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Research Article

Can Ethyl 7-Hydroxy-2-Imino-2H-Cramen-Carboxylate, a Newly Synthesized Coumarin Derivative, Inhibit the Biochemical and Histopathological Toxic Effects of Bisphenol A on the Cardiovascular System of Male Rats?

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Abstract

Objective: The present study examined the toxic effects of Bisphenol A, which is a commonly used industrial chemical, on male Wistar albino rats' cardiovascular system, and potential protective effects of Ethyl 7-hydroxy-2-imino-2H-cramen-3-carboxylate, a newly synthesized coumarin derivative, against this toxicity.

Method: A total of 10-12 weeks of age and 250-300 g weighing 28 male Wistar Albino rats were used in the present study. Four groups (control, bisphenol-A, Coumarin, and Bisphenol-A+Coumarin) were formed from the rats. The rats were administered Bisphenol and/or Coumarin via orogastric route on alternate days. Biochemical, histopathological, and histomorphometric analyses were performed on heart and vascular tissues at the end of the experiment.

Results: As a result of biochemical analyses, Bisphenol administration was found to reduce total antioxidant capacity significantly and increase total oxidant status and malondialdehyde levels, indicating that Bisphenol induces oxidative stress. It was found that administering Coumarin showed antioxidant activity by restoring these parameters toward normal levels. While myofiber degeneration and morphological alterations in the cardiac tissue of the Bisphenol group were observed through histopathological examinations, these effects were alleviated with Coumarin treatment.

Conclusion: Molecule Ethyl 7-hydroxy-2-imino-2H-cramen-3-carboxylate was shown to have a protective effect against Bisphenol-induced cardiovascular toxicity, suggesting that the molecule may serve as a potential therapeutic agent against oxidative stress-related cardiac and vascular damage.

Keywords: Antioxidant, Bisphenol A, Cardiovascular System, Coumarin

INTRODUCTION

Bisphenol A (BPA), which is used in the production of polycarbonate plastics and epoxy resins, toys, dental monomers, and water pipes (Vandenberg et al., 2007), is one of the most produced chemicals in the world. While it is taken primarily through diet, a small amount also comes from dermal contact (Kang et al., 2023; Vandenberg et al., 2007). BPA is a well-known endocrine disruptor (Acconcia et al., 2015). Throughout the world, one of the most common cause of death among both men and women is cardiovascular diseases (Kang et al., 2023). A large number of studies have shown a positive association between urinary and blood BPA levels and cardiovascular diseases (Kang et al., 2023; Melzer, et al., 2010; Melzer et al., 2012). Urinary or serum BPA concentrations have been shown to be positively associated with the risk of cardiovascular diseases including myocardial infarction, stroke, and coronary artery disease. BPA exposure may also result in cardiac arrhythmias and atherosclerosis (Kang et al., 2023; Melzer et al., 2012; Yan et al., 2011).

Coumarins are polyphenolic compounds found as secondary metabolites in various plant families (Flores-Morales et al., 2023). They are naturally present in large amounts in plants and essential oils, in addition to the possibility of being synthesized in the laboratory (Flores-Morales et al., 2023; Venugopala et al., 2013). Its functionality is increased with its ability to attach different functional groups at various positions on the molecule. Ethyl 7-Hydroxy-2-Imino-2H-Cramen-Carboxylate (CM) belongs to the class of hydroxy coumarins and it is effective in scavenging free radicals due to its phenolic structure (Akgül et al., 2024; Kurt et al., 2019). Because of their significant biological activities, coumarin and its derivatives have been extensively researched. A large number of studies have shown their antimicrobial, antiviral, antimitotic, antioxidant, anti-inflammatory, anticancer, and anticoagulant benefits. Coumarins play an important role in the development of new drug candidates because of these remarkable properties.

The aim of the present study is to examine the protective effects of the newly synthesized Ethyl 7-Hydroxy-2-Imino-2H-Cramen-Carboxylate molecule on the toxicity induced in the cardiovascular tissues of rats as a result of BPA exposure.

METHOD

Adıyaman University Animal Experiments Local Ethics Committee (Ethics committee no: 2022/006) approved the experimental protocol. Adıyaman University Experimental Animal Production Application and Research Center provided the animals used in the experimental. The whole experimental protocol was conducted at this center. For a total of 30 days, standard laboratory conditions (12/12 light/dark cycle, 21 ± 1 °C, and 55 ± 5% relative humidity) were used to house the animals, which were fed ad libitum and had unlimited access to fresh water.

