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Sıçanlarda Amiodaronun Sebep Olduğu Akciğer Hasarında Beyaz Lahana Ekstraktının Koruyucu Rolü

Protective Role of White Cabbage Extract Against Amiodarone-Induced Lung Damage in Rats

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ÖZ

Amaç: Bu çalışmada amiodaron'un sebep olduğu akciğer hasarında beyaz lahananın koruyucu etkileri araştırılmıştır.

Materyal ve Metot: Bu çalışmada, sıçanlar 4 gruba ayrılmıştır. Kontrol grup: dokunulmamış sıçanlar, WCAE grup, sıçanlara 7 gün 500 mg/kg beyaz lahana ekstraktı verildi; AMD grup, sıçanlara 7 gün 100 mg/kg amiodaron (AMD) verildi; AMD+WCAE grup, sıçanlara aynı dozlarda beyaz lahana ekstraktı ve AMD verildi.

Bulgular: AMD+WCAE grubunda, beyaz lahana ekstraktı tedavisi interstisyal ödem ve konjesyonun azalmasına, alveolar yapılarda iyileşme ve bunun yanı sıra parankimdeki enflamatuvar hücre infiltrasyonun gerilemesine sebep olmuştur. Ek olarak, AMD+WCAE grubunda parankimde kollajen liflerinin birikmesinde önemli derecede bir azalma görülmüştür. Akciğerdeki glutatyon seviyesi, total antioksidan kapasitesi ve glutatyon-S-transferaz, paraoksonaz and karbonik anhidraz aktiviteleri azalırken, lipit peroksidasyon, ileri okside protein ürünleri, total oksidan durumu, reaktif oksijen türleri, oksidatif stres indeksi, nitrik oksit ve hidroksiprolin seviyeleri, katalaz, süperoksit dismutaz, glutatyon peroksidaz, glutatyon redüktaz, laktat dehidrogenaz and ksantin oksidaz aktiviteleri AMD grubunda artmıştır. Beyaz lahana ekstraktı tedavisi AMD'un neden olduğu bu seviyeleri ve aktiviteleri tersine çevirmiştir.

Sonuç: Beyaz lahana ekstraktının amiodaron'un sebep olduğu akciğer hasarını azaltabileceği sonucuna varabiliriz.

Anahtar Kelimeler: Akciğer, amiodaron, beyaz lahana ekstraktı, oksidatif stres

ABSTRACT

Objective: It was intended to study the protective roles of white cabbage on amiodarone induced lung damage.

Materials and Methods: Rats were distributed into 4 groups, Control group, intact animals; WCAE group, animals given white cabbage extract (WCAE, 500 mg/kg) for 7 days; AMD group, animals administered amiodarone (AMD, 100 mg/kg) for 7 days; AMD+WCAE group, animals given white cabbage extract and amiodarone at the same dose.

Results: White cabbage extract treatment in AMD+WCAE group showed reduced interstitial edema and congestion, an improvement in alveolar structures besides regression of inflammatory cell infiltration in lung parenchyma. Moreover, a prominent reduction in the amount of collagen fibers deposition in the parenchyma was seen in AMD+WCAE group. Lung levels of glutathione and total antioxidant capacity and activities of glutathione-S-transferase, paraoxonase and carbonic anhydrase were decreased while the activities of lipid peroxidation, advanced oxidized protein products, total oxidant status, reactive oxygen species, oxidative stress index, nitric oxide and hydroxy proline levels, catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, lactate dehydrogenase and xanthine oxidase were increased in AMD group. Administration of white cabbage extract reversed these levels and activities in AMD group.

Conclusion: In conclusion, white cabbage extract can ameliorate amiodarone induced lung damage.

