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Effect of Ankaferd blood stopper on Cadmium-induced heart damage in male rats

Efecto de Ankaferd Blood Stopper sobre el daño cardíaco inducido por cadmio en ratas macho

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ABSTRACT

Cadmium (Cd), a widespread environmental contaminant, is known to cause tissue injury through mechanisms involving oxidative stress, inflammation, and apoptosis. The heart is particularly vulnerable to such toxic effects. Ankaferd Blood Stopper, a standardized herbal hemostatic agent, also exhibits notable antioxidant, anti-inflammatory, and anti-apoptotic activities. This study aimed to explore the potential protective effects of Ankaferd Blood Stopper against cadmium-induced cardiac injury, evaluating whether Ankaferd Blood Stopper administration mitigates histopathological and apoptotic damage in cardiac tissue caused by cadmium toxicity in rats. Thirtytwo male Wistar Albino rats (350–450 g) were divided into four groups (n=8 each): Control (saline, i.p.), Cd (2.5 mg/kg $CdCl_2$, i.p.), Ankaferd Blood Stopper (0.5 mL ABS, i.p.), and Cd + Ankaferd Blood Stopper ($CdCl_2$ + Ankaferd Blood Stopper, both i.p.). After treatment, cardiac tissues were collected and evaluated using histopathological staining and Caspase-3 immunohistochemistry. Blood samples were also collected for biochemical analysis. Cadmium exposure resulted in marked myocardial damage, including inflammatory infiltration, vascular congestion, and disorganized myofibers. Caspase-3 expression confirmed increased apoptotic activity. Ankaferd Blood Stopper administration significantly reduced histopathological lesions and Caspase-3 immunoreactivity in the Cd + Ankaferd Blood Stopper group, suggesting a protective effect. Ankaferd Blood Stopper effectively attenuated cadmium-induced cardiac injury, likely due to its antioxidant and anti-inflammatory properties. These findings indicate that Ankaferd Blood Stopper may offer therapeutic benefits in preventing or alleviating heavy metal-induced cardiovascular damage. Additional research is needed to validate these effects in long-term and clinical models.

Keywords: Cadmium; cardiac damage; ankaferd blood stopper; rat

RESUMEN

El cadmio (Cd), un contaminante ambiental ampliamente distribuido, es conocido por causar lesiones tisulares a través de mecanismos que implican estrés oxidativo, inflamación y apoptosis. El corazón es particularmente vulnerable a estos efectos tóxicos. Ankaferd Blood Stopper, un agente hemostático herbal estandarizado, también presenta notables actividades antioxidantes, antiinflamatorias y antiapoptóticas. Este estudio tuvo como objetivo explorar los posibles efectos protectores del Ankaferd Blood Stopper frente a la lesión cardíaca inducida por cadmio. Evaluar si la administración de Ankaferd Blood Stopper mitiga el daño histopatológico y apoptótico en el tejido cardíaco causado por la toxicidad por cadmio en ratas. Treinta y dos ratas macho Wistar Albino (350–450 g) se dividieron en cuatro grupos (n=8 cada uno): Control (solución salina, i.p.), Cd (2,5 mg/kg de $CdCl_2$, i.p.), Ankaferd Blood Stopper (0,5 mL de Ankaferd Blood Stopper, i.p.) y Cd + Ankaferd Blood Stopper ($CdCl_2$ + Ankaferd Blood Stopper, ambos i.p.). Tras el tratamiento, se recolectaron los tejidos cardíacos y se evaluaron mediante tinción histopatológica e inmunohistoquímica de Caspasa-3. También se obtuvieron muestras de sangre para análisis bioquímico. La exposición al cadmio provocó un daño miocárdico marcado, que incluyó infiltración inflamatoria, congestión vascular y fibras musculares desorganizadas. La expresión de Caspasa-3 confirmó un aumento de la actividad apoptótica. La administración de Ankaferd Blood Stopper redujo significativamente las lesiones histopatológicas y la inmunorreactividad de Caspasa-3 en el grupo Cd + Ankaferd Blood Stopper, lo que sugiere un efecto protector. El Ankaferd Blood Stopper atenuó de forma eficaz la lesión cardíaca inducida por cadmio, probablemente gracias a sus propiedades antioxidantes y antiinflamatorias. Estos hallazgos indican que el Ankaferd Blood Stopper podría ofrecer beneficios terapéuticos para prevenir o aliviar el daño cardiovascular inducido por metales pesados. Se recomienda realizar más investigaciones para validar estos efectos en modelos clínicos y a largo plazo.