Ethyl 7-Hydroxy-2-Imino-2H-Cramen Carboxylate (CM) molecule was synthesized as previously described in the literature (Akgül et al., 2024; Volmajer et al., 2005). A total of 28 male Wistar albino rats (250 ± 10 g body weight), randomly assigned to 4 groups: control (n=7), CM (n=7), BPA (n=7), CM+BPA (n=7) were used in the study. BPA was dissolved in distilled water and administered at a dose of 20 µg/kg via orogastric gavage every other day (Bindhumol et al., 2003). CM was also dissolved in distilled water and administered at a dose of 20 mg/kg via orogastric gavage every other day (Çitil, 2022). In order to prevent complex formation between them, care was taken to administer BPA and CM on alternate days. The animals were sacrificed, and heart and vascular tissues were placed in 10% formalin at

the end of the experimental protocol. Until the day of analysis, heart tissue was stored at -80°C for biochemical analyses.

Biochemical Analyses

By using a BioSpec Products Mini-BeadBeater-16 (OK, USA), Heart tissue was homogenized in cold phosphate-buffered saline (PBS) (pH 7.4). The supernatant was collected after the homogenate was centrifuged at 5000 rpm for 25 minutes at 4°C and the resulting supernatant was used to perform all biochemical analyses. A previously described method (Ohkawa et al., 1979) was used to measure the level of malondialdehyde (MDA), an indicator of lipid peroxidation. ELISA kits were used to measure total antioxidant capacity (TAS) and total oxidant status (TOS) by following the manufacturer's instructions provided in the kit manual. The ratio of TOS to TAS was considered the oxidative stress index (OSI).

Histopathological Analyses

Histopathological evaluation was carried out in the Department of Histology and Embryology at the Faculty of Medicine, Adıyaman University. Tissue samples obtained from sacrificed animals were fixed in 10% formalin solution for one week. An automatic tissue processor (Leica TP1020, Nussloch, Germany) was used for routine histological processing (including alcohol, xylene, and paraffin series). Thermo Shandon Finesse ME microtome (Thermo Fisher Scientific, Cheshire, UK) was used to section paraffin blocks at 5 µm thickness and Hematoxylin-Eosin and Masson's trichrome staining methods were used for staining. The sections were exposed to histomorphometric and histopathological analyses. A Carl Zeiss Axiocam ERc5 digital camera attached to a microscope (Carl Zeiss Microscopy GmbH, 07745 Jena, Germany) was used for imaging.

Histomorphometric Analyses

Analyses were conducted with ImageJ software. In order to analyse aortic and femoral artery tissues, the mean of 10 measurements per image was taken for lumen diameter, and the mean of 5 measurements per image was taken for the thicknesses of the layers. For lumen diameter measurements, images stained with H&E at ×4 objective magnification were used and for layer thickness measurements, ×40 objective magnification images were used. In order to analyse heart tissue, the mean of 5 measurements per image was used for myocardial layer thickness, and the mean of measurements from 30 cells with the shortest diameters was used for myocyte diameters. for myocardial thickness measurements, images stained with H&E at ×4 objective magnification were used and for myocyte diameter measurements, ×40 objective magnification images were used.

Statistical Analysis

Descriptive statistics such as frequency, percentage, arithmetic mean, standard deviation, confidence intervals, and table were used to describe the variables in the study. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess normal distribution of the data. Parametric ANOVA test was applied for normally distributed data. Threshold for statistical significance was set at $p<0.05$. SPSS 22.0 for Windows software package was used to conduct statistical analyses.

RESULTS

Effects of CM on BPA-Induced ROS Formation

Mean ± standard deviation values of total antioxidant status (TAS), total oxidant status (TOS), malondialdehyde (MDA) levels, and oxidative stress index (OSI) parameters for the control, BPA, CM, and BPA + CM groups are shown in Table 1. TAS levels were found to

decrease significantly ($p < 0.01$), while TOS and OSI levels were found to increase significantly ($p < 0.01$) in BPA group. TAS levels increased and TOS and OSI levels decreased with CM administration. When compared with the BPA group, these parameters were found to improve in the BPA + CM group, while the values did not differ significantly from those of the control group. MDA levels were not found to be statistically significantly different among the groups.

