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Caesalpinia digyna root extract and bergenin alleviate myocardial infarction in rats by modulating oxidative stress, inflammation, and fibrotic pathways

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ABSTRACT

Objective: To evaluate the cardioprotective potential of *Caesalpinia digyna* root extract (CDRE) and its major bioactive constituent, bergenin, against isoproterenol (ISO)-induced myocardial infarction (MI) in rats.

Methods: CDRE was prepared *via* methanolic extraction and standardized using RP-HPLC. MI was induced in Sprague-Dawley rats by ISO administration. Animals were pretreated with the extract and bergenin prior to the ISO challenge. Cardioprotective effects were assessed by measuring serum cardiac biomarkers, evaluating myocardial hypertrophy, inflammation, and fibrosis, and determining the expression of Nrf2, FGF21, NF-κB p65, and brain natriuretic peptide.

Results: Pretreatment with the CDRE and bergenin significantly attenuated ISO-induced MI, as evidenced by reduced creatine kinase-MB and lactate dehydrogenase levels and improved histopathological architecture. CDRE and bergenin markedly alleviated myocardial hypertrophy, inflammatory infiltration, and fibrotic changes. They also upregulated Nrf2 and FGF21 expression, and downregulated NF-κB p65 and brain natriuretic peptide expression.

Conclusions: The findings demonstrate significant cardioprotective effects of CDRE and bergenin, by modulating oxidative stress, inflammation, and fibrotic pathways, validating its traditional use for the management of MI.

KEYWORDS: *Caesalpinia digyna*; Bergenin; Isoproterenol; Myocardial infarction; Myocardial damage

1. Introduction

Cardiovascular disease (CVD) encompasses a group of heart and vascular disorders, including coronary artery disease, cerebrovascular

Summary

Question: Do *Caesalpinia digyna* root extract (CDRE) and bergenin attenuate isoproterenol-induced myocardial infarction *via* modulation of cardiac remodeling events?

Findings: Pretreatment with CDRE and bergenin significantly reduced serum myocardial injury markers and myocardial inflammation, fibrosis, and cardiomyocyte cross-sectional area. CDRE and bergenin also lowered the levels of malondialdehyde, tumor necrosis factor-α, transforming growth factor-β1, and brain natriuretic peptide. Furthermore, they upregulated antioxidant and metabolic regulators Nrf2 and FGF21, while downregulating NF-κB p65 and brain natriuretic peptide expression.

Meaning: Pretreatment with CDRE and bergenin conferred significant cardioprotection against isoproterenol-induced myocardial infarction by modulating oxidative stress, inflammation, and fibrotic remodeling pathways. These findings highlight their promise as natural therapeutic candidates for the management of cardiovascular diseases.

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disease, myocardial infarction (MI), pulmonary embolism, deep vein thrombosis, *etc.* According to the World Health Organization, CVD has remained the leading cause of mortality worldwide for over a decade, accounting for 32% of all global deaths[1]. According to global projections, the burden of CVDs is expected to rise sharply from 2025 to 2050, with prevalence increasing by 90%, crude mortality by 73.4%, and crude disability-adjusted life years by 54.7%, culminating in an estimated 35.6 million deaths in 2050 compared to 20.5 million in 2025[2]. Among CVDs, MI is the most clinically encountered form of ischaemic heart disease and a major cause of morbidity and mortality worldwide. MI is characterized by the necrosis of cardiomyocytes resulting from an imbalance between myocardial oxygen demand and coronary blood supply[3,4].

In the event of myocardial ischaemia, the excessive production of reactive oxygen species (ROS) plays a pivotal role in inducing oxidative stress, which eventually leads to cardiomyocyte apoptosis[3–5]. The ROS generation triggers a robust inflammatory response, and to compensate for the irreversible loss of cardiac tissue, the heart undergoes repair and remodeling processes such as cardiac hypertrophy and cardiac fibrosis[4,5]. As a result, antioxidants have gained increasing attention as a therapeutic intervention to prevent and mitigate progression of MI[6]. However, the clinical application of synthetic antioxidants is constrained by potential toxicity and adverse effects, driving growing interest in natural antioxidants, which are considered safer and more biocompatible.

To investigate the cardioprotective potential of naturally derived antioxidants, the well-established rat model of isoproterenol (ISO)-induced MI was utilized, given its reproducibility and close resemblance to human pathological features. ISO, a β -adrenergic sympathomimetic agonist, causes severe cardiac stress through positive chronotropic and inotropic effects, accompanied by excessive ROS. These effects closely mimic the morphological and metabolic changes observed in human acute MI[6–9].

Among the numerous natural medicinal plants, *Caesalpinia digyna* (*C. digyna*) (family: Leguminosae) has drawn remarkable attention for its pharmacological properties and traditional use in a wide variety of ailments. *C. digyna* is a large scandent thorny shrub native to the Eastern Himalayas and Eastern Ghats, with a maximum growth height of 10 meters. It is used traditionally as an antidiabetic, astringent, nervine tonic, and febrifuge. It is also applied externally to relieve sores and has been used in the treatment of phthisis and scrofulous conditions[10]. Commercially, it is a key ingredient of Geriforte®—a rejuvenating tonic manufactured by Himalaya Drug Co. Geriforte® is designed for systemic health improvement and has been reported to significantly improve antioxidant status, thereby reducing oxidative stress in elder patients[11]. In addition, Geriforte® has been reported to exhibit immunomodulatory properties and eliminate harmful effects caused by radiation[12,13]. Phytochemical investigations on the roots of *C. digyna* have identified various

bioactive constituents, including bergenin (a major compound), caesalpinflavans D-F, caesalpinine A, caesalpinine C, caesalpinnone B, ellagic acid, gallic acid, intricatinol, pipecolic acid, and tannins[14–17].

