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# AMELIORATIVE EFFECTS OF HYDROALCOHOLIC OCIMUM BASILICUM LEAF EXTRACT ON BIOCHEMICAL AND HISTOLOGICAL ALTERATIONS IN CISPLATIN-INDUCED CARDIOTOXICITY IN MALE WISTAR RATS

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**ABSTRACT**

Cardiotoxicity is a common side effect of cisplatin (CIS) chemotherapy, often accompanied by gastrointestinal, renal, and hematological toxicities. This study investigated cardioprotective potential of hydroalcoholic basil leaf extract against CIS-induced toxicity in rats, evaluated through Troponin-T, high-sensitivity C-reactive protein (Hs-CRP), superoxide dismutase (SOD), malondialdehyde (MDA) levels, and cardiac histopathology. A quasi-experimental design was employed with eight groups of rats (n = 6 per group): normal, negative control, positive control (vitamin C), and treatment groups receiving basil extract (400 and 800 mg/kg body weight). CIS administration significantly elevated Troponin-T, Hs-CRP, and MDA levels while reducing SOD activity. Treatment with basil extract, particularly at 800 mg/kg, markedly attenuated these changes, restoring biochemical markers toward normal values. Histopathological analysis further confirmed the cardioprotective effect. In conclusion, basil leaf extract demonstrates promising potential as a cardioprotective agent against CIS-induced cardiotoxicity.



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## 1. INTRODUCTION

Cisplatin (CIS) is a platinum-based chemotherapy drug widely used in the treatment of various human cancers, including ovarian, testicular, and bladder malignancies. It can be administered alone or in combination with other anticancer agents [1]. Despite its effectiveness, the clinical application of CIS and related platinum compounds is limited by the development of resistance and toxicity. Understanding the chemical properties, transport, metabolic pathways, and molecular actions of these drugs is therefore essential. Evidence indicates that the therapeutic and toxic effects of platinum drugs arise not only from covalent binding of platinum complexes to DNA but also from interactions with RNA and numerous proteins. These processes contribute to both drug resistance and toxicity. Notably, increased expression of cellular transporters and enhanced repair of platinum-DNA adducts are considered key mechanisms driving resistance to platinum-based chemotherapy [2].

Cardiotoxicity is a well-recognized complication of cancer chemotherapy. Cisplatin (CIS), a potent platinum-based agent, is associated with multiple adverse effects, including myelotoxicity, gastrointestinal toxicity, ototoxicity, neurotoxicity, cardiotoxicity, and nephrotoxicity. The cardiotoxic manifestations of CIS have been documented extensively, ranging from heart failure, angina, acute myocardial infarction, thromboembolic events, autonomic cardiovascular dysfunction to hypertension, hypotension, myocarditis, pericarditis, and severe congestive cardiomyopathy. Reports of CIS-induced arrhythmias include supraventricular tachycardia, ventricular arrhythmias, atrial fibrillation, sinus bradycardia, and, in rare cases, complete atrioventricular block. Proposed mechanisms involve vascular endothelial damage, coronary vasospasm, oxidative and nitrosative stress, impaired platelet function and apoptosis (via the ERK signaling pathway), platelet aggregation, electrolyte imbalance, abnormalities in ventricular repolarization and QT interval, systolic and diastolic dysfunction, reduced cardiomyocyte contractility, mitochondrial injury, and increased endoplasmic reticulum stress. Acute cardiovascular toxicity is thought to result from direct endothelial damage, evidenced by elevated von Willebrand factor released during chemotherapy. Long-term toxicity has been attributed to diffuse endothelial injury and the exacerbation of cardiovascular risk factors, ultimately leading to coronary artery disease, persistent ventricular dysfunction, and severe congestive cardiomyopathy [3].