Table 1. Biochemical analysis results of tissue samples from the study group

Parameter	Control	BPA	CM	BPA + CM
TAS (mmol Trolox Equiv./L)	14.70 ± 1.32	11.90 ± 1.5[a]	16.66 ± 2.31	12.63 ± 1.17
TOS (µmol H_2O_2 Equiv./L)	2.98 ± 0.47	4.10 ± 0.64[b]	2.44 ± 0.35	3.28 ± 0.55
MDA (nmol/g wet tissue)	116.90 ± 15.89	129.57 ± 19.12	129.37 ± 12.77	136.48 ± 7.68
OSI (mmol Trolox/mmol H_2O_2)	0.21 ± 0.03	0.42 ± 0.07[c]	0.15 ± 0.02	0.26 ± 0.06

[a] Indicates a statistically significant difference between the BPA group and both the control and coumarin groups ($p<0.01$). [b] Indicates a statistically significant difference between the BPA group and all other groups ($p<0.01$). [c] Indicates a statistically significant difference between the BPA group and all other groups ($p<0.01$).

Histopathological evaluation of heart tissue

Except for the BPA group, no pathological findings were observed in groups. In these groups, morphological structure of the fibers forming the myocardium and the nuclear localization were normal (Figure 1 A1-C1-D1). There were no signs of myonecrosis, fibrosis, or inflammation and no connective tissue edema was seen between the muscle fibers (Figure 1 A2-C2-D2). An increased number of fibers with localized morphological alterations were found in the BPA group (Figure 1 B1-B2).

Histopathological Evaluation of Aortic Tissue

In all groups, it was found that the surface of the innermost layer of the vessel wall, the tunica intima had a thin and smooth endothelium. The elastic lamellae in the middle layer, the tunica media, were arranged in a parallel and concentric manner. The smooth muscle cells located between the elastic lamellae appeared normal. The outermost layer, the tunica adventitia, consisted of loose connective tissue (Figure 2).

Histopathological Evaluation of Femoral Artery Tissue

Vessels were found to show a thin and smooth endothelium, a finely undulated internal elastic lamina, and concentrically arranged smooth muscle cells in the examinations of all groups. The adventitia was composed of connective tissue, with prominent collagen fiber structures. The intima, media, or adventitia layers were not found to have any pathological findings (Figure 3).