Keywords: Amiodarone, lung, oxidative stress, white cabbage extract

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INTRODUCTION

Amiodarone (AMD) is a class III antiarrhythmic drug and due to its iodine containing structure, AMD has a tendency to accumulate in lungs and thyroid gland, leading to the dysfunction of the involved organs.[1]

Clinically, amiodarone related lung damage is a well-known cause of severe pulmonary fibrosis in the long term, causing a significant mortality and morbidity. It was shown that AMD treatment results in thickening of alveolar septa with fibrosis, inflammatory cellular infiltration and disruption of the alveolar epithelium. AMD related lung damage is shown to be secondary to multifunctional etiologies like hypersensitivity, direct toxic action and increased oxidative stress.[2]

Limiting the oxidative stress related to AMD exposure in the lung tissue via antioxidant agents could be a reasonable approach for preventing the lung damage. For this purpose, substances with proven the antioxidant action like fish oil, L-carnitine and alpha lipoic acid and so forth have been shown to limit the tissue damage related to AMD.[3-5]

Brassica vegetables (including cabbage, cauliflower and broccoli) are reported to have a high concentration of antioxidant compounds, such as phenols and flavonoids.[6] The use of white cabbage was shown to tackle the oxidative damage and induces a protective action against endothelial, cardiac, hepatic and renal injury in several studies.[7]

Herein, we aimed to investigate the alterations in biochemical markers of oxidative stress and morphology related to AMD treatment in lungs and to study the effect of white cabbage extract (WCAE) on AMD related lung damage in rats.

MATERIALS AND METHODS

***Ethics Committee Approval*:** In this study, female Sprague Dawley rats (8-12 weeks old, 300-350 g) were obtained from the Marmara University Faculty of Medicine Animal Laboratory. All procedures were performed according to the Guide for the Care and Use of Laboratory Animals. Experimental protocols were approved by the Institutional Animal Care and Use Committee of the University (Date: 26.11.2014, decision no:71.2014mar) and followed the Institutional Animal Care and Use Committee of Marmara University.

***Experimental Design**:* Animals were distributed into 4 groups, each group consists of 5 animals. Control group , intact animals; WCAE group, animals given WCAE (500 mg/kg) for 7 days; AMD group, animals administered AMD (100 mg/kg) for 7 days, AMD+WCAE group, animals given WCAE and AMD at the same dose. In all groups, WCAE and AMD were given by gavage technique. In AMD+WCAE group, WCAE was applied one hour prior to AMD. After sacrification on day 8, the lung tissues were taken for both histological and biochemical analysis.

Preparation of White Cabbage Aqueous Extract (WCAE): The white cabbage leaves were obtained from local markets of Istanbul, Turkey. The leaves were washed carefully with distilled water and then dried at room temperature. After they were dried, the leaves (100 g) were extracted by adding distilled water (1000 mL) and boiled for 8 hours. At the end of the process, the extract filtered and lyophilized. The lyophilized extract was freshly dissolved in distilled water and the applied to the animals for 7 days.

Biochemical Analyses: Lung tissues were homogenized by using 0.9% NaCl to make up (10%, w/v) homogenates. The preparates were centrifuged at +4 °C and 10000 x g for 10 minutes. The supernatants were collected for determining biochemical parameters as described previously in our study[8-10]; reduced glutathione (GSH), lipid peroxidation (LPO), advanced oxidized protein products (AOPP), hydroxy proline (HP), catalase (CAT), carbonic anhydrase (CA), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), total antioxidant capacity (TAC), total oxidant status (TOS), reactive oxygen species (ROS), oxidative stress index (OSI), nitric oxide (NO), xanthine oxidase (XO), lactate dehydrogenase (LDH) superoxide dismutase (SOD), paraoxonase (PON) and lung protein levels were determined.

Histological Analyses: For light microscopic investigations, after fixing in 10% neutral buffered formaldehyde, lung samples were processed routinely before embedding in paraffin. Paraffin sections (5-µm-thick) were stained with hematoxylin and eosin (HE) for morphologic evaluation and Masson's trichrome for detection of collagen fibers. Sections were investigated by a photomicroscope (Olympus BX51, Tokyo, Japan) and photographed with a camera (Olympus DP72, Tokyo, Japan). Histopathological damage scoring was done at least five microscopic areas for each sample on the basis of following criteria: vascular congestion, interstitial edema, inflammatory cell infiltration and alveolar structural disturbance. Each criterion was semiquantitatively scored as 0: normal, 1: mild, 2: moderate and 3: severe damage. The maximum score was 12. To calculate the percentage of the mean area of collagen fiber deposition, 5 images from 5 non-overlapping areas in each lung sample were used and quantitation was done by image analysis software (Image J, v.2.1, NIH, USA).