Several pharmacological studies have reported its diverse bioactivities. *In vitro* assays revealed significant inhibitory effects on α -glucosidase, α -amylase, and dipeptidyl peptidase-IV, supporting its antidiabetic potential[10,18]. In *in vivo* assays, *C. digyna* root extract (CDRE) significantly reduced blood glucose levels in streptozotocin (STZ)-induced diabetic rats[10] and lowered blood pressure in *N*-nitro-L-arginine methyl ester-induced hypertensive rats[19]. Further, the methanolic extract of *C. digyna* (Rottl.) leaves exerts prominent *in vitro* thrombolytic activity by dissolving human blood clots, along with significant dose-dependent antinociceptive and anti-inflammatory activities. Moreover, ADMET analysis and molecular docking studies revealed that the isolated compounds caesalpinine A and caesalpinine C possess promising antinociceptive activity by targeting cyclooxygenase (COX-1 and COX-2) and thrombolytic activity *via* binding to tissue plasminogen activator[17]. In a recent study, the ethyl acetate extract of *C. digyna* (Rottl.) fruit demonstrated potent anti-breast cancer activity against MCF-7 and MDA-MB-231 cell lines, with IC₅₀ values of (23.53 $\pm$ 1.61) μ g/mL and (15.57 $\pm$ 3.74) μ g/mL, respectively[14].

The antioxidant properties of *C. digyna* have been well documented. The root and fruit extract and its active constituent, bergenin, exhibited potent *in vitro* free radical scavenging activity against ABTS, DPPH, hydrogen peroxide, hydroxyl, and superoxide radicals. These bioactive components also inhibit lipid peroxidation in a dose-dependent manner and enhance endogenous antioxidant enzymes such as catalase and superoxide dismutase[11,14,16]. Similar antioxidant effects were observed in STZ-induced diabetic rats treated with CDRE (500 and 750 mg/kg body weight) and bergenin (10 mg/kg body weight)[10]. Further, in *N*-nitro-L-arginine methyl ester-induced hypertensive rats, CDRE at doses of 200 and 400 mg/kg body weight significantly elevated nitric oxide and cGMP levels, along with activities of enzymatic and non-enzymatic antioxidants[19]. The methanolic leaf extract of *C. digyna* also demonstrated notable *in vitro* antioxidant and anti-inflammatory activities and alleviated carrageenan-induced paw edema in mice at 400 mg/kg[16].

Bergenin, the principal phytoconstituent of *C. digyna* root, exhibited pronounced antidiabetic, antioxidant, and hypolipidemic effects in STZ-induced type 2 diabetic rats following 14 days of continuous administration at 10 mg/kg/day[10]. Moreover, bergenin (3 mg/kg/day) significantly reduced cardiac injury markers, including cardiac troponin I, creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), while mitigating ST-segment elevation, and suppressing inflammatory responses in ISO-induced MI rats[20]. Pretreatment with bergenin also ameliorated myocardial inflammation,

oxidative stress, fibrosis, and ferroptosis in rats with left anterior descending artery-induced ischemia-reperfusion injury. *In vitro*, bergenin mitigated oxidative stress, ferroptosis, and mitochondrial dysfunction in oxygen-glucose deprivation/reoxygenation-stimulated H9C2 cells, which were mediated by activation of SIRT1 signaling pathway, 5'adenosine monophosphate-activated protein kinase phosphorylation, and peroxisome proliferator-activated receptor-gamma coactivator-1alpha expression[21].

To date, studies on the cardioprotective potential of *C. digyna* are few. However, its well-documented antioxidant and anti-inflammatory properties, strongly suggest its potential cardioprotective activity. Altogether, the aforementioned pharmacological findings substantiate the traditional use of *C. digyna* and its constituent bergenin. Hence, the present study aims to evaluate the cardioprotective potential of *C. digyna* root extract and to compare its efficacy with pure bergenin.

2. Methods

2.1. Plant materials

C. digyna root powder was purchased from Abirami Botanical, Tamil Nadu, India. Pure bergenin powder was purchased from Carbosynth Limited, Compton, United Kingdom.

2.2. Chemicals

Blocking One Solution was purchased from Nacalai Tesque Inc., Kyoto, Japan, and diethyl ether was obtained from Fisher Scientific, New Hampshire, United States of America. ISO was sourced from Tokyo Chemical Industry Co. Ltd., Tokyo, Japan, while ketamine, xylazine, and tiletamine were obtained from National University of Malaysia, Selangor, Malaysia. Methanol was purchased from Thermo Fisher, Massachusetts, USA, and phosphate-buffered saline was obtained from Vivantis Technologies Sdn Bhd, Selangor, Malaysia. Radioimmunoprecipitation assay buffer was purchased from Cayman Chemicals, Michigan, USA.

2.3. Extraction of plant materials

C. digyna root powder was successively extracted (100 g) with 500 mL of methanol (50 °C) in a Soxhlet extractor for 8 h. The resulting CDRE was concentrated to dryness at 65 °C under reduced pressure (101 kPa) using a rotary evaporator. The methanolic extract yielded dark brown solid residues weighing 2.71 g (2.71%). The extract was stored at room temperature until further use.

2.4. HPLC analysis

CDRE was standardized using bergenin as a marker compound and analyzed for the presence of other phytochemicals (*p*-coumaric acid and quercetin) by reversed-phase high-performance liquid chromatography.

2.4.1. Bergenin standardization

Bergenin (1 mg) was dissolved in 1 mL of methanol to prepare the stock solution. Standard bergenin solution with concentrations 10, 20, 30, 40, and 50 µg/mL was prepared by diluting the stock solution with the mobile phase and used to plot the calibration curve. Separation was achieved on an Ascentis Express C8 column (15 cm × 4.6 mm i.d., 5 µm) with a mobile phase consisting of methanol and water at a volume ratio of 20:80 delivered at a flow rate of 1.0 mL/min. Detection was performed at 275 nm, and the retention time of bergenin was found to be 6.311 min. The mobile phase was filtered through a 0.2 µm membrane filter and degassed before use. The injection volume was 20 µL, and analyses were performed at ambient temperature.

