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REVIEW ARTICLE

Cardioprotective Activity of *Clerodendrum serratum* In Attenuation of Myocardial Infarction Induced by Isoprenaline

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Abstract

Clerodendrum serratum (L.) Moon, commonly known as "Bharangi" in Ayurvedic medicine, has been traditionally used for its therapeutic properties. The goal of this study is to determine if the ethanolic extract of *Clerodendrum serratum* (CS) leaves may prevent myocardial infarction (MI) in rats that have been caused by isoprenaline. Male Wistar rats were pre-treated with 200 and 400 mg/kg b.wt of CS extract orally for 28 days, and on the 29th and 30th day, isoprenaline (85 mg/kg b. wt) was subcutaneously applied to induce MI. On the thirty-first day, the animals were killed, and serum and heart tissue homogenates were used to assess several biochemical markers. Treatment with CS extract greatly ($p < 0.05$) reduced the elevated levels of serum cardiac markers, including troponin-T, lactate dehydrogenase (LDH), and creatine kinase-MB (CK-MB). It also enhanced the antioxidant status by raising the levels of catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA). Histopathological examination of the heart tissues revealed a significant reduction in the extent of myocardial damage in the CS-treated groups. Over all our study provides evidence that the ethanolic extract of *Clerodendrum serratum* leaves exhibits cardioprotective activity against isoprenaline-induced MI by improving antioxidant status and reducing cardiac damage. Further investigations are needed to elucidate the active compounds and molecular mechanisms involved in the observed effects.

Keyword: *Clerodendrum serratum,* Bharangi, Phytochemicals, Cardioprotective Activity

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Introduction

Coronary heart disease (CHD), Peripheral vascular disease, and congestive heart failure are among the various heart and blood vessel conditions referred to as cardiovascular disease (CVD) (CHF). (Salma et al ., 2020). Non-communicable disease, with major health issues on a global scale, is ischemic heart disease. By 2020, it will dominate the global source of death, predicts the World Health Organization (WHO). Acute myocardial infarction (MI), which is the most serious form of ischemic heart disease, is brought on by a mismatch between the supply and demand of coronary blood (Geeta et al., 2016). Epigenetic mechanisms control at least a portion of the pathological processes due to the effects of gene-environment interactions.

Massive cardiac muscle is lost due to the specific mechanism causing MI, which has been linked to apoptosis, inflammation, and oxidative stress. The left ventricle then undergoes structural and functional changes to maintain normal pump function, which ultimately results in heart failure (HF). Apoptotic genes that may be involved in MI pathogenesis through apoptosis have been found over the past few decades using various human genetics approaches. The Bcl-2 family represents one of two main gene classes that regulate apoptotic activity, and the caspase family represents the other. Pro- and anti-apoptotic members of the Bcl-2 family affect cytochrome c release, which in turn affects the successive activation of Casp9 and Casp3 by either stabilising (Bcl-2-like) or destabilising (Bax-like) the mitochondrial membrane. Additionally, membrane-dependent triggers like tumour necrosis factor (TNF-)/TNF-R interaction may cause Casp8 activation, which ultimately results in Casp3 activation. When Casp3 is activated, the cardiac muscle begins to apoptosis, which results in MI (Islam et al., 2020). An adrenergic agonist, isoprenaline is a synthesised catecholamine. According to Jordan et al., it can cause myocardial infarction at greater doses. Isoprenaline undergoes auto-oxidation, which results in the production of extremely cytotoxic free radicals. These free radicals promote membrane phospholipid peroxidation, severely damaging the cardiac membrane. After that, the inflammatory process begins with neutrophils infiltrating the infarcted area, where they can encourage myocardial cell damage by releasing proteolytic enzymes. Internally, it generates harmful reactive oxygen species. As a result, the model is employed as a new technique to cause myocardial infarction in research animals (Mundugaru et al., 2016).