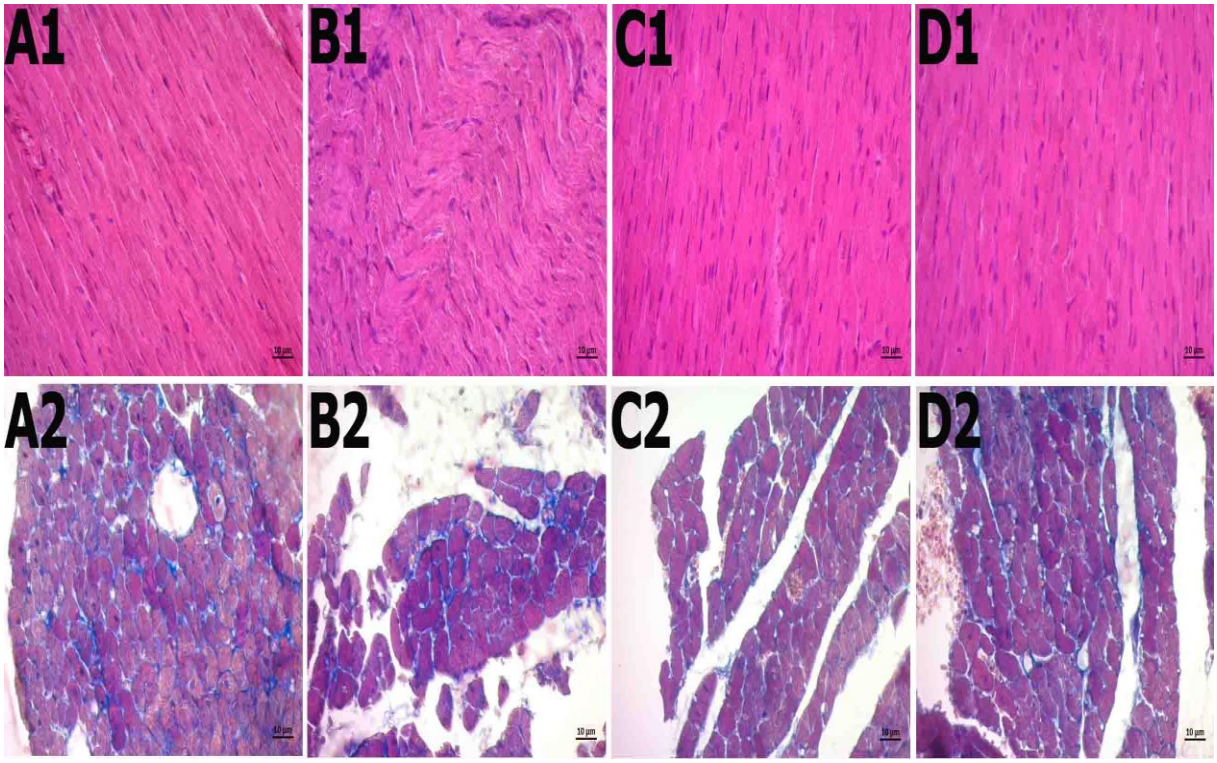

Figure 1. A, B, C, and D represent the histological images of the Control, BPA, Coumarin, and BPA+Coumarin groups, respectively, at ×40 objective magnification. A1, B1, C1, and D1 are stained with Hematoxylin & Eosin, while A2, B2, C2, and D2 are stained with Masson's trichrome. In the BPA group, muscle fibers with morphological alterations are present. No signs of edema or fibrosis were observed in any of the groups

Histomorphometric Results

When compared with the other groups, BPA group was found to have statistically significant differences in the aortic tissue with respect to media layer thickness, adventitia layer thickness, and vessel diameter ($p<0.05$). In terms of intima layer thickness, media layer thickness, adventitia layer thickness, and vessel diameter, statistically significant differences were found in the BPA group in the analysis of the femoral artery tissue ($p<0.01$). Myocardial layer thickness and myocyte diameter were found to be similar in all groups ($p>0.05$). Table 2 shows the results of the analysis (Table 2).