2.4.2. Phytochemicals identification

Individual standard solutions of *p*-coumaric acid and quercetin (10 µg/mL each) were prepared and injected into the column under gradient elution conditions. The mobile phase consisted of methanol and water with gradient ratios of 70:30, 60:40, 40:60, 20:80, and 5:95 at 0, 3, 5, 8, and 11 min, respectively. The flow rate was maintained at 1.0 mL/min, and detection was performed at 275 nm. The retention times of *p*-coumaric acid and quercetin were 6.741 and 8.215 min, respectively. For all analyses, the mobile phase was filtered through a 0.2 µm membrane filter and degassed, with an injection volume of 20 µL, and all experiments were performed at ambient temperature.

2.5. Experimental animals and study design

Male Sprague-Dawley rats (7-8 weeks old) were obtained from the Animal Holding Facility, Monash University Malaysia. Animals were maintained under standard environment conditions (room temperature, 12-hour light/12-hour dark cycle), and were fed with standard rat chow and water *ad libitum*. The animals were allowed to acclimatize to the animal holding facility for one week before the start of experimental procedures.

Rats were randomly divided into five groups (*n*=5 per group). Group 1 (normal control) and group 2 (disease control) received 0.5% carboxymethyl cellulose orally for 14 d. Group 3 and 4 received CDRE at doses of 200 and 400 mg/kg body weight, respectively, while group 5 received bergenin at 10 mg/kg body

weight[10,16,19]. All treatments were administered by oral gavage once daily for 14 d. On day 13, Groups 2-5 were challenged with ISO at 85 mg/kg body weight. All animals in each group were weighed prior to the administration of anesthesia. 24 hours after ISO administration, all animals were euthanized using an overdose of a mixed anesthetic consisting of ketamine, xylazine, and tiletamine. Blood samples and heart tissues were subsequently collected for biochemical, histological, and molecular analyses. In addition, heart weight (HW) and the heart weight-to-body weight ratio (HW/BW) were determined.

2.5.1. Biochemical analysis

The collected blood samples were subjected to centrifugation at 14 000 rpm for 15 min at 4 °C. The supernatant (serum) was carefully separated and stored until analysis. Serum samples were sent to Universiti Putra Malaysia, Selangor, Malaysia, for the determination of CK-MB, LDH, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG).

2.5.2. Histological analysis

The midsection of the heart was fixed in 10% neutral buffered formalin and utilized for histological evaluation. Hematoxylin and eosin staining was performed to assess myocardial inflammation and hypertrophy, while Masson's trichrome staining was used to evaluate collagen deposition and fibrosis. For the inflammatory and fibrotic assessments, images were captured at 10× magnification using a light microscope, whereas cardiomyocyte cross-sectional area was measured from the hematoxylin and eosin-stained sections at 40× magnification. Area of inflammation and fibrosis, along with cardiomyocyte cross-sectional area, were quantified using ImageJ software (NIH, USA).

2.5.3. Assessment of oxidative stress, inflammation, fibrosis, and hypertrophy

Heart tissue stored at -80 °C were thawed and homogenized in radioimmunoprecipitation assay buffer. The homogenates were centrifuged, and the resulting supernatants were collected for subsequent biochemical analyses.

Oxidative stress was evaluated by measuring malondialdehyde (MDA) levels, an end product of lipid peroxidation, using a thiobarbituric acid reactive substance assay kit, according to the manufacturer's protocol (Cayman Chemicals, Michigan, USA). Inflammatory status was assessed by quantifying tumour necrosis factor alpha (TNF- α) levels with a commercial ELISA kit (Biolegend, California, USA). Fibrosis was determined by measuring transforming growth factor-beta 1 (TGF- β 1) using an ELISA kit (Elabsience, Texas, USA). Cardiac hypertrophy was assessed by quantifying brain natriuretic peptide (BNP) levels with an ELISA kit (Elabsience, China), following the manufacturers' protocols.

2.5.4. Western blot analysis

The total protein concentrations in heart tissue homogenates were determined using a bicinchoninic acid protein assay kit (Thermo Fischer, Massachusetts, USA). Equal amounts of protein (30 μ g per sample) from each group were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and subsequently transferred onto polyvinylidene fluoride membranes (Qiagen Biotechnology, Hilden, Germany). Membranes were blocked with Blocking One solution and then incubated overnight at 4 °C with the following primary antibodies: nuclear factor erythroid 2 related factor 2 (Nrf2; GeneTex-GTX55732, California, USA), nuclear factor kappa-light-chain-enhancer of activated B cells p65 subunit (NF- κ B p65; GeneTex-GTX50374, California, USA), fibroblast growth factor 21 (FGF21; GeneTex-GTX111877, California, USA), and BNP (GeneTex-GTX05213, California, USA). All primary antibodies were used at a dilution of 1:1000. Following incubation with the primary antibodies, the membranes were washed three times with Tris-buffered saline containing Tween-20 to remove unbound antibodies before incubation with secondary antibodies. The membranes were then incubated with horseradish peroxidase-conjugated secondary antibody for 90 min at room temperature, washed for three times, and visualized using ChemiDoc imaging system (Bio-Rad, California, USA). β -actin was used as a loading control. The level of β -actin (GeneTex-GTX109639) was estimated in every sample. Protein band intensities were quantified using densitometry software (*i.e.*, ImageJ), and the band intensities were normalized to that of β -actin.

2.6. Statistical analysis

Data were expressed as mean $\pm$ standard error of the mean (SEM). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's or Bonferroni *post hoc* test where appropriate. A *P*-value < 0.05 was considered to be statistically significant. All analyses were conducted using GraphPad Prism version 5 (GraphPad Software, San Diego, CA, USA).

2.7. Ethical statement

All experimental procedures were conducted in accordance with the principles of laboratory animal care and were approved by the Institutional Animal Ethical Committee (Approval No.: BP1-01/14(28)2017; approval date: 10 May, 2017).