Materials and Methods

Animals

Male and female albino Wistar rats (India) weighing 150 g to 200 g were used in the present study. Animals were housed under standard laboratory conditions at a mean (±SD) temperature of 25±2°C, relative humidity of 50±15% and a 12 h light-dark cycle. A commercially available pellet diet (Amrut rat feed, Pranav Agro Industries Ltd, India) and water were provided ad libitum. The experimental protocol was performed according to the guidelines of the Committee for Control and Supervision of Experiments on Animals (New Delhi, India) and was approved by the Institutional Animal Ethical Committee of Chalapathi Institute of Pharmaceutical Sciences, Andhra Pradesh, India (registration number: 1048/PO/Re/S/07/CPCSEA, Approval number: 04/ IAEC/CLPT/2002-23).

Drugs and chemicals

Isoprenaline batch no: ISPRA1702; Mfg: MB/05/228; Nangal area, Swarghat road, Nalagarh, Solan, Himachal Pradesh – 174101, H.O: Ram mandir road, Goregaon (w), Mumbai 400104. Disprin batch no: KX492; Mfg: at 61 & 62, Hotagalli Ind, area, Mysore – 570018. Okhla Industrial Estate, Delhi – 110020, India.

Experimental design

A total of 20 Wistar albino rats (weight 200-250 gm) were divided into 5 groups at random using the Rando programme, with 4 animals in each group. Rats were given ISO (85 mg/kg) subcutaneously (s.c.) for two days on day 28 and day 29 at a 24-hour interval to induce MI in them. Study groups were distributed as follows: Group 1 (normal control): Rats received normal saline s.c. on days 28 and 29 and distilled water orally for 30 days. Group 2 (ISO control): rats were administered ISO (85 mg/kg s.c. on days 28 and 29 and distilled water orally for 30 days. Rats in Group 3 (active control) received ISO (85 mg/kg) s.c. on Days 28 and 29, and Aspirin (10 mg/kg) orally for 30 days. Group 4: Low dosage of *Clerodendrum serratum*.

ECG Examination

The electrocardiogram (ECG) of tiny animals was done in vivo, as previously mentioned. 15– 18 During surgery and the first postoperative week, the rats were observed in the supine posture using standard limb leads and the RM6240 multichannel physiological signal collection system (Chengdu Instrument Factory, Chengdu, China). To see if surgically ligating the left anterior descending coronary artery has resulted in the ECG anomalies typical of transmural myocardial ischaemia, three electrodes were connected to the paws and a simultaneous trace was taken.) (Hou et al., 2011). All of the groups' sedated, supine rats were used for the ECG measurements on SD animals. Acupuncture needle electrodes were inserted following 30 minutes of full anaesthesia induction. As per the ECG design, subcutaneously along lead.

II. Rats under anaesthesia had their ECGs monitored for one minute every five minutes using a Power Lab coupled to a Bio Amp, and the results were analyzed using. (AD Instrument, Australia (Sajid et al., 2022). Only a single precor dial lead was employed, and it was positioned at the human V4 position. Calculations and comparisons between the groups were made for heart rate, RR interval, QT interval, corrected QT interval, and QRS interval. (Geeta et al., 2016). Following 4 weeks following ligation, the levels of LVEDD, LVESD, LVEF, and LVFS were significantly different among the five groups, as determined by ANOVA. According to post hoc analyses, there was no statistically significant difference between the LVEDD, LVESD, LVEF, and LVFS values in group B and group C (P>0.05) (Luo et al., 2016).

Serum collection

Rats had their retro-orbital sinuses sampled for blood. The serum obtained after centrifuging the collected blood samples at 1538 g for 10 min in a cooling centrifuge (2k15; Sigma/Laborz centrifuges) was used to calculate the levels of AST, LDH, and CK. After receiving adrenaline for 24 hours, rats were slaughtered while receiving very little ether anaesthesia. The MPW-120 from Medical Instruments was used to separate and homogenise hearts in 20% (w/v) ice-cold phosphate buffer. Malondialdehyde (MDA), reduced glutathione (GSH), nuclear factor kappa B (NF-B), and interleukin-1beta (IL-1) cardiac contents were then determined by centrifuging the homogenate using a cooling centrifuge (2k15; Sigma/ Lab or centrifuge) at 1538g for 5 min. (Salma et al., 2020).