Statistical Analyses: All analysis was done via GraphPad Prism 6.0 (GraphPad Software, San Die-

go, California, USA). The values were given as means ± standard deviation (SD). The data were evaluated using an unpaired t-test and analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. A P value less than 0.05 was regarded statistically significant.

RESULTS

Administration of WCAE significantly decreased GSH levels and increased AOPP levels in control group ($p<0.05$, Figure 1). Administration of AMD significantly decreased GSH levels ($p<0.001$, Figure 1) and increased LPO, AOPP and HP levels in control group in a significant manner, respectively ($p<0.001$; $p<0.0001$; $p<0.05$, Figure 1). WCAE reversed these levels in AMD group as statistically significant, respectively ($p<0.0001$; $p<0.05$; $p<0.001$, Figure 1).

WCAE increased GPx activity in control group significantly ($p<0.05$, Figure 2). CAT, SOD, GPx and GR activities were increased, and GST activity was decreased after AMD administration in control group in a significant manner, respectively ($p<0.01$; $p<0.001$; $p<0.0001$, Figure 2). In AMD+WCAE group, all the activities given in this figure were reversed significantly when we compared to AMD group, respectively ($p<0.05$; $p<0.01$; $p<0.0001$, Figure 2).

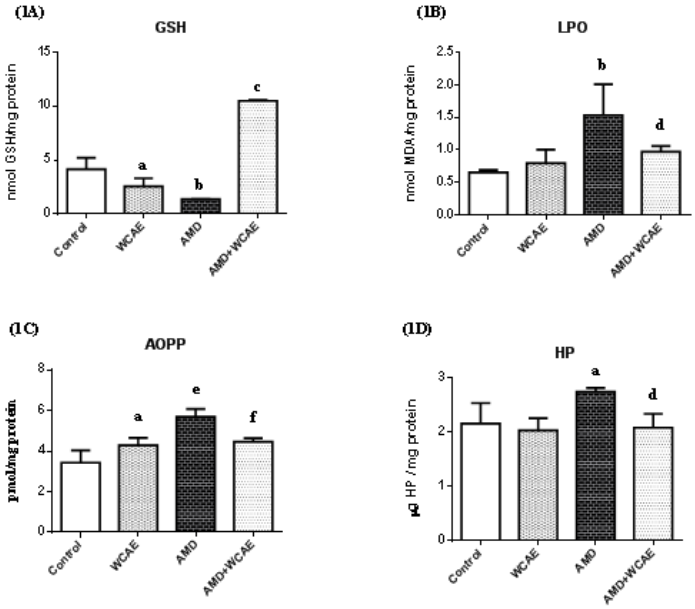

Figure 1. Comparison of biochemical markers in experimental groups. The lung GSH (1A), LPO (1B), AOPP (1C) and HP (1D) levels of experimental groups; [a]: P<0.05 vs control group; [b]: P<0.001 vs control group; [c]: P<0.0001 vs AMD group; [d]: P<0.05 vs AMD group; [e]: P<0.0001 vs control group; [f]: P<0.001 vs AMD group.