Palabras clave: Cadmio, daño cardíaco, ankaferd blood stopper, rata

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INTRODUCTION

Ankaferd Blood Stopper® (ABS) is a therapeutic preparation employed in the management of both minor and major bleeding owing to its hemostatic activity. The formulation consists of extracts derived from the root of *Urtica dioica* (nettle), the dried leaves of *Vitis vinifera* (grape) and *Glycyrrhiza glabra* (licorice), the dried rhizome of *Alpinia officinarum* (galangal), and the dried herb of *Thymus vulgaris* (thyme). In recent years, researchers have focused not only on the hemostatic effects of ABS but also on its antioxidant, antimutagenic, and anti-inflammatory properties [1 , 2 , 3].

The term *heavy metal,* which has gained increasing attention in recent years and holds a significant place in the literature, is widely used to describe metals or metalloids often associated with contamination and potential toxicity or eco-toxicity. The definition of heavy metals typically refers to metals with a density greater than 5 g/cm^3 [4 , 5].

Heavy metals can have toxic effects, posing serious health risks, particularly for fetuses, infants, and children, as these groups are more vulnerable to heavy metal exposure due to their higher consumption relative to body weight. Prolonged exposure to high doses of heavy metals during pregnancy facilitates placental transfer, potentially causing severe and permanent brain damage in the fetus. As a result, later in life, affected individuals may experience learning difficulties, memory impairment, and behavioral disorders such as aggression and hyperactivity [6 , 7].

Cadmium (Cd), a toxic heavy metal discovered by Friedrich Stromeyer in 1817, is naturally present in air, water, and soil as part of Group 2B on the periodic table. Cd is a pervasive environmental and occupational pollutant. Today, it is primarily used in the production of nickel-cadmium batteries, pigments, and plastic stabilizers, while its applications in alloys, solders, and galvanization have declined. Additionally, Cd exposure has become inevitable due to its presence as a major compound in cigarettes. Both natural and anthropogenic activities contribute significantly to environmental Cd levels. Occupational exposure to Cd primarily occurs in mining, battery production, Cd-containing pigment manufacturing, Cd alloy processing, and electronic waste recycling. Due to its long biological half-life (15–20 years) and persistence in the environment and body tissues, Cd remains a major public health concern, Moreover, previous experimental studies have shown that toxic exposures can result in cardiac necrosis and histopathological alterations in rodents, highlighting the vulnerability of the heart to toxic agents [6 , 8].

Chronic Cd exposure, even at low doses, leads to its accumulation in the liver, kidneys, and heart due to its long half-life (15–20 years). Regardless of the route of intake, Cd enters the bloodstream and binds to proteins and other blood components [9]. The International Agency for Research on Cancer (IARC) classifies Cd as a human carcinogen. Although Cd is not a strong mitogen, it acts as a tumor promoter (initiator) due to its impact on gene expression. Cd contributes to carcinogenesis through several mechanisms, including abnormal gene expression, inhibition of DNA repair enzymes, oxidative stress induction, and E-cadherin dysfunction. Approximately 5% of ingested Cd is absorbed through the gastrointestinal tract, whereas about 90% of inhaled Cd is absorbed through the lungs. Once absorbed, Cd is rapidly distributed throughout the body, accumulating predominantly in the liver and kidneys, which together constitute the majority of the total Cd body burden [10].