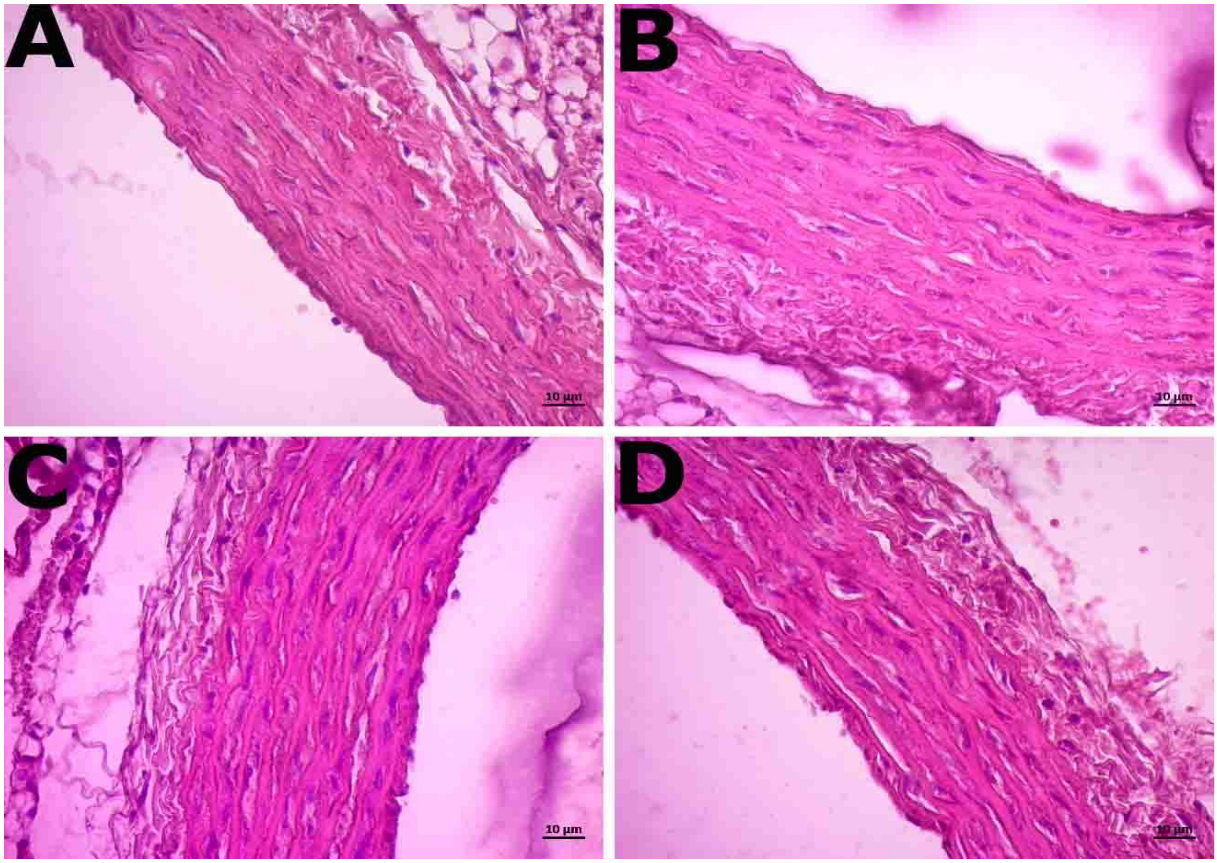

Figure 2. A, B, C, and D represent the histological images of the Control, BPA, Coumarin, and BPA+Coumarin groups, respectively, at ×40 objective magnification. A1, B1, C1, and D1 are stained with Hematoxylin & Eosin, while A2, B2, C2, and D2 are stained with Masson's trichrome. In the BPA group, muscle fibers with morphological alterations are present. No signs of edema or fibrosis were observed in any of the groups.

DISCUSSION

Widely used in the production of polycarbonate plastics and epoxy resins, Bisphenol A (BPA) is a high-production volume chemical and it is used in food containers, water bottles, and the linings of metal cans. Humans are primarily exposed to BPA through dietary intake because of its widespread use. It is an endocrine-disrupting chemical (EDC) with estrogenic activity and can interfere with hormonal signaling even at low doses (Rochester, 2013).

Recently, there is a growing interest in the potential cardiovascular effects of BPA exposure. An association between BPA and various cardiovascular conditions such as hypertension, atherosclerosis, and myocardial dysfunction has been suggested by epidemiological and experimental studies (Melzer et al., 2010; Gao & Wang, 2014). When the global burden of cardiovascular diseases is considered, these findings raise significant public health concerns.