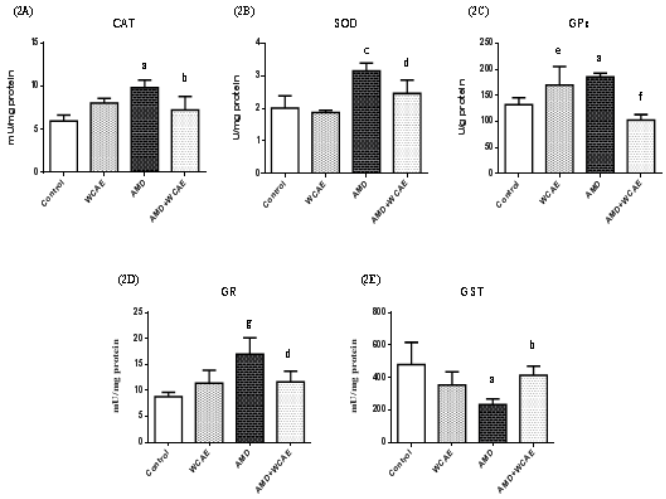

Figure 2. Comparison of biochemical markers in experimental groups. The lung CAT (2A), SOD (2B), GPx (2C), GR (2D) and GST (2E) activities of experimental groups; [a]: P<0.01 vs control group; [b]: P<0.05 vs AMD group; [c]: P<0.001 vs control group; [d]: P<0.01 vs AMD group; [e]: P<0.05 vs control group; [f]: P<0.0001 vs AMD group; [g]: P<0.0001 vs control group.

Diminished TAC and elevated TOS, ROS and OSI levels were determined in AMD group as compared to control group and the alterations in these levels were in a significant manner, respectively ($p<0.01$; $p<0.0001$; $p<0.05$, Figure 3). Administration of WCAE to AMD group significantly reversed these levels, respectively ($p<0.01$; $p<0.05$; $p<0.0001$, $p<0.001$, Figure 3).

AMD treatment increased NO levels, XO and LDH activities but decreased PON and CA activities in control group as statistically significant, respectively ($p< 0.05$; $p< 0.0001$; $p< 0.01$, Figure 4). WCAE significantly reversed all the parameters in AMD group which were mentioned in Figure 4, respectively ($p< 0.01$; < 0.0001; $p< 0.05$; $p< 0.001$).

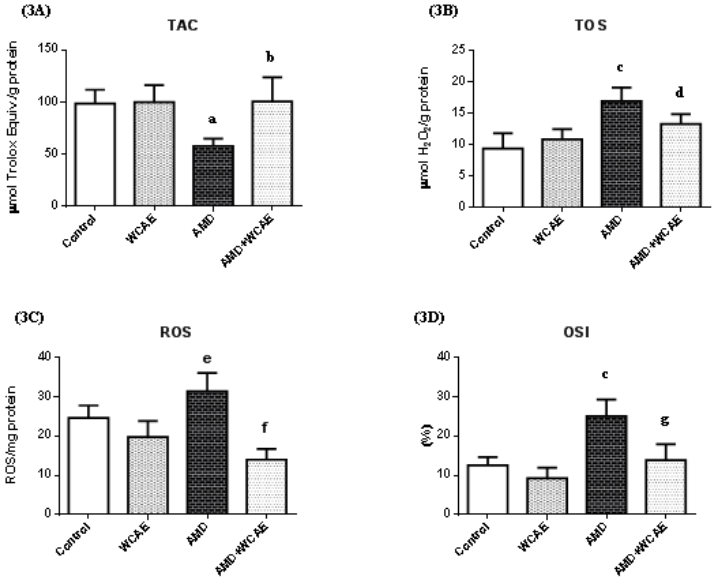

Figure 3. Comparison of biochemical markers in experimental groups. The lung TAC (3A), TOS (3B); ROS (3C) and OSI (3D) levels of experimental groups; [a]: P<0.01 vs control group; [b]: P<0.01 vs AMD group; [c]: P<0.0001 vs control group; [d]: P<0.05 vs AMD group; [e]: P<0.05 vs control group; [f]: P<0.0001 vs AMD group; [g]: P<0.001 vs AMD group.