3. Results

3.1. Phytochemical identification by HPLC analysis

The HPLC chromatographic profile of CDRE was analyzed to

identify and quantify its major bioactive constituents. The analysis confirmed the presence of bergenin, *p*-coumaric acid, and quercetin. The standard chromatograms of these compounds exhibited sharp, well-resolved peaks at specific retention times, which corresponded with peaks observed in the CDRE chromatogram, indicating their presence in the extract. Bergenin was quantified using the calibration curve ($y = 20.534x - 14.702$; $R^2 = 0.9908$), and its content in CDRE was 3.0 mg/g dried extract. *p*-Coumaric acid and quercetin were identified by matching retention times with standards. These results demonstrated bergenin as a major phytoconstituent of CDRE, along with the presence of *p*-coumaric acid and quercetin (Figures 1 and 2).

3.2. Biochemical analysis

Myocardial injury markers CK-MB and LDH were significantly elevated in the MI group compared to the normal control group ($P < 0.05$). However, treatment with CDRE and bergenin significantly reduced ($P < 0.05$) the levels of both enzymes compared with the MI group (Table 1).

In the lipid profile, the MI group showed significantly increased levels of total cholesterol, LDL, and TG ($P < 0.05$), along with decreased HDL levels, when compared to the normal group. Treatment with CDRE and bergenin lowered total cholesterol and LDL levels, but the differences were not significant. TG levels were significantly reduced in all treatment groups ($P < 0.05$). Liver enzymes ALT, AST, and ALP were elevated in the MI group, and the treatment groups showed a decreasing trend, but the changes were not significant.

3.3. Morphometric analysis

Both HW and the HW/BW ratio, as indices of cardiac hypertrophy, are presented in Table 2. The HW/BW ratio was significantly increased in the MI group. However, pretreatment with CDRE and bergenin significantly reduced this ratio ($P < 0.05$).

3.4. Histopathological analysis

The effects of CDRE and bergenin on cardiac histopathology are shown in Figures 3 and 4. Hearts from MI rats exhibited extensive ISO-induced histopathological changes, as evidenced by significant increases in inflammatory cell infiltration between the myocardial fibers, marked myocardial fibrosis characterized by dense collagen deposition replacing normal cardiac tissue, and enlarged cardiomyocyte cross-sectional area associated with disorganized myocardial fiber arrangement ($P < 0.05$). In contrast, pretreatment with CDRE and bergenin significantly reduced the percentage area of inflammation and fibrosis, as well as cardiomyocyte cross-sectional area ($P < 0.05$), restoring these parameters toward near normal levels.

3.5. Quantification of MDA, TNF- α , TGF- β 1, and BNP

As shown in Figure 5, the concentrations of MDA, TNF- α , TGF- β 1, and BNP were elevated in MI rats compared to the normal control group, but significant differences were only found for TGF- β 1 and BNP ($P < 0.05$). Treatment with CDRE significantly reduced TGF- β 1 and BNP ($P < 0.05$). Bergenin treatment also lowered the levels

Table 1. Effects of CDRE and bergenin on biochemical parameters in MI rats (mean $\pm$ SEM).

Parameters	Normal	MI	CDRE 200 mg/kg	CDRE 400 mg/kg	Bergenin 10 mg/kg
ALP (U/L)	298.00 $\pm$ 4.20	339.00 $\pm$ 18.34	296.00 $\pm$ 27.49	268.00 $\pm$ 19.31	259.0 $\pm$ 22.50
ALT (U/L)	52.80 $\pm$ 1.07	69.80 $\pm$ 8.15	60.70 $\pm$ 6.69	55.80 $\pm$ 5.39	64.00 $\pm$ 6.75
AST (U/L)	74.3 $\pm$ 3.9	91.8 $\pm$ 2.2*	85.0 $\pm$ 5.2	80.7 $\pm$ 6.8	89.7 $\pm$ 5.2
CK-MB (U/L)	214.0 $\pm$ 8.3	446.0 $\pm$ 21.4*	289.0 $\pm$ 14.7 [#]	219.0 $\pm$ 24.3 [#]	225.0 $\pm$ 24.8 [#]
LDH (U/L)	209.8 $\pm$ 14.5	477.3 $\pm$ 25.1*	389.7 $\pm$ 12.4	318.0 $\pm$ 11.8 [#]	275.8 $\pm$ 22.6 [#]
Total cholesterol (mmol/L)	1.40 $\pm$ 0.06	2.12 $\pm$ 0.07*	2.00 $\pm$ 0.16	1.65 $\pm$ 0.15	1.68 $\pm$ 0.16
HDL (mmol/L)	2.02 $\pm$ 0.16	1.34 $\pm$ 0.07	1.75 $\pm$ 0.12	1.77 $\pm$ 0.12	1.85 $\pm$ 0.23
LDL (mmol/L)	0.22 $\pm$ 0.01	0.53 $\pm$ 0.02*	0.38 $\pm$ 0.06	0.33 $\pm$ 0.06	0.38 $\pm$ 0.08
TG (mmol/L)	0.47 $\pm$ 0.05	1.27 $\pm$ 0.17*	0.48 $\pm$ 0.06 [#]	0.42 $\pm$ 0.06 [#]	0.59 $\pm$ 0.06 [#]

* $P < 0.05$ compared to the normal group; [#] $P < 0.05$ compared to the MI group. CDRE: *Caesalpinia digyna* root extract. MI: myocardial infarction. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK-MB: creatine kinase-MB; LDH: lactate dehydrogenase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

Table 2. Effect of CDRE and bergenin on morphometric parameters in MI rats (mean $\pm$ SEM).