ABS (Ankaferd Health Products Ltd., Istanbul, Turkey) is a hemostatic agent formulated by blending five herbal ingredients in specific proportions, which have been traditionally used in Turkish medicine for centuries. In addition to its hemostatic properties, ABS modulates vascular endothelial function, blood cell activity, angiogenesis, cell proliferation, and vascular dynamics through the regulation of several biological mediators.

MATERIAL AND METHODS

Animals and experimental protocols

This study was approved by the Süleyman Demirel University Animal Experiments Local Ethics Committee with the decision dated September 5, 2024 (No: 06/78). All experiments were conducted at the Süleyman Demirel University Animal Production and Experimental Research Center in accordance with the ethical guidelines established by the committee.

A total of 32 male Wistar Albino rats (*Rattus norvegicus*), weighing 350–450 g, were used in the study. The rats were obtained from the Süleyman Demirel University Animal Production and Experimental Research Center (Isparta, Turkey). The animals were randomly divided into four experimental groups (n = 8 per group) as follows:

- Group I (Control group): Received 0.5 mL of physiological saline intraperitoneally (i.p.).
- Group II (Cadmium ($CdCl_2$) group): Received 2.5 mg/kg cadmium chloride ($CdCl_2$) dissolved in sterile saline at a volume of 1 mL/kg body weight, administered intraperitoneally (i.p.).
- Group III (ABS group): Received 0.5 mL ABSi.p.
- Group IV (Cd + ABS group): Received 2.5 mg/kg $CdCl_2$dissolved in sterile saline at a volume of 1 mL/kg body weight, followed by 0.5 mL of ABS administered intraperitoneally (i.p.).

The ABS group received 0.5 mL/kg ABS (Ankaferd Health Products Ltd., Turkey) intraperitoneally from the right inguinal region on the day of the experiment. The Cd group received 2.5 mg/kg cadmium chloride ($CdCl_2$, Catalog No: 13667, Alfa Aesar, USA) dissolved in sterilsaline and administered intraperitoneally from the right inguinal region [11].

Forthe Cd + ABS group, treatment was administered as follows: $CdCl_2$ (2.5 mg/kg, i.p.) was injected first,and one hourlater,0.5 mL/kg of ABS was administered intraperitoneally at the same site.

One day (d) after Cd administration, all rats were anesthetized using 90 mg/kg Ketamine HCl and 10 mg/kg Xylazine. Following euthanasia, blood and heart tissue samples were collected for biochemical and histopathological analyses.

Histopathological examination

The heart tissues collected from the animals were fixed in 10% buffered formaldehyde solution. Prior to tissue processing, the samples were washed overnight with running tap water, followed by dehydration in graded Ethanol, clearing with Xylene, and embedding in paraffin. Sections of 4–5 µm thickness were obtained from the paraffin blocks using a rotary microtome

(Leica RM2235, Leica Biosystems, Wetzlar, Germany) and subsequently stained with hematoxylin and eosin (H&E).

Histopathological examination and scoring were performed using a light microscope (Zeiss Primo Star, Carl Zeiss Microscopy GmbH, Jena, Germany). A modified semi-quantitative scoring system was applied to evaluate the findings, categorized as follows:

(0): No pathological findings (normal myocardial architecture).

(+1): Mild findings, including slight myofibrillar disorganization or focal nuclear pyknosis. (+2): Moderate findings, such as evident myofibrillar loss, capillary congestion, or localized necrosis.

(+3): Severe findings characterized by extensive myofibrillar degeneration, interstitial edema, and widespread necrosis [12].