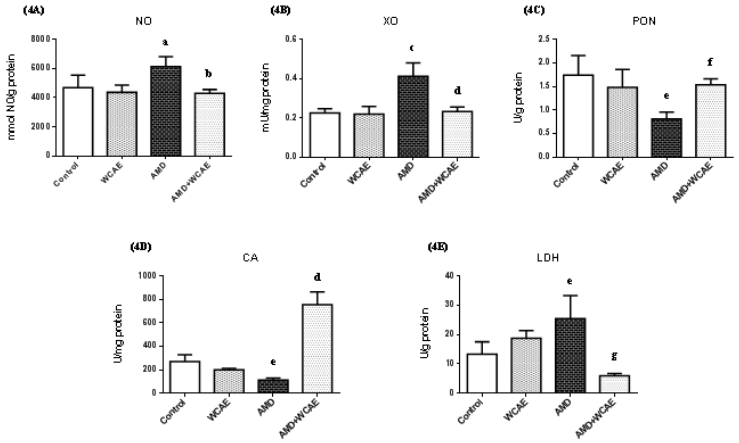

Figure 4. Comparison of biochemical markers in experimental groups. The lung NO levels (4A), XO (4B), PON (4C), CA (4D) and LDH (4E) activities of experimental groups; [a]: P < 0.05 vs control; [b]: P < 0.01 vs AMD group; [c]: P < 0.0001 vs control group; [d]: P < 0.0001 vs AMD group; [e]: P < 0.01 vs control group; [f]: P < 0.05 vs AMD group; [g]: P < 0.001 vs AMD group.

Lung tissues of control and WCAE groups showed a regular parenchyma morphology including alveoli and interstitium, whereas AMD treatment caused severe interstitial edema with vascular congestion, degenerated alveolar structures and moderate inflammatory cells infiltration mainly lymphocytes in the lung parenchyma. AMD+WCAE group showed reduced interstitial edema and congestion, an improvement in alveolar structures besides regression of inflammatory cell infiltration in lung parenchyma. Higher histopathological damage score of lung tissue in AMD group were significantly reduced by treatment with WCAE ($p < 0.001$; Fig. 5).

In control and WCAE groups, collagen fibers were regularly distributed in lung parenchyma, however prominently increased collagen fiber accumulation was detected in the inter-alveolar septa, around bronchioles and blood vessels in AMD group. AMD+WCAE group showed a reversal of the increased amount of collagen fiber accumulation seen in AMD group. The increased percentage of the mean area of collagen fiber accumulation in AMD group was significantly reduced by treatment with WCAE ($p < 0.01$; Figure 5).

DISCUSSION AND CONCLUSION

Amiodarone is described as having amphiphilic character with its benzofuran ring and N-diethylamino side chain part.[11] Although these parts lead to AMD to be physiologically more active, AMD starts an unwanted accumulation by using these parts for both the entrance into cell and exodus throughout the cell. The accumulated AMD inhibits phospholipid metabolism by blocking lysosomal phospholipase.[12]

Lung GSH status has been declared as an indicator for an effective pulmonary response[2] and besides, AMD has been reported as being transformed to quinone reactives which are tended to bind GSH.[13] Taylor et al.[14] emphasizes the possibility of oxidant sourced damage of AMD by triggering the formation of malondialdehyde products associated with LPO levels. AOPP is a marker for non-enzymatic protein oxidation especially due to increased reactive oxygen species (ROS) levels.[15] Elevations at these altered levels may not be alone enough to describe ROS-related AMD toxicity, but also HP. Because the alterations in cellular protein levels may affect lung collagen deposition which can be measured for evaluation of HP.[4] Al-Shammari et al.[2] re-