Basil (Ocimum basilicum L.), a member of the Lamiaceae family, is a rich source of phytochemicals with diverse pharmacological properties [4]. Its bioactive constituents include carotenoids, terpenoids, alkaloids [5], saponins, flavonoids, tannins, and essential oils. These compounds exhibit antioxidant activity, inhibit bacterial growth, and provide therapeutic benefits for digestive disorders [6]. Basil has also been reported to possess renoprotective [7], anticarcinogenic, neuroprotective, cardioprotective, anticoagulant, and immunomodulatory effects [8]), as well as analgesic, antipyretic, anti-inflammatory, antidiabetic, hepatoprotective, hypolipidemic, and anti-stress activities. Furthermore, basil essential oil demonstrates fungistatic, insecticidal, and nematicidal properties [9]. Spectroscopic analysis has identified a tetracyclic triterpenoid as one of its isolated bioactive compounds [10]. The antioxidant content of basil leaves has been shown to confer protective effects against pathological conditions such as atherosclerosis, ischemia, cancer, cataracts, and liver dysfunction [11]. Notably, studies on hydroalcoholic extracts of basil leaves have demonstrated both therapeutic and prophylactic value in the management of Myocardial infarction [12].

Based on the background outlined above, this study aims to evaluate the ameliorative effects of hydroalcoholic Ocimum basilicum leaf extract on cisplatin-induced cardiotoxicity in male Wistar rats. Cardiotoxicity was assessed through serum biomarkers (Troponin-T, Hs-CRP, SOD, MDA) and cardiac histopathology. The working hypothesis proposed that basil leaf extract would mitigate both biochemical and histological indicators of cardiotoxicity compared with the cisplatin-only group.

## 2. RESEARCH METHOD

### 2.1 Materials

The materials used in this study included surgical instruments, laboratory glassware, aluminum foil, a blender (Miyako), porcelain cups and crucibles, a desiccator, incubator, drying cabinet, microtubes, slides and cover slips, test tube racks and clamps, cuvettes, and a vortex mixer. Additional equipment comprised a light microscope, analytical balance (Vibra AJ), oral sonde, electric oven (Stork), water bath (Yenaco), rotary evaporator, centrifuge, moisture determination apparatus, UV spectrophotometer (Microlet 3000), furnace (Nabertherm), veterinary scales (Presica), a spectrophotometer capable of absorbance readings at 340 nm, accurate pipetting devices, interval timers, and a constant-temperature bath or heating block set at $37^0C$.

The reagents used were hydroalcoholic basil leaf extract, cisplatin, NaCl, 10% formalin, CMC-Na, chloroform, metformin, hs-TnT reagent, hs-CRP reagent, SOD reagent, calcium carbonate (CaCO3), EDTA, liquid paraffin, toluene, and acetone.

## 2.2 Extraction Protocol

The hydroalcoholic extract of basil leaves (EHDK) was prepared using an ultrasound-assisted extraction method. Approximately 500 g of basil leaf powder was subjected to cold hydroalcoholic percolation with 96% ethanol at a powder-to-solvent ratio of 1:1 (w/v). The mixture was agitated for 48 hours at 200-250 rpm and then filtered through filter paper. Maceration and ultrasound-assisted extraction were repeated until a clear filtrate was obtained. The ethanolic extract was subsequently concentrated using a rotary evaporator at $45 - 50^0C$, followed by evaporation in a water bath to remove residual solvent. The resulting residue was weighed to determine the extractive yield and stored in an airtight container at $4^0C$ [13].

## 2.3 Animals

Male Wistar rats (Rattus norvegicus), approximately 2 months old and weighing around 200 g, were used in this study. The animals were acclimatized for 2 weeks, provided with ABS-2 pellets (5-10 g/day), and given drinking water ad libitum. Prior to cisplatin induction, the rats were fasted for 12 hours. Cisplatin was freshly prepared by dissolving in 0.01 M citrate buffer (pH 4.5), and used within 10-15 minutes. It was administered intraperitoneally, with the dose adjusted according to body weight.