Parameters	Normal	MI	CDRE 200 mg/kg	CDRE 400 mg/kg	Bergenin 10 mg/kg
BW (g)	216.00 $\pm$ 3.05	199.00 $\pm$ 2.08	208.00 $\pm$ 1.45	212.00 $\pm$ 2.40	209.00 $\pm$ 1.76
HW (g)	0.89 $\pm$ 0.02	1.26 $\pm$ 0.04*	1.06 $\pm$ 0.02 [#]	0.93 $\pm$ 0.01 ^{##}	1.06 $\pm$ 0.02 [#]
HW/BW (g/kg)	4.14 $\pm$ 0.03	6.33 $\pm$ 0.17*	5.11 $\pm$ 0.08 [#]	4.38 $\pm$ 0.07 ^{##}	5.07 $\pm$ 0.09 [#]

* $P < 0.05$ compared to the normal group; [#] $P < 0.05$, ^{##} $P < 0.001$ compared to the MI group. HW: heart weight, BW: body weight, HW/BW: heart weight to body weight ratio.

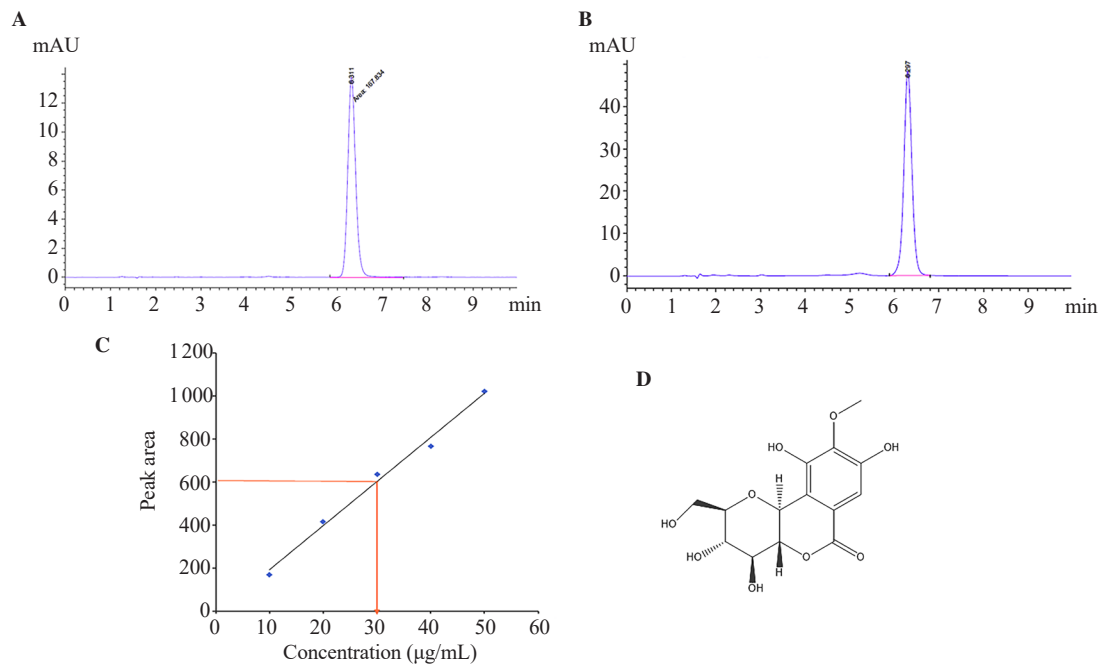


Figure 1. Chromatogram of (A) bergenin, (B) *Caesalpinia digyna* root extract (CDRE), (C) calibration curve of bergenin, and (D) chemical structure of bergenin.

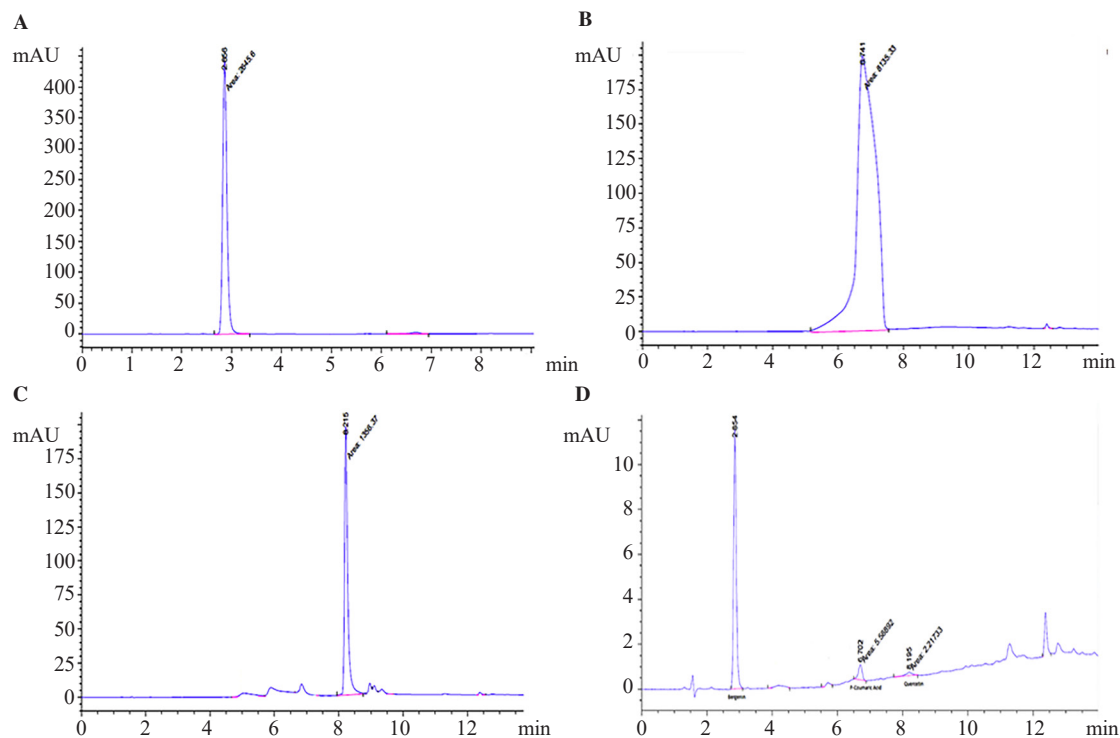


Figure 2. Chromatogram of bergenin (A), *p*-coumaric acid (B), quercetin (C), and CDRE (D).

of MDA, TNF- α , TGF- β 1 and BNP compared to the MI group; however, the reduction was statistically significant only for TGF- β 1 ($P < 0.05$).