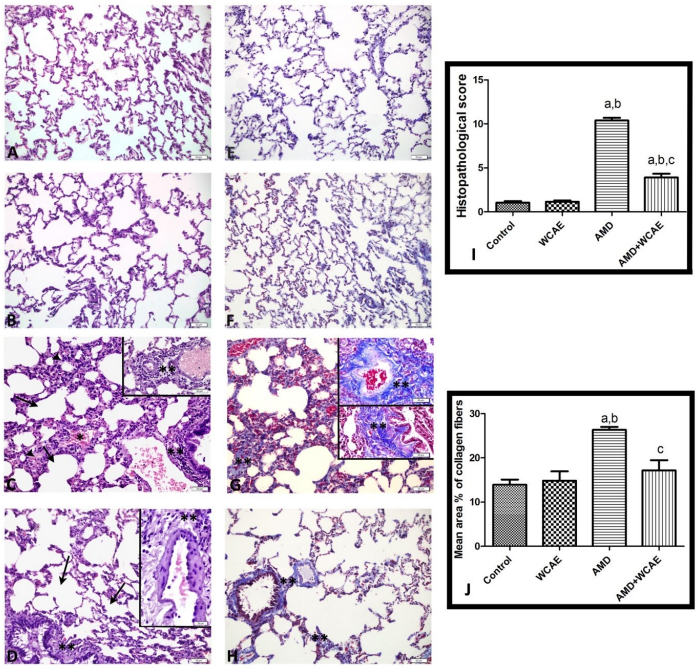

Figure 5: Histological findings of lung tissue in experimental groups. Representative photomicrographs of lung tissue (A-H): Regular lung parenchyma morphology in control (A) and WCAE (B) groups; Severe interstitial edema with vascular congestion (*) which causes the decrease in alveolar space (arrowheads), distended alveolar walls (arrows) and moderate perivascular and peribronchiolar lymphocyte infiltration (**-inset) in AMD group (C); Regression of inflammatory cell infiltration (**) and regular alveolar morphology (arrows) in AMD+WCAE group (D); Regular distribution of collagen fibers in control (E) and WCAE (F) groups; A prominent increase in the collagen fibers accumulation in the inter-alveolar septa, around bronchioles and blood vessels (**) in AMD group (G); A marked reduction in the collagen fiber accumulation in the inter-alveolar septa, around bronchioles and blood vessels (**) in AMD+WCAE group (H); HE stain (A-D) and Masson's trichrome stain (E-H); The graph of histopathologic damage score (I) and the percentage of the mean area of collagen fiber deposition (J) of lung tissue; [a]: $P<0.001$ vs control; [b]: $P<0.001$ vs WCAE group; [c]: $P<0.001$ vs AMD group (I). [a]: $P<0.001$ vs control; [b]: $P<0.01$ vs WCAE group; [c]: $P<0.01$ vs AMD group (J).

ported an elevation of HP levels of AMD induced lung injury in rats. Our results for GSH, LPO and HP are in accordance with other publications.[2,4,14,16] Turkyilmaz and Yanardag[17] reported that AMD induced hepatotoxicity resulted an elevation of carbonylated protein product and we observed an elevation in AOPP levels of AMD treated rats with the same logic. In our study, we determined diminished GSH and increased levels of LPO, AOPP and HP in lung tissue of AMD administered rats. The sulfur-containing compounds are very effective on Brassica species and they are known as having organic poly sulfur compounds which contain highly reactive sulfur atoms while they are in a reduced position. This property explains their antioxidant ability.[18] Moreover, one of the other Brassica species, red cabbage, has been declared as having preventive effect on LPO and protein structure alteration on chemical induced damage.[19] Ibrahim Fouad and Mousa[4] indicated the importance of alpha lipoic acid as having sulfur moiety in its structure and protective effect on AMD-induced pulmonary fibrosis. Based on these approaches and information, we can say that WCAE increased GSH levels and decreased LPO, AOPP and HP levels probably by its sulfur ingredients and antioxidant activity.

AMD disrupts the membrane structure by activating protein C and triggering this molecule as related oxygen radicals.[14] In the present study, we got increased activities of SOD, CAT, GPx and GR in AMD treated lung tissues. This elevation is an indicator for the deleterious effect on mitochondrial process of AMD. Besides, GST activity was found to be decreased as a conclusion of diminished GSH levels, a substrate for its detoxification activity. We also approached from another angle as determining decreased TAC and increased TOS, ROS and OSI levels produced by AMD. Nicolescu et al.[20] showed that AMD has increased ROS levels in human peripheral lung epithelial cells. WCAE reversed these enzymatic alterations and disruption of antioxidant system. Cabbage includes many vitamins, phenolic compounds and glucosinolates. These substances are the main characters which construct the antioxidant property of this plant.[21]