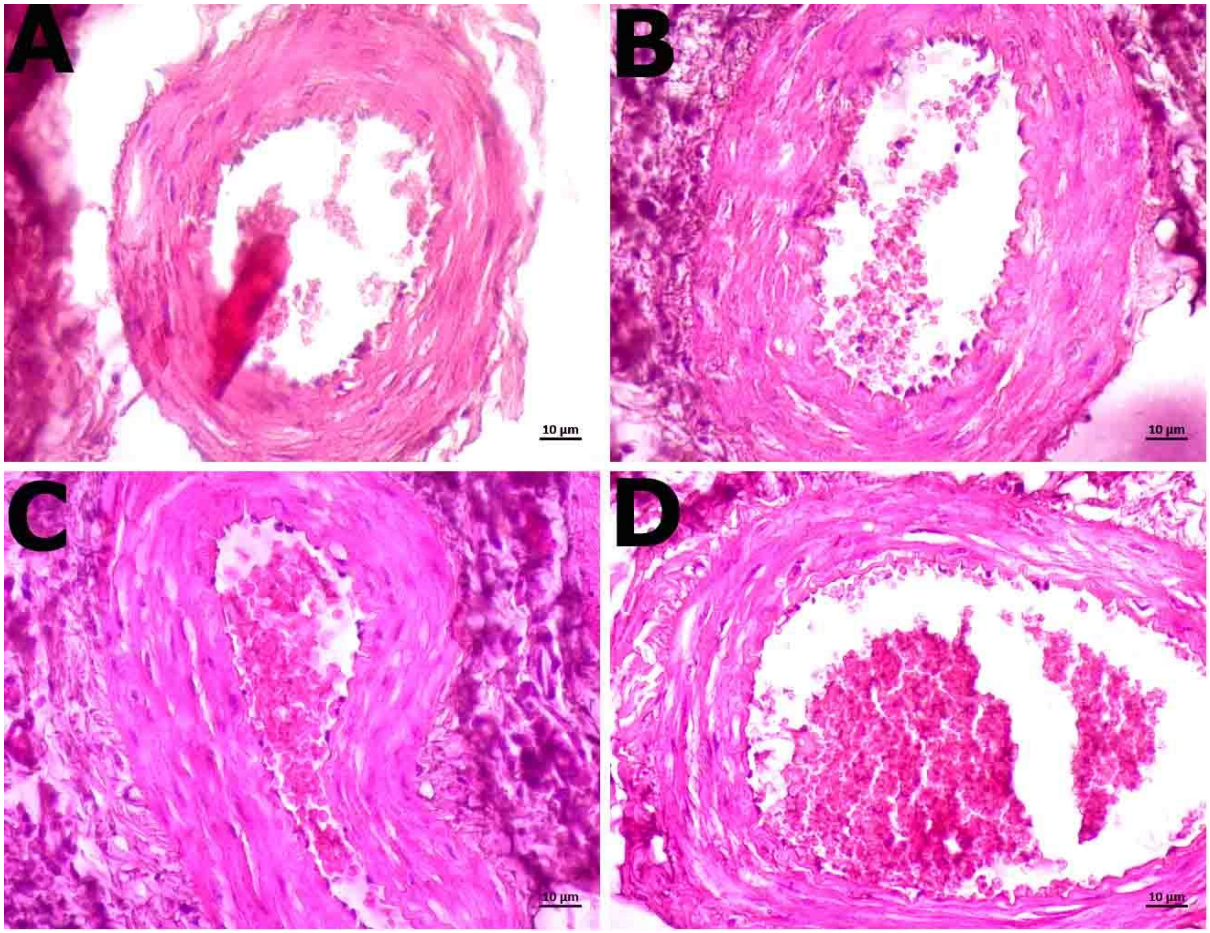

Figure 3. A, B, C, and D represent histological images of the control, BPA, Coumarin, and BPA+Coumarin groups, respectively, under x40 objective magnification. Normal tissue appearance (Hematoxylin & Eosin staining).

Coumarins are a class of naturally occurring phenolic compounds widely found in plants, particularly in the families *Apiaceae* and *Rutaceae*. Recently, their diverse pharmacological properties, including anticoagulant, anti-inflammatory, vasodilatory, and antioxidant effects, many of which are relevant to cardiovascular health have started to attract increasing attention (Venugopala et al., 2013). Warfarin, a well-known synthetic coumarin derivatives, is extensively used as an oral anticoagulant to prevent and treat thromboembolic disorders (Holbrook et al., 2012). Beyond anticoagulation, natural coumarins such as esculetin, scopoletin, and umbelliferone have demonstrated vasoprotective and cardioprotective effects in various experimental models (Kumar et al., 2013). Several studies have reported that coumarin molecules have antioxidant properties against various oxidative stress agent (Borges et al., 2005; Lin et al., 2008; Wu et al., 2007).

Coumarin-derived molecules have been reported to have free radical scavenging effects (Venugopala et al., 2013. In this context, a study conducted by Akgül et al. (2024) revealed that ethyl 7-hydroxy-2-imino-2H-cramen-3-carboxylate, a synthesized coumarin derivative has a protective effect against bisphenol A-induced kidney toxicity.

Table 2. Histomorphometric measurement results of aorta, femoral artery, and heart tissues