## 2.4 Experimental Design

Inclusion Criteria

The inclusion criteria in this study were:

a. Age 2.5 - 3 months

b. Weight 180 - 220 grams

c. Male gender

d. Healthy condition (active and not disabled)

Exclusion Criteria

The exclusion criteria in this study were:

a. Male white rats are not active

b. Male white rats died during the study period

Table 1: Experimental group design and treatment schedule

| No. | Group | Induction | Sample |
|---|---|---|---|
| 1. | Normal | (-) | (-) |
| 2. | Control (-) | Cisplatin 10 mg/kg BW | (-) |
| 3. | Positive control 1 | Cisplatin 10 mg/kg BW<br>Day 1 | Vitamin C 1.62 mg/kg BW<br>Day 3 |
| 4. | Positive control 2 | Cisplatin 10 mg/kg BW<br>Day 3 | Vitamin C 1.62 mg/kg BW<br>Day 1 |
| 5. | Test 1 (400) | Cisplatin 10 mg/kg BW<br>Day 1 | EHDK 400 mg/kg BW<br>Day 3 |
| 6. | Test 2 (400) | Cisplatin 10 mg/kg BW<br>Day 3 | EHDK 400 mg/kg BW<br>Day 1 |
| 7. | Test 3 (800) | Cisplatin 10 mg/kg BW<br>Day 1 | EHDK 800 mg/kg BW<br>Day 3 |
| 8. | Test 4 (800) | Cisplatin 10 mg/kg BW<br>Day 3 | EHDK 800 mg/kg BW<br>Day 1 |

In groups 3 and 4 (positive controls 1 and 2), using Vitamin C as a positive control because the content of vitamin C in basil leaves (18 mg) is more than that of vitamin E (0.8 mg), according to [14] C can reduce oxidative stress levels, which may have a major role in the pathogenesis of atherosclerosis and CVD.

## 2.5 Data Analysis

The data were analyzed using SPSS version 22. Normality was tested using the Shapiro-Wilk test ($p > 0.05$), followed by a homogeneity test. Parametric data were analyzed using one-way ANOVA, and significant differences ($p < 0.05$) were followed by Tukey's HSD post hoc test. If the data were not normally distributed, the Kruskal-Wallis test was used.

# 3. RESULTS

## 3.1 Phytochemical Screening Results

The phytochemical screening results are presented in Table 2.

Table 2: Phytochemical screening results.

| No. | Compound | Result |
|---|---|---|
| 1. | Flavonoid | + |
| 2. | Alkaloid | + |
| 3. | Tannin | + |
| 4. | Saponin | + |
| 5. | Glycoside | - |
| 6. | Steroid | - |

Information:

(+) The extract contains compounds.

(-) The extract does not contain any compounds.

Table 2 shows that the hydroalcoholic extract of basil leaves contains flavonoid compounds, alkaloids, tannins, saponins, and glycosides. While steroids are not densely packed in extracts because hydroalcoholic extracts are polar solvents, non-polar compounds such as steroids cannot be attracted unless these compounds have other groups attached to polar compounds such as flavonoids or glycosides.

## 3.2 Troponin-T Levels

As shown in Table 3, cisplatin induction markedly increased serum Troponin-T levels, whereas treatment with EHDK reduced these levels toward the normal range.

Table 3: Effect of EHDK on serum Troponin-T levels in cisplatin-induced rats

| No. | Groups | Induction | Test material | Troponin-T levels (ng/mL ± SD) |
|---|---|---|---|---|
| 1. | Normal | (-) | (-) | 10,37 ± 0,188* |
| 2. | Control (-) | CIS 10 mg/kg BW | (-) | 180,89 ± 1,974 |
| 3. | Positive control 1 | CIS 10 mg/kg BW Day 1 | Vitamin C 1.62 mg/kg BW Day 3 | 15,89 ± 3,984* |
| 4. | Positive control 2 | CIS 10 mg/kg BW Day 3 | Vitamin C 1.62 mg/kg BW Day 1 | 12,84 ± 4,873* |
| 5. | Test 1 (400) | CIS 10 mg/kg BW Day 1 | EHDK 400 mg/kg BW Day 3 | 35,753 ± 2,873* |
| 6. | Test 2 (400) | CIS 10 mg/kg BW Day 3 | EHDK 400 mg/kg BW Day 1 | 30,89 ± 8,41* |
| 7. | Test 3 (800) | CIS 10 mg/kg BW Day 1 | EHDK 800 mg/kg BW Day 3 | 12,84 ± 2,984* |
| 8. | Test 4 (800) | CIS 10 mg/kg BW Day 3 | EHDK 800 mg/kg BW Day 1 | 10,83 ± 3,644* |