Although NO has many stimulating effects in organism, its excess production leads to react many molecules like superoxide anion and the further products will be more dangerous by attacking many macromolecules.[22] XO, a key enzyme for purine catabolism, plays an important role for the formation of uric acid. However uric acid has been reported as inflammation elevator effect which further causes cell death.[23] We determined increased NO levels and XO activities in AMD treated lung tissues. PON is one of the important antioxidant enzymes and it is vulnerable under oxidative circumstances. In addition, in lung diseases like chronic obstructive pulmonary disease and related chronic oxidative stress, PON has been declared as being observed with its lowered activity.[24] AMD decreased PON activity probably by the reason of its oxidant stimulator activity which we mentioned above by explaining the alterations in antioxidant parameters. Hazineci et al.[25] mentioned the ROS-triggering effect of AMD on heart tissue, and they prevented its ROS triggering effect on heart tissue by using white cabbage as considering and proving its antioxidant potential. Based on this approach, we may assume that the alteration of NO levels, XO and PON activities as positively may have been related to the powerful antioxidant capacity of WCAE.

In this study, AMD inhibited CA in lung tissue. Kılınç et al.[26] showed that some cardiovascular therapeutics have inhibited CA isoenzymes. When we consider the susceptibility of CA to pH alterations, we may put forward for the inhibitory effect of AMD on CA by its elevator effect on hydrogen ion concentration by the rapid entry-exit cycle of AMD which was explained by Stravitz and Sanyal.[27] AMD also causes an elevation in LDH activities of lung tissues. According to one approach by Kim et al.[28] the glucose elevator effect of AMD has been mentioned and this situation has also been related to its disrupting effect on mitochondrial dysfunction which could explain the reason of LDH elevation by AMD. According to the study of Turkyilmaz and Yanardag[17] on AMD induced hepatotoxicity, vitamin U have diminished LDH activity by scavenging the radicals produced by AMD. So, we may assume that WCAE may have reversed the CA and LDH activities by its antioxidant composition.

Al-Shammari et al[2] revealed that AMD induced lung damage becomes histologically evident as early as one week after exposure with vascular congestion, interstitial capillary dilation with lymphocyte infiltration. They also found that the severity of lung damage is correlated to the duration of exposure. In an experimental study by Gado et al[5], lung damage was established via a 10 day course of AMD application and they showed that L-carnitine could ameliorate lung dysfunction related to AMD via a mechanism which involves the production of NO rather than lipid peroxidation. Similar to these results, we observed severe interstitial edema with vascular congestion, degenerated alveolar structures and moderate inflammatory cells infiltration mainly lymphocytes in the lung parenchyma after 1 week of AMD application. Concurrent treatment with WCAE prevented the lung damage in rats exposed to AMD, probably through its antioxidant potential. Another important issue with AMD treatment is collagen deposition in the lung tissue, eventually leading the development of pulmonary fibrosis. In a study by

Fouad and Mousa[4], administration of AMD causes significant increases in the lung HP and collagen contents. In the same study, they showed that the use of an antioxidant agent, alpha lipoic acid, could reverse the oxidative stress, fibrosis, and inflammation parameters. In accordance with their results, we found that treatment with WCAE ameliorated the collagen deposition and increased HP content induced by AMD application.

In conclusion, AMD induced lung damage continues to be an important health issue in patients exposed to the agent. Due to its powerful antioxidant capacity, WCAE might have a protective role in amelioration of AMD induced lung damage.

Ethics Committee Approval: Our study was approved by the Institutional Animal Care and Use Committee of the University (Date: 26.11.2014, decision no:71.2014mar) and followed the Institutional Animal Care and Use Committee of Marmara University.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept –RY, EA; Supervision –RY, IBT, EA; Materials –RY, IBT, EA; Data Collection and/or Processing – RY, IBT, EA; AM; Analysis and/ or Interpretation – RY, IBT, EA, AM; Writing –RY, IBT, EA.

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