3.6. Western blot results

Western blot analysis was performed to assess the protein expression of Nrf2, NF- κ B p65, FGF21, and BNP (Figure 6).

Expression of Nrf2 and FGF21 was significantly reduced in the MI group compared to the normal control group ($P < 0.05$), whereas pretreatment with CDRE and bergenin enhanced their expression, with a significant difference only observed at 400 mg/kg for FGF21. On the other hand, NF- κ B p65 and BNP expression were significantly elevated in the MI group ($P < 0.05$), whereas these expressions were significantly reduced in the treatment groups ($P < 0.05$).

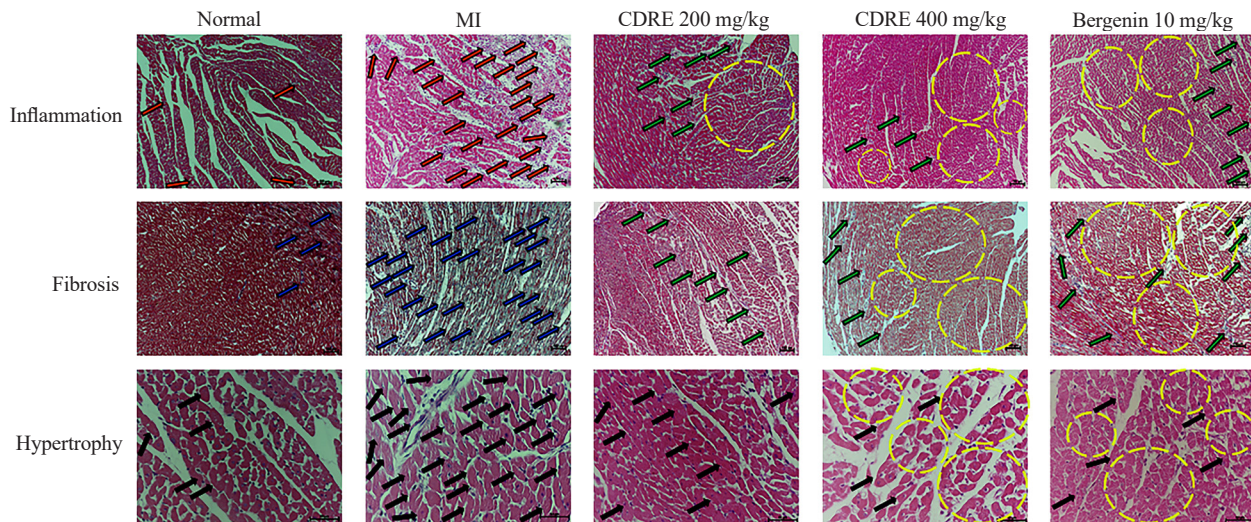


Figure 3. Effects of CDRE and bergenin in isoproterenol (ISO)-induced rats. Histology of heart sections from 5 groups of rats stained with hematoxylin and eosin to demonstrate inflammation (top panel; $\times 10$) and hypertrophy (bottom panel; $\times 40$), respectively, whereas Masson's trichrome ($\times 10$) was used to assess fibrosis (middle panel) among the five groups. The myocardium of the MI group exhibits marked histopathological alterations characterized by extensive infiltration of inflammatory cells between the myocardial fibers (red arrows), pronounced fibrosis with dense collagen deposition replacing normal myocardial architecture (blue arrows), and enlarged cardiomyocytes with prominent nuclei accompanied by disorganized muscle fiber arrangement (black arrows). In contrast, treatment with CDRE and bergenin markedly attenuates these pathological changes, as evidenced by reduced inflammatory cell infiltration, decreased collagen deposition, and improved organization of myocardial fibers (green arrows). Furthermore, the treated groups demonstrate relatively smaller and uniformly arranged cardiomyocytes with near-normal myocardial architecture (yellow circle).

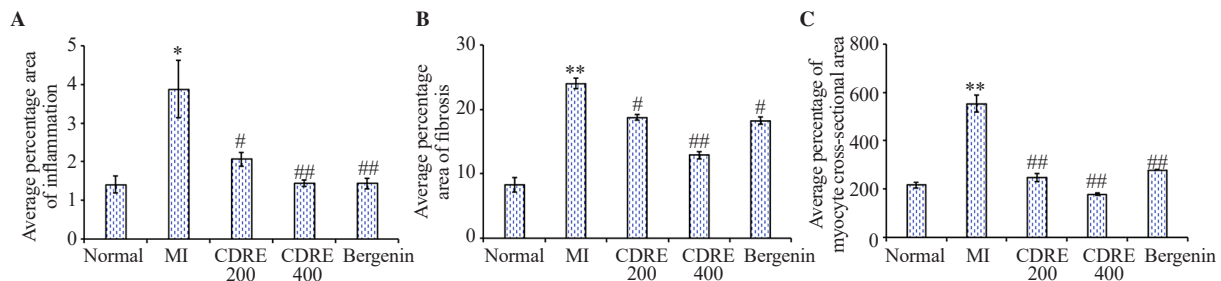


Figure 4. Effects of CDRE (200 and 400 mg/kg) and bergenin (10 mg/kg) on inflammation (A), fibrosis (B), and hypertrophy (C) assessed through histopathological analysis. * $P < 0.05$, ** $P < 0.001$ compared to the normal group; # $P < 0.05$, ## $P < 0.001$ compared to the MI group.