$*p < 0.05$ versus the negative control group.

The cTnT levels in the cisplatin (CIS) treatment group were the highest and significantly different from all other groups. This elevation is attributed to CIS-induced free radical formation, which increases oxidative stress through reactive species such as superoxide anions and hydrogen peroxide (H2O2). Although the redox cycle of the quinone moiety does not alter the anthracycline chromophore, it may contribute to cardiotoxicity by generating reactive oxygen species (ROS) beyond the detoxification capacity of cardiomyocytes [15]. Because approximately 50% of cardiomyocyte organelles are mitochondria, these cells are particularly vulnerable to CIS-induced damage [16]. Oxidative stress disrupts Ca2+ homeostasis by inducing mitochondrial permeability transition and altering calcium transport, ultimately leading to cardiac cell injury or death [17] and the release of biomarkers into the circulation.

Flavonoids exert protective effects primarily through their antioxidant activity, including iron chelation [18] and inhibition of carbonyl reductase-1 (CBR-1) [19]. They also safeguard intracellular calcium regulation [20], thereby preventing myocardial damage. As antioxidants, flavonoids can directly interact with Ca2+-ATPase [21], inhibit cardiomyocyte apoptosis, and protect against calcium depletion [22].

When cisplatin (CIS) generates free radicals, endogenous antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase can neutralize these reactive species [23]. However, the heart contains relatively low levels of endogenous antioxidants, making it the primary target for CIS-induced oxidative damage [24]. Flavonoids enhance the activity of endogenous antioxidants and further reduce free radical burden [25]. They inhibit key enzymes involved in superoxide xanthine, such as xanthine oxidase, and also suppress cyclooxygenase, lipoxygenase, and NADH oxidase, thereby limiting free radical generation [26].

Iron strongly catalyzes the formation of hydroxyl radicals ($OH$) in two key steps. First, the ferric cisplatin ($Fe3+$)-CIS complex is reduced to a ferrous complex (FeTT 2+)-CIS, which can react with $O_2$ to generate superoxide ($O2-$). This superoxide is subsequently converted to $H_2O_2$ or reduced to OH. Second, the ferrous CIS complex reacts directly with $H_2O_2$ (produced during CIS reduction), resulting in hydroxyl radical formation (Torres and Simic, 2012). Flavonoids inhibit the formation of iron chelates [27], thereby preventing the generation of these free radicals. In addition, flavonoids possess strong antioxidant activity [28], which contributes to their protective role against CIS-induced cardiotoxicity [29]. Beyond direct radical scavenging, basil extract may also enhance endogenous antioxidant activity in the heart [30].

Antioxidant testing has confirmed that basil reduces free radical levels. In the vitamin C group treated with CIS, normal myofibril structures were preserved, and hemorrhage was minimal, indicating that vitamin C effectively mitigates free radical damage. Vitamin C, a potent antioxidant, reduces lipid peroxidation, lipid peroxides, inhibits cell apoptosis, maintains cell morphology by stabilizing the cytoskeleton, and stimulates cardiomyocytes to repair damage following CIS exposure [31].

## 3.3 Hs-CRP Levels

As shown in Table 4, serum Hs-CRP levels were highest in the cisplatin-only group and decreased following treatment with vitamin C or EHDK.