Immunohistochemical analyzes

Apoptotic activity was evaluated using immunohistochemical detection of Caspase-3. Tissue sections (4–5 µm thick) were initially deparaffinized and dehydrated. Subsequently, the sections were sequentially incubated with 3% hydrogen peroxide, Ultra-V Block (Thermo Fisher Scientific, Waltham, MA, USA), primary antibodies (Bioss Antibodies, Beijing, China), secondary antibody (Thermo Fisher Scientific, Waltham, MA, USA), and streptavidin peroxidase (Thermo Fisher Scientific, Waltham, MA, USA). The sections were then stained using 3,3'-diaminobenzidine (DAB) solution (Vector Laboratories, Burlingame, CA, USA), followed by nuclear counterstaining with hematoxylin [13].

A previously reported semi-quantitative scoring system was adapted to evaluate immunoreactivity. The intensity of immunostaining was scored as follows:

0: Negative

1: Weak

2: Moderate

3: Strong

The percentage of positively stained cells was calculated and categorized as follows:

0%–4% = 1

5%–19% = 2

20%–39% = 3

40%–59% = 4

60%–79% = 5

80%–100% = 6

A composite "Quick" score was calculated by multiplying intensity and percentage scores to obtain a final immunoreactivity value.

Statistical analysis

The data obtained were analyzed using GraphPad Prism 9 software. One-way ANOVA was performed to compare differences among the groups, and Tukey's test was used to determine significant differences between groups. A P-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSIONS

Histopathology

The histopathological findings are summarized in TABLE I. Longitudinal and cross-sections of the control and ABS groups exhibited normal myocardial histology, with regularly arranged muscle fibers (FIGS. 1; A, E, B, F). No significant differences were observed between the ABS group and the control group (all P > 0.05).

In contrast, the Cd group demonstrated significant histopathological alterations, including pyknotic nuclei, myofiber damage (characterized by loss of striations, eosinophilia, and disorganization), and capillary congestion, when compared to the control group (all P < 0.001) (FIGS. 1; I, J).

However, a significant reduction in myocardial degradation, necrosis, and inflammatory infiltration was observed in the Cd + ABS group compared to the Cd group (all P < 0.001) (FIGS. 1; M, N).

TABLE I
Histopathological findings in cardiac tissue of experimental rat groups

Grup/parameter	Control			Abs			Cd			Cd+Abs		
	Min.	Max.	Med.	Min.	Max.	Med.	Min.	Max.	Med.	Min.	Max.	Med.
Pyknotic nucleus	0	1	0	0	1	0	2	3	2	0	1	0
Myofiber damage	0	1	0	0	1	0	2	3	2.50	0	1	0.50
Capillary cognestion	0	0	0	0	0	0	2	3	3	0	2	1

ABS: Ankaferd Blood Stopper; Cd: Cadmium; Min.: Minimum; Max.: Maximum; Med.: Median.

The table shows the minimum, maximum, and median scores of histopathological alterations observed in the cardiac tissue of rats from the Control, ABS, Cd, and Cd+ABS groups. Parameters evaluated included pyknotic nucleus, myofiber damage, and capillary congestion.

Immunohistochemistry

TABLE II presents the semi-quantitative scoring results for Caspase-3 immunoreactivity across all groups. No immunoreactivity was observed in the control and ABS groups (FIGS. 1; C, D, G, H). Compared to the control group, Caspase-3 activity was significantly increased in the Cd group ($P < 0.001$) (FIGS. 1; K, L). However, a significant reduction in Caspase-3 immunoreactivity was observed in the Cd + ABS group compared to the Cd group ($P < 0.001$) (FIGS. 1; O, P).

TABLE II
Multiplicative Quick score results of caspase-3 immunohistochemistry in cardiac tissue of control and experimental rat groups. Data are presented as median (Q25–Q75), minimum, and maximum values.

Grup/parameter	Control			Abs			Cd			Cd+Abs		
	Med. (Q25-Q75)	Min.	Max.	Med. (Q25-Q75)	Min.	Max.	Med. (Q25-Q75)	Min.	Max.	Med. (Q25-Q75)	Min.	Max.
Caspase-3 immunoreactivity	0 (0-0)	0	0	0 (0-0.5)	0	1	12(10-16.5)	10	18	3(2.5-4)	2	4

ABS: Ankaferd Blood Stopper; Cd: Cadmium; H&E: Hematoxylin and Eosin; Q25–Q75:Interquartile range (25th–75th percentiles), representing the middle 50% of the data distribution.