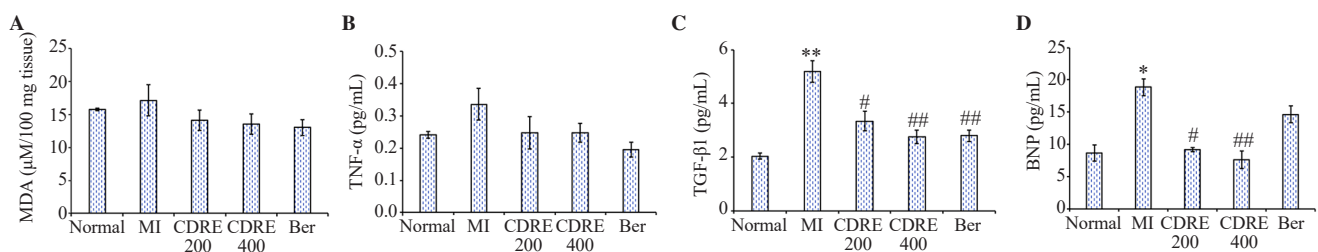


Figure 5. Effects of CDRE (200 and 400 mg/kg) and bergenin (10 mg/kg) on malondialdehyde (MDA) (A), tumour necrosis factor alpha (TNF- α) (B), transforming growth factor-beta 1 (TGF- $\beta 1$) (C), and brain natriuretic peptide (BNP) (D). * $P < 0.05$, ** $P < 0.001$ compared to the normal group; # $P < 0.05$, ## $P < 0.001$ compared to the MI group. Ber: bergenin.

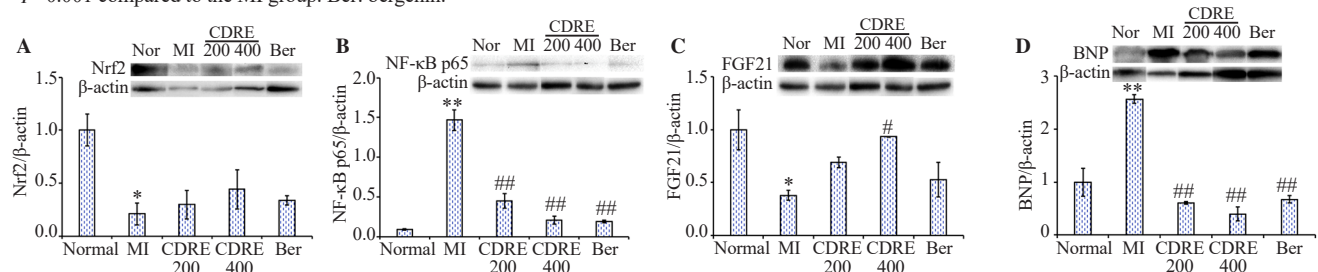


Figure 6. Effects of CDRE (200 and 400 mg/kg) and bergenin (10 mg/kg) on protein expressions of Nrf2 (A), NF- κ B p65 (B), FGF21 (C), and BNP (D). * $P < 0.05$, ** $P < 0.001$ compared to the normal group; # $P < 0.05$, ## $P < 0.001$ compared to the MI group. Nor: normal.

4. Discussion

In this study, MI was induced in the male Sprague-Dawley rats through a single subcutaneous injection of ISO at a dose of 85 mg/kg body weight[7,22]. Previous studies have shown that administration of high doses ISO can trigger infarct-like pathological lesions in the heart of experimental animals, which closely resembles the myocardial pathological characteristics of human MI[23].

Several mechanisms have been proposed for ISO-induced myocardial damage; however, the production of ROS *via* auto-oxidation of catecholamines is considered one of the most significant pathogenic factors[24,25]. Excessive ROS generation occurs when endogenous antioxidants fail to scavenge surplus ROS, therefore leading to oxidative stress. This oxidative stress results in lipid peroxidation, as evidenced by elevated MDA levels, a common biomarker of cell membrane damage[8,26,27]. Free radicals-mediated oxidative damage impairs the structural integrity and physiological function of cardiomyocytes, which increases membrane permeability and subsequently causes leakage of cytosolic enzymes into blood circulation. These events account for the rise in serum levels of CK-MB, LDH, AST, and ALT in ISO-induced myocardial injury models[28]. In line with these established mechanisms, our study demonstrated that ISO administration increased cardiac MDA levels, as well as serum CK-MB, LDH, ALP, ALT, and AST levels in MI rats. Pretreatment with either CDRE (both 200 and 400 mg/kg body weight) or bergenin (10 mg/kg body weight) exhibited marked protection against ISO-induced myocardial injury, as evidenced by reductions in CK-MB, LDH, ALP, AST, and ALT levels compared with the MI group, which indicate that CDRE and bergenin could maintain membrane integrity and block enzyme leakage. These results are consistent with previous investigations reporting similar protective effects of phytoconstituents against ISO-induced cardiotoxicity[29,30]. Furthermore, the cardioprotective effects of CDRE and bergenin were supported by the downregulation of oxidative biomarkers such as MDA and the upregulation of Nrf2, thereby enhancing the expression of antioxidant enzymes through activation of antioxidant response elements in target genes. Our results are in line with previous studies demonstrating similar protective effects of phytoconstituents against ISO-induced oxidative stress and inflammation[30,31].

ISO administration also resulted in a significant increase in HW in rats. This may be attributed to increased water content, oedematous intramuscular space, and extensive necrosis of cardiac muscle fibers, which is consistent with previous research conclusions. Such changes are well recognized as indicators of pathological cardiac hypertrophy, a compensatory response to sustained myocardial injury[22]. Pretreatment with CDRE or bergenin significantly decreased HW, the HW/BW ratio, and cardiomyocyte cross-

sectional area, suggesting both treatments could attenuate ISO-induced cardiac hypertrophy and pathological remodeling. These findings are consistent with earlier reports showing that antioxidant-rich phytoconstituents can mitigate ISO-induced cardiac hypertrophy by suppressing oxidative stress and preserving myocardial structure integrity[7,32,33].