Hs-CRP is a chronic inflammatory marker synthesized by the liver, and elevated levels are recognized as an independent risk factor for cardiovascular disease (Verma, 2004; Ramanand, 2014). Purba's study demonstrated a significant association between increased hs-CRP levels and vessel score (p-value = 0.0001), with higher hs-CRP concentrations correlating with coronary artery stenosis greater than 50% (Amanullah, 2010). Similarly, Blackburn et al. reported in a cohort of 1,051 dyslipidemic patients that elevated CRP was significantly associated with the severity of carotid artery stenosis ($p - value < 0.0001$) [32].

Although the precise mechanism linking dyslipidemia and inflammation remains unclear, epidemiological data indicate that dyslipidemic patients exist in a proinflammatory state characterized by increased cytokines, such as TNF- and IL-6, which stimulate hs-CRP and CAM expression. Inflammation within arterial walls is particularly driven by oxidized LDL. Evidence further suggests that hs-CRP may directly contribute to atherogenesis by inducing ICAM expression. Both oxidized LDL and superoxide anions in hypercholesterolemic patients impair nitric oxide (NO) release and production, leading to endothelial dysfunction and subsequent expression of inflammatory mediators (Tang, 2014).

Table 4: Effect of EHDK on serum Hs-CRP levels in cisplatin-induced rats

| No. | Groups | Induction | Test material | Hs-CRP levels (ng/mL ± SD) |
|---|---|---|---|---|
| 1. | Normal | (-) | (-) | 25,83 ± 6,873* |
| 2. | Control (-) | CIS 10 mg/kg BW | (-) | 102,784 ± 1,983 |
| 3. | Positive control 1 | CIS 10 mg/kg BW Day 1 | Vitamin C 1.62 mg/kg BW Day 3 | 35,78 ± 4,783* |
| 4. | Positive control 2 | CIS 10 mg/kg BW Day 3 | Vitamin C 1.62 mg/kg BW Day 1 | 30,783 ± 2,461* |
| 5. | Test 1 (400) | CIS 10 mg/kg BW Day 1 | EHDK 400 mg/kg BW Day 3 | 40,731 ± 5,74* |
| 6. | Test 2 (400) | CIS 10 mg/kg BW Day 3 | EHDK 400 mg/kg BW Day 1 | 41,873 ± 3,861* |
| 7. | Test 3 (800) | CIS 10 mg/kg BW Day 1 | EHDK 800 mg/kg BW Day 3 | 31,974 ± 5,973* |
| 8. | Test 4 (800) | CIS 10 mg/kg BW Day 3 | EHDK 800 mg/kg BW Day 1 | 27,734 ± 1,983* |

### 3.4 SOD Levels

As shown in Table 5, cisplatin administration decreased SOD levels, whereas EHDK treatment increased SOD toward the normal group values.

Three forms of superoxide dismutase in humans: Cu-Zn-SOD or SOD1 is located in the cytosol and nucleus, Mn-SOD or SOD2 is in the mitochondria, and extracellular SOD (EC-SOD) or SOD3 is extracellular. SOD1 and SOD3 contain copper and zinc, while SOD2, a mitochondrial enzyme, contains manganese. 20,25-28 Among the SOD isoenzymes, Mn-SOD is the first and the most important of the defenses against toxic superoxide ion. Second, CuZn-SOD in the cytosol also supports the protective function of MnSOD by neutralizing O2- in the cytosol and that leaks from the mitochondria. EC-SOD will neutralize O2- on the outside of the cell surface and in the extracellular matrix and fluids. In addition to protecting the cell surface but also removes O2- from blood vessels.