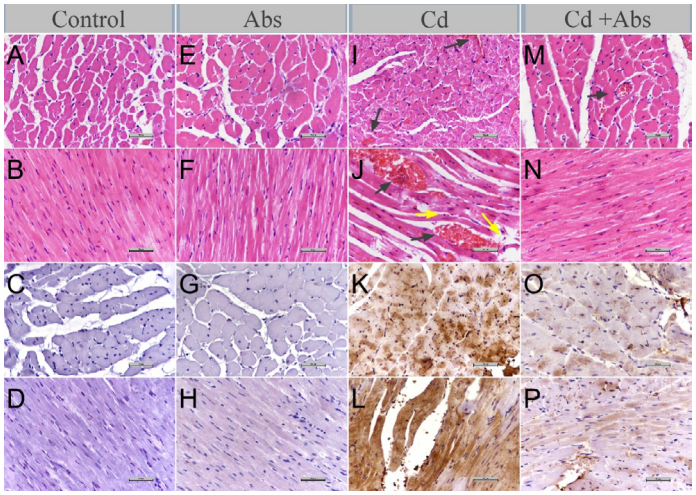

FIGURE 1. Photomicrographs of longitudinal and cross sections of cardiac muscles: In H&E staining, normal cardiac muscle histology with regularly arranged fibrils was observed in the control (A, B) and ABS (E, F) groups. In contrast, the Cd group exhibited pyknotic nuclei (yellow arrow), diffuse vascular congestion (black arrow), and myofibrillar damage characterized by loss of striations, eosinophilia, and muscle disorganization (I, J). A reduction in these pathological findings was observed in the Cd + ABS group compared to the Cd group (M, N). In immunohistochemical analysis, no immunoreactivity was detected in the control (C, D) and ABS (G, H) groups. However, strong Caspase-3 immunoreactivity was observed in the Cd group (K, L). A significant decrease in immunoreactivity was noted in the Cd + ABS group compared to the Cd group (O, P). (Scale bar = 50 µm).

Tissue repair and wound healing are intricate processes involving inflammation, fibroplasia, neovascularization, wound contraction, and epithelial resurfacing of the wound defect [14]. The procoagulant pathway is activated, inflammatory cells are recruited, and the process transitions into phases of cellular proliferation and tissue repair/resolution of damage. One of the primary causes of tissue damage is oxidative reaction products and free radicals [15 , 16].

The term “oxidative stress” refers to an imbalance in redox homeostasis, where the excessive generation of free radicals exceeds the cellular defense mechanisms. Antioxidants are crucial in maintaining protection against oxidative damage [17 , 18]. The first line of defense against oxidative damage consists of antioxidant enzymes such as glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase (CAT) [19]. These enzymes function synergistically, and fluctuations in their activity may push cells into a state of oxidative stress [20]. In this context, CAT and SOD activities have been suggested as valuable biomarkers for assessing healing potential [21 , 22 , 23].

While most previous experimental studies on hemorrhagic disorders have focused on the hemostatic and wound repair effects of therapeutic agents using clinical or histopathological approaches, the effects of ABS on antioxidant enzyme activities such as CAT and SOD have not been explored extensively [24 , 25].

To the best of current knowledge, no prior research has examined the effects of ABS, a local hemostatic agent used in surgery, on CAT and SOD activities. Therefore, this study aimed to investigate the potential effects of ABS on early-stage soft tissue healing in a cadmium-induced injury model by evaluating its impact on CAT and SOD activity.