HPLC analysis of the reference standards showed sharp and well-resolved peaks for bergenin ($R_t = 2.856$ min), *p*-coumaric acid ($R_t = 6.741$ min), and quercetin ($R_t = 8.215$ min). Consistent with these standards, HPLC profiling of CDRE confirmed the presence of bergenin ($R_t = 2.854$ min), *p*-coumaric acid ($R_t = 6.702$ min), and quercetin ($R_t = 8.195$ min). These phytoconstituents are well-documented for their antioxidant and cardioprotective properties, which provide a mechanistic basis for the therapeutic effects of CDRE in our ISO-induced MI rat model.

As discussed earlier, ISO-induced myocardial injury is largely mediated by excessive ROS generation from catecholamine auto-oxidation, leading to lipid peroxidation, calcium overload, mitochondrial dysfunction, and disruption of membrane integrity. This cascade contributes to elevated MDA levels and leakage of cytosolic enzymes such as CK-MB, LDH, AST, and ALT into the peripheral blood circulation.

The bergenin constituent in CDRE is biologically critical for cardioprotection, as it has been reported that bergenin can suppress oxidative stress, apoptosis, and inflammation[21] through activation of the Nrf2/antioxidant response elements signaling pathway, thereby enhancing endogenous antioxidant enzyme expression[34]. Similarly, *p*-coumaric acid exhibits free radical scavenging and lipid peroxidation inhibitory activity[9], which could explain the attenuation of cardiac MDA levels observed in our study. Quercetin, a flavonoid with established cardioprotective effects, not only neutralizes excess ROS but also prevents hypertrophy, apoptosis, and pathological remodeling of cardiomyocytes[35]. This aligns with our findings of reduced HW, HW/BW, and cardiomyocyte cross-sectional area in treatment groups.

Thus, the synergistic combination of bergenin, *p*-coumaric acid, and quercetin endows significant cardioprotective efficacy to CDRE. The synergistic interactions among these compounds likely accounts for reducing oxidative stress biomarkers and preserving membrane integrity, thereby mitigating ISO-induced myocardial damage.

Following ISO-induced ischemia, inflammation occurs as a part of the body's response to limit and repair the injury. The ischemic myocardium undergoes local necrosis and cardiomyocyte apoptosis, which further amplifies free radical generation and leads to the accumulation of cellular debris. This debris is subsequently cleared by macrophages and neutrophils through phagocytosis, a process that stimulates the release of pro-inflammatory cytokines such as TNF- α . This mechanism explains the elevated cardiac TNF- α levels in ISO-

induced MI rats, which is consistent with previous reports utilizing the same model. Another hallmark confirming the myocardial injury in ISO-treated rats is the histopathological evidence of myocardial degeneration. Typical features include myocyte enlargement, coagulative necrosis, separation of cardiac muscle fibers, and infiltration of inflammatory cells[29,31]. The findings of the present study corroborate these observations. Pretreatment with CDRE and bergenin reduced cardiac TNF- α levels and thus attenuated myocardial injury. Histological examination further supported these effects, revealing decreased inflammatory infiltration and fibrosis, along with intact myocardial architecture and a higher proportion of normal-sized cardiomyocytes. These outcomes strongly suggest that the anti-inflammatory and antioxidant phytoconstituents of CDRE, including bergenin, contribute to cardioprotection against ISO-induced MI.

Besides the infiltration of inflammatory cells, sustained endogenous sympathetic stimulation following excessive β -adrenergic activation by ISO resulted in cardiomyocyte hypertrophy and fibrosis, as observed in morphometric analysis. These pathological changes are associated with increased myocardial stiffness and reduced left ventricular distensibility, resulting from a higher proportion of collagen fibers within the myocardium[22]. Consistent with the histological findings, the cardioprotective effects of CDRE and bergenin were further supported by the reduced protein expression of BNP and TGF- β 1—biomarkers indicative of cardiac hypertrophy and fibrosis, respectively. Both are well-established indicators of myocardial injury caused by the potent catecholamine, ISO[22]. This observation aligns with earlier studies. CGEN-856S inhibits angiotensin II-induced cardiac hypertrophy through enhanced NO production[36]; formononetin suppresses fibrosis-related proteins (Collagen III, fibronectin, TGF- β 1, and vimentin) and genes (Collagen Ia1 & IIIa1, TGF- β 1)[37]; and schisantherin A reduces cardiomyocyte hypertrophy, *via* downregulating BNP expression[7] in experimental models of ISO-induced myocardial injury.

NF- κ B p65 is a key regulator in cardiac hypertrophy, mediating the translocation of p65 from the cytoplasm to the nucleus to activate target genes[38]. Inhibition of this pathway by natural products alleviates oxidative stress, inflammation, and hypertrophy in various cardiovascular diseases[39]. FGF21 is another crucial protective factor, whose absence has been linked to cardiac hypertrophy, dilatation, and dysfunction[40]. A previous study on Danhong injection derived from *Rhizoma Salviae miltiorrhizae* and *Flos Carthami* showed both BNP reduction and NF- κ B pathway suppression[41]. These findings are consistent with our present results, where pretreatment with CDRE and bergenin could inhibit NF- κ B p65 pathway and increase FGF21 expression, thereby reinforcing their cardioprotective potential.

The present study demonstrates that oral administration of CDRE

(200 mg/kg and 400 mg/kg) and its major constituent, bergenin (10 mg/kg), exerts significant protection against ISO-induced MI in rats, as evidenced by the modulation of biomarkers associated with inflammation, fibrosis, and cardiac hypertrophy. These findings suggest a potential cardioprotective role of CDRE and bergenin. However, further investigations are required to elucidate the precise molecular mechanisms underlying these effects. In addition, several limitations exist in this work, such as the lack of myocardial infarct size measurement, detection of apoptosis-related markers, and electrocardiographic evaluation, which should be addressed in future investigations to establish a definite causal relationship and to evaluate the translational relevance of these findings.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

PVT conceived and designed the study, performed the experiments, conducted formal data analysis, curated the data, and prepared the original draft of the manuscript. SR supervised the project, secured funding, and contributed to conceptualization of the research work. PM contributed to methodology development, software analysis, and data visualization. BR critically reviewed and edited the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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