Aorta	Control	BPA	Coumarin	BPA + Coumarin
Tunica intima (µm)	2.646 ± 0.23	2.343 ± 0.24	2.387 ± 0.52	2.488 ± 0.30
Tunica media (µm)	45.512 ± 1.21	37.846 ± 4.85[a]	43.833 ± 1.62	42.630 ± 1.70
Tunica adventitia (µm)		30.492 ± 1.88[b]	34.026 ± 1.33	31.420 ± 1.66
Lumen diameter (µm)	316.633 ± 76.55	183.542 ± 43.33[c]	308.726 ± 58.66	291.245 ±125.27
[a]: Indicates a statistically significant difference between the BPA group and all other groups (p<0.05). [b]: Indicates a statistically significant difference between the BPA group and the control and coumarin groups (p<0.05). [c]: Indicates a statistically significant difference between the BPA group and the control group (p<0.05).				
Femoral Artery	**Control**	**BPA**	**Coumarin**	**BPA + Coumarin**
Tunica intima (µm)	2.945 ± 0.20	2.184 ± 0.24[a]	2.651 ± 0.32	2.536 ± 0.35
Tunica media (µm)	29.449 ± 0.86	20.882 ± 0.67[b]	27.188 ± 1.19	23.672 ± 1.06
Tunica adventitia (µm)	23.563 ± 5.12	17.498 ± 0.99[c]	22.018 ± 3.80	18.411 ± 1.48
Lumen diameter (µm)	58.157 ± 3.38	43.250 ± 6.57[d]	55.485 ± 2.03	54.344 ± 0.66
[a]: Indicates a statistically significant difference between the BPA group and all other groups (p<0.05). [b]: Indicates a statistically significant difference between the BPA group and all other groups (p<0.01). [c]: Indicates a statistically significant difference between the BPA group and the control group (p<0.01). [d]: Indicates a statistically significant difference between the BPA group and all other groups (p<0.01).				
Heart	**Control**	**BPA**	**Coumarin**	**BPA + Coumarin**
Myocardial layer (µm)	1001.708 ± 136.97	870.234 ± 87.86	983.735 ± 109.13	974.769 ± 95.104
Cardiomyocyte diameter (µm)	9.059 ± 0.64	8.260 ± 0.75	8.679 ± 1.02	8.307 ± 0.65

*No statistically significant differences were found between the groups (p>0.05).

Biochemical findings indicated that BPA administration increased oxidative stress in cardiac tissue. A significant decrease in total antioxidant status (TAS) and a significant increase in total oxidant status (TOS) were detected in the BPA group, suggesting that BPA triggers lipid peroxidation by promoting the production of reactive oxygen species (ROS). This result is consistent with previous studies suggesting that BPA may cause cardiotoxicity through oxidative stress and inflammation mechanisms (Bindhumol et al., 2003). The result that BPA causes morphological alterations in cardiac tissue was also supported by histopathological examinations. BPA group was found to have degeneration and necrosis in myocardial fibers, along with increased intercellular spaces, although these changes were minimal in the control and CM-treated groups. This result is in parallel with the results in literature that BPA induces inflammation and cellular damage in cardiac tissues (Hu et al., 2016). It was found that administering CM helped to mitigate these adverse effects both biochemically and histologically. The potent antioxidant capacity of CM is highlighted with the increase in TAS levels and the decrease in the oxidative stress index (OSI). Various studies involving various organ systems have also reported free radical scavenging, anti-inflammatory, and cytoprotective properties of coumarin derivatives (Akgül et al., 2024; Kostova, 2005; Venugopala et al., 2013).

BPA group showed a reduction in the thickness of the aortic and femoral artery walls, structural vascular damage, and narrowing of the vessel

lumen in histomorphometric analyses. Studies which show BPA can result in vascular endothelial dysfunction and reduced vascular elasticity are in parallel with these findings (Alonso-Magdalena et al., 2006). CM administration had a significant protective effect on these parameters, helping to preserve vascular integrity in the present study. CM's antioxidant and anti-inflammatory actions on the vascular endothelium may have caused this effect.

The fact that there were no statistically significant differences in myocardial layer thickness and cardiomyocyte diameter among the groups suggests that BPA may not exert acute or short-term effects on these parameters, or that such effects may become more pronounced at later stages or with higher doses.

CONCLUSION

In conclusion, the present study shows that BPA exerts toxic effects on the cardiovascular system at both biochemical and histological levels, and that the newly synthesized CM compound can significantly reduce these harmful effects. The resulting potential cardioprotective properties of CM suggest that further pharmacological studies are required to support its therapeutic potential.

Limitations of the Study

However, several important limitations should be noted. The protective effects of Ethyl 7-Hydroxy-2-Imino-2H-Cramen-Carboxylate can primarily investigated through mechanisms related to cell death and stress pathways. Another limitation of this study is that electron microscopic analyses were not examined to verify the results.

Declaration of Interests: The authors declare that they have no conflict of interest.

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Ethical Approval: Ethical approval for this study was obtained from the Department of Animal Experiments Local Ethics Committee of Adıyaman University (Decision No: 2022/006). The welfare and living conditions of the animals used in the research fully complied with ethical standards.

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