ROS are atoms or small molecules that do not have electron pairs that are ready to accept other electrons or transfer unpaired electrons to other molecules. ROS are normally produced by cellular metabolism, but changes in the amount and nature of ROS are released in various disease states. Among the ROS produced by living cells, O2- is a proinflammatory compound that damages cells. O2- damages endothelial cells, increases microvascular permeability, and promotes neutrophil migration at foci of inflammation. The concentration of ROS is regulated by a balance between the production and elimination of ROS by antioxidants. Proper balance is essential for normal cell and tissue function. ROS are produced in many metabolic processes, including mitochondrial respiration and enzyme activity (cytochrome P-450, NADPH oxidase, myeloperoxidase, NO synthase, and xanthine oxidase). Antioxidant enzymes capture ROS present in the body, including SOD, glutathione peroxidase, and catalase. In addition, water-soluble antioxidants (glutathine, vitamin C, and uric acid) and fat-soluble antioxidants (vitamin E, carotenoids, and bilirubin) are essential for protecting cell membranes and plasma lipoproteins. SOD catalyzes the dismutation of O2- into O2 and H2O2.

Superoxide radicals or anions (negatively charged atoms) are produced when oxygen has an excess of electrons. This occurs through normal metabolic processes, such as the catalytic transformation of various molecules by enzymes. SOD is responsible for catalyzing the conversion of superoxide to oxygen and hydrogen peroxide. This transformation is called dismutation, which is the name of the enzyme.4 Although H2O2 is also a pro-oxidant compound, it is then converted by the enzyme catalase in lysosomes or glutathione peroxidase in the mitochondria into water and oxygen.

Table 5. Representative cardiac histopathology images for all groups are presented in Figures 1-4.

Table 5: Effect of EHDK on serum SOD levels in cisplatin-induced rats.

| No. | Groups | Induction | Test material | SOD levels (ng/mL ± SD) |
|---|---|---|---|---|
| 1. | Normal | (-) | (-) | 50,873 ± 1,73* |
| 2. | Control (-) | CIS 10 mg/kg BW | (-) | 10,874 ± 2,87 |
| 3. | Positive control 1 | CIS 10 mg/kg BW Day 1 | Vitamin C 1.62 mg/kg BW Day 3 | 51,85 ± 2,084* |
| 4. | Positive control 2 | CIS 10 mg/kg BW Day 3 | Vitamin C 1.62 mg/kg BW Day 1 | 53,83 ± 7,39* |
| 5. | Test 1 (400) | CIS 10 mg/kg BW Day 1 | EHDK 400 mg/kg BW Day 3 | 30,873 ± 2,863* |
| 6. | Test 2 (400) | CIS 10 mg/kg BW Day 3 | EHDK 400 mg/kg BW Day 1 | 32,873 ± 1,973* |
| 7. | Test 3 (800) | CIS 10 mg/kg BW Day 1 | EHDK 800 mg/kg BW Day 3 | 48,863 ± 5,29* |
| 8. | Test 4 (800) | CIS 10 mg/kg BW Day 3 | EHDK 800 mg/kg BW Day 1 | 52,868 ± 8,376* |

## 3.5 MDA Levels

As shown in Table 6, MDA levels increased markedly after cisplatin induction and decreased after treatment with EHDK, especially at the 800 mg/kg BW dose.

Table 6: Effect of EHDK on serum MDA levels in cisplatin-induced rats.

| No. | Groups | Induction | Test material | MDA levels (ng/mL ± SD) |
|---|---|---|---|---|
| 1. | Normal | (-) | (-) | 5,12 ± 0,66* |
| 2. | Control (-) | CIS 10 mg/kg BW | (-) | 40,78 ± 1,46 |
| 3. | Positive control 1 | CIS 10 mg/kg BW Day 1 | Vitamin C 1.62 mg/kg BW Day 3 | 7,12 ± 0,983* |
| 4. | Positive control 2 | CIS 10 mg/kg BW Day 3 | Vitamin C 1.62 mg/kg BW Day 1 | 6,41 ± 0,44* |
| 5. | Test 1 (400) | CIS 10 mg/kg BW Day 1 | EHDK 400 mg/kg BW Day 3 | 12,30 ± 2,53* |
| 6. | Test 2 (400) | CIS 10 mg/kg BW Day 3 | EHDK 400 mg/kg BW Day 1 | 12,01 ± 1,36* |
| 7. | Test 3 (800) | CIS 10 mg/kg BW Day 1 | EHDK 800 mg/kg BW Day 3 | 6,653 ± 0,75* |
| 8. | Test 4 (800) | CIS 10 mg/kg BW Day 3 | EHDK 800 mg/kg BW Day 1 | 5,11 ± 0,63* |