In this study, Cd was administered intraperitoneally (i.p.) as a single dose of 2.5 mg/kg. Non-biodegradable Cd and cadmium chloride ($CdCl_2$) enter the body and accumulate through bioaccumulation in the food chain, adversely affecting kidney function [26 , 27]. The kidneys, bones, and lungs are the primary target organs for Cd toxicity. Reports on $CdCl_2$ toxicity suggest that metal accumulation in the renal cortex following both sub-chronic and chronic exposure significantly impairs kidney function [28].

Loss of cardiac tissue structural integrity, characterized by complex matrix network formation, focal necrotic areas, fibrosis, and irregular myofibrillar branching, has been documented in previous studies [29 , 30 , 31]. These studies suggest that Cdinduces oxidative stress, which mediates cardiovascular tissue damage. Furthermore, oxidative stress and inflammation are closely associated with Cd exposure [32 , 33]. Similarly, in the present study, necrosis and fibrosis were observed in cadmium-exposed cardiac tissue.

The findings of the present study suggest that i.p. administration of ABS was more effective than oral gavage, in agreement with previous studies [11]. The 0.5 mL i.p. dose used.

In the present study, the therapeutic efficacy of ABS was verified. Thus, identifying an effective dosage of ABS was essential for reducing inflammation. The ii.p administration of ABS at 0.5 mg/kg was found to be effective and beneficial in the present model, providing a suitable framework for future experimental studies requiring animal models. Moreover, the results of the present study indicated that ABS treatment significantly reduced myofibrillar damage in cadmium-exposed animals.

Given the interrelationship between inflammation and oxidative stress, alterations inantioxidant enzyme activity observed in cadmium-treated rats may reflect an increased requirement for CAT and SOD activities. These changes could serve as indirect indicators of systemic inflammation in these animals [34].

ABS is a standardized extract derived from five medicinal plants (*Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum,* and *Urtica dioica*). Several studies have demonstrated that these plants exert beneficial effects on the antioxidant system. Cheel *et al.* [35] (demonstrated that *Glycyrrhiza glabra* exhibits potent antioxidant and free radical scavenging properties. Furthermore, a study by Hong *et al*. [36] reported that *G. glabra* treatment significantly increased blood SOD, CAT, and GSH-Px levels, as well as total antioxidant activity. In this study, ABS exhibited a greater wound-healing potential than NHAA and demonstrated promising effects on SOD activity in the cadmium-treated group.

CONCLUSION

This study demonstrated that cadmium exposure induces significant structural and functional damage in cardiac tissue, primarily through mechanisms involving oxidative stress, inflammation, and apoptosis. The observed histopathological and immunohistochemical changes, including myofibrillar disorganization, vascular congestion, and elevated Caspase-3 expression, confirm the cardiotoxic effects of cadmium.

Importantly, administration of Ankaferd Blood Stopper markedly alleviated these pathological alterations. Ankaferd Blood Stopper significantly reduced myofiber degeneration, inflammation, and apoptotic activity in the myocardium. These protective effects are likely due to the strong antioxidant and anti-inflammatory properties of the phytochemicals contained in Ankaferd Blood Stopper.

The findings of the present study confirm that cadmium exposure induces significant cardiac tissue damage, characterized by oxidative stress, inflammation, and fibrosis. However, Ankaferd Blood Stopper administration significantly reduced inflammatory responses and fibrotic changes in cadmium-exposed heart tissue. These results suggest that Ankaferd Blood Stopper may have therapeutic potential in mitigating cadmium-induced cardiac damage by modulating oxidative stress and inflammation.

The results of the present study highlight the therapeutic potential of Ankaferd Blood Stopper in counteracting heavy metal-induced cardiac injury. Future investigations are warranted to further elucidate the underlying mechanisms and explore clinical applications in occupational and environmental health contexts.

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Declarations

Ethics approval and consent to participate

This study was approved by the Süleyman Demirel University Animal Experiments Local Ethics Committee with the decision dated September 5, 2024 (No: 06/78).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author declares that they have no competing interests.

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Conflict of interest

The author mentioned that they had no conflicts of interest.

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