II	Group III	$\chi 2$	MC_p
None	8	-	-	23.289*	<0.001*
Cytoplasmic vacuolization	-	8 (100%)	-	23.289*	<0.001*
Increased eosinophilia	-	6 (75%)	8	18.407*	<0.001*
Cellular swelling	-	6 (75%)	-	13.568*	0.001*
Membrane disintegration	-	6 (75%)	-	13.568*	0.001*
Nuclear pyknosis	-	6 (75%)	-	13.568*	0.001*
Fibrosis (mild)	-	2 (25%)	-	2.984	0.303
Fibrosis (moderate)	-	-	-	–	–
Fibrosis (severe)	-	-	-	–	–

$\chi 2$: Chi square test
p: *p value* for comparing between the studied groups
MC: Monte Carlo
*: Statistically significant at $p \leq 0.05$

DISCUSSION

Thioacetamide is considered as a highly poisonous organo-sulfur chemical and is rapidly metabolized to reactive metabolites (thioacetamide-S-oxide and reactive oxygen species) by Flavin-containing monooxygenases and cytochrome P450[26,27].

On exposure TAA it rapidly distributes to tissues and has been reported to be a genotoxic toxicant and rodent carcinogen[28]. A lot studies have been conducted to explain morphological and biochemical abnormalities that occur in the organs of TAA-treated rats[29-32].

Bruck *et al*.[26] found that these reactive metabolites bind to cellular macromolecules responsible for the change in cell permeability and Ca++ absorption, which is consistent with the findings of our study[26]. The interruption of calcium storage increases nuclear volume, enlarges nucleoli, and inhibits mitochondrial action, explaining the cellular alterations observed in the recent study[26,27].

The heart and lung changes which was observed by TAA treatment could be a consequence of oxidative stress. Prakasam *et al*.[33] stated that this oxidative stress results from the increased production of reactive oxygen species ROS, which have been shown to damage many biological molecules and causing lipid peroxidation[33].

Generation of a large amount of ROS due to TAA can overwhelm the antioxidant defense mechanism and damage cellular ingredients such as lipids, proteins, and DNA; this in turn can impair cellular structure and function, so TAA exert their toxic effect mainlybthrough disturbance of the normal balance between both the oxidants andhantioxidants levels[34].

Flavonoids are a vast category of natural polyphenolic compounds that can serve as antioxidants in biological systems and are extensively dispersed in the plant kingdom. One of the most prevalent flavonoids, quercetin may be found in high levels in vegetables, fruits, tea, and olive oil[35].

In the present work, Concurrent treatment of Quercetin and TAA preserved the histological architecture of the heart and lungs. Quercetin has been shown to have anti-inflammatory properties in *vitro* and in experimental models of inflammatory disorders, according to Camuesco *et al*.[35] Bona *et al*.[36] also described Quercetin's significant antioxidant impact in relieving the toxic effect of TAA-induced tissue damage by lowering oxidative stress, apoptosis, and inflammation.

According to Abosalem *et al*.[37] quercetin includes a lot of phenolic hydroxyl groups and is a powerful oxygen free radical scavenger and metal chelator. It also inhibits xanthine oxidase and lipid peroxidation while scavenging and stabilising iron[37]. Tissue damage caused by lipid peroxidation and interstitial matrix deterioration involves the superoxide anion and the hydroxyl radical[37].

In addition, it has been demonstrated that using quercetin lowers the metabolic changes produced by cirrhosis, resulting in increased lifespan in experimental animals[38].

Many studies[39,40] have also shown that quercetin can protect against acute injury by inhibiting apoptotic cell death and reducing oxidative stress damage by enhancing the body's defensive capability.

Behling[41] explained the cytoprotective effect of Quercetin that it may be due to its ability to interact with and penetrate the lipid bilayer[42].

The antioxidant, free radical scavenging (highly reactive species implicated in peroxidation), anti-inflammatory, calcium channel blocking, microsomal enzyme inhibitory action, inhibition of nitric oxide production, and prevention of collagen accumulation are all possible mechanisms for quercetin's protective effect. By decreasing oxidative stress and/or directly interfering in apoptotic pathways, quercetin may have a potential therapeutic impact on organ damage[42].

CONCLUSION

The present study evaluated the induced changes of TAA on heart and lungs in an experimental model and it was proved that TAA administration had a negative impact on both heart and lungs. meanwhile, quercetin exerted

a protective effect when it was administrated with TAA. Further studies should be conducted in order to assess its adverse effects of TAA on other organs and investigate materials ameliorate their toxic effects.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

الدور الوقائي للكرسيتين في الوقاية من إصابة القلب والرئة المستحدثة بالثيوأسيتاميد في ذكور الجرذان البيضاء البالغة

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المقدمه: يعتبر الثيواسيتاميد أحد المركبات العضوية الكبريتية التي لم تتم دراسة مخاطرها المحتملة بشكل كامل. يعد انتاج فصائل الاكسحين المتفاعلة هو السبب الرئيسى للتغيرات الهيستولوجية التى يحدثها الثيوأسيتاميد في العديد من الأعضاء.يعتبر الكيرسيتين مركب مضاد للأكسدة ذو تأثير قوى ، و يحتمل ان يضعف من هذا التأثير.

الهدف: أجريت هذه الدراسة لتقييم التغيرات الهيستولوجية المستحدثة بواسطة الثيوأسيداميد على القلب و الرئة فى الجرذان البالغة وكذلك الدور المحتمل للكيرسيتين في تخفيف هذه التغييرات.

مواد وطرق البحث: تم تقسيم ٢٤ من ذكور الجرذان البيضاء إلى ٣ مجموعات متساوية: المجموعة الأولى (المجموعة الضابطة) ، المجموعة الثانية مجموعة (الثيوأسيداميد) : بجرعة ٥٠ مجم / كجم / يوم والمجموعة الثالثة تلقيت كل من: ٥٠ مجم / كجم / يوم من الثيوأسيداميد و الكرسيتين المذاب في الماء المقطر. تم ذبح الجرذان بعد ٢٨ يومًا و أخذ عينات القلب و الرئتين وتثبيتهما من أجل الدراسة الهيستولوجية و الفحص بالميكروسكوب الضوئى بعد ان تم صبغها بصبغتى الهيماتوكسيلين و الايوسين و ماثون تراي كروم . بالإضافة إلى ذلك تم صبغ عينات القلب بصبغة PAS. كما تم فحص عينات الرئة فحص كيميائي مناعي لـ CD٦٨. فى النهاية, تم تحليل النتائج النهائية احصائياً ثم تفسيرها .

النتائج: تسبب الثيوأسيتاميد إلى زيادة التغيرات في القلب والرئة. تم ملاحظة ان على انخفاض كبير في درجة الإصابة في تناول الكيرسيتين المتزامن مع الثيوأسيتاميد مما أدى إلى تحسن في بنية الرئة والقلب.

الخلاصة: إن إعطاء الثيوأسيتاميد تأثير سلبي على كل من القلب والرئتين. أما إعطاء الكيرسيتين كان له تأثير وقائيً عندما تم إعطاؤه مع الثيوأسيتاميد.