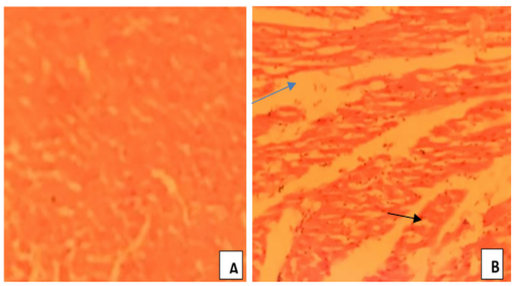


Figure 1: Cardiac histopathology results. (A) Normal group; (B) negative control group.

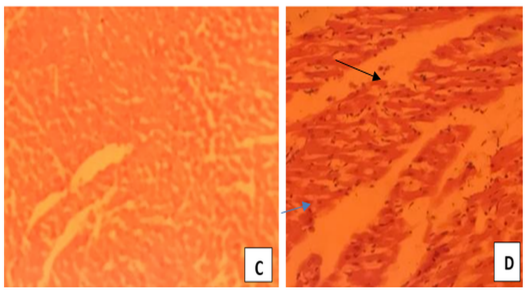


Figure 2: Cardiac histopathology results. (C) Positive control 1; (D) positive control 2.

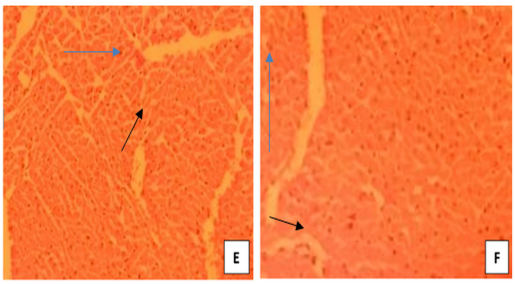


Figure 3: Cardiac histopathology results. (E) EHDK 400 mg/kg BW, regimen 1; (F) EHDK 400 mg/kg BW, regimen 2.

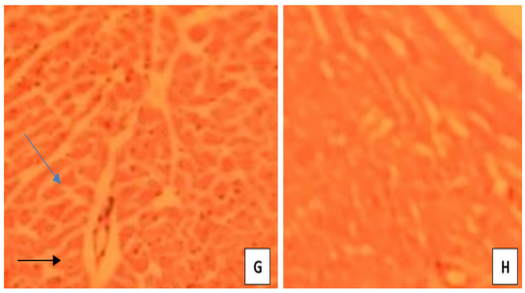


Figure 4: Cardiac histopathology results. (G) EHDK 800 mg/kg BW, regimen 1; (H) EHDK 800 mg/kg BW, regimen 2.

As shown in Figures 1-4, the cisplatin-only group exhibited the most severe histopathological alteration, whereas the treatment groups showed less congestion and necrosis, particularly at the 800 mg/kg BW dose. Blue arrows indicate vascular congestion, and black arrows indicate myocyte necrosis.

## 4. CONCLUSION

This study demonstrated that hydroalcoholic basil leaf extract exerted protective effects against cisplatin-induced cardiotoxicity in male Wistar rats. Among the biochemical parameters assessed, the 800 mg/kg BW dose produced values most comparable to the normal group, with reduced Troponin-T, Hs-CRP, and MDA levels and elevated SOD activity relative to the cisplatin-only group. Histopathological findings corroborated these results, indicating reduced cardiac injury following EHDK treatment. Collectively, the findings support the cardioprotective potential of basil leaf extract, although further methodological refinement and quantitative histopathological analysis are still needed to enhance reproducibility and strengthen interpretation.

## 5. ACKNOWLEDGMENTS

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