Serum biochemical parameters

Serum AST level

Using the Reitman and Frankel (1957) approach, serum AST was measured. At 505 nm, the concentration was determined spectrophotometrically. The serum AST concentration is given as U/L..

Serum LDH level

According to manufacturer directions, the LDH level was calculated using an enzyme method and measured spectrophotometrically at 340 nm (Chrono Lab, France). The expression for serum LDH amount is U/L.

Histopathological examination

After the animals were killed, the myocardial tissues were preserved in a 10% formalin-saline solution. The preserved tissues were cleaned, dehydrated with alcohol, and immersed in paraffin, then cut with a rotary microtome into serial sections, each of which is stained differently with hematoxylin and eosin (H & E) (Fajobi et al., 2020). The slices were examined and captured on camera with an Olympus BX50 digital microscope (Japan) (Neto et al., 2022).

Immunohistochemical analysis

Bcl-2 and activated caspase-3 were stained using immunohistochemistry as previously mentioned. Deparaffinization, rehydration, and hydrogen peroxide blocking in 3% were performed on the cardiac sections. Next, the sections were treated with primary antibodies against mouse monoclonal anti-Bcl-2 (1:200 dilution, Santa Cruz Biotechnology) and rabbit polyclonal anti-caspase-3 (1:1000 dilution, BD Biosciences, Le Pont-de-Claix, France). To see the immune response, diaminobenzidine chromogen was introduced. The specimens were then cover-slipped and hematoxylin counterstained. In ten random high-power fields, activation of caspase-3 and Bcl-2 was rated semi-quantitatively based on the proportion of immune-stained cells in the high-power field (40X). Grade 0: no staining; 1: staining positive in 25% of cells/HPF; 2: staining positive in 25 –50% of cells/HPF; 3: staining positive in > 50% of cells/HPF (Salma et al., 2020).

Statistical analysis

One-way ANOVA was used for the statistical analyses, and either the student's t-test for unpaired samples or the Newman-Keuls post-test for groups was used thereafter. All data were reported as means standard errors (SEM). Software called Graph Pad Prism Version 5.0 was used to create the diagrams (San Diego, CA, USA). The findings were deemed significant when p 0.05 (El-Marasy et al., 2020).

Results

Clerodendrum serratum's effects on the HR, RR, and ST intervals of rats with isoprenaline - induced MI reveal that, in comparison to normal rats, rats with MI induced by a single intraperitoneal injection of

isoprenaline at a dose of 2 mg/kg for two consecutive days had significantly lower HR by 30.69%, higher RR intervals by 60.36%, and higher ST intervals by 561.54%. When compared to control (MI) rats, oral pre-treatment with *Clerodendrum serratum* at doses of 15, 30, and 60 mg/kg resulted in a significant increase in HR of 57.37, 35.98, and 32.94%, a decrease in RR interval of 30.63, 30.26, and 26.20%, and a decrease in ST interval of 32.94, 26.20, and 76.74%, respectively.

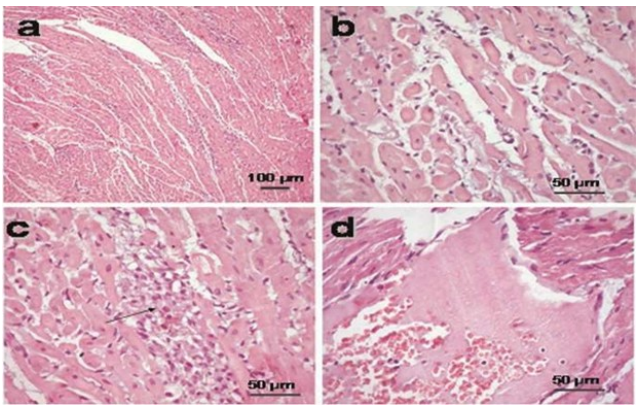

Figure 1: Histological image of myocardial tissue treated by standard and plant extract

Clerodendrum serratum's impact on serum biochemical markers

As shown, blood levels of AST, LDH, and CK increased significantly after isoprenaline- induced MI by 50.96, 71.31, and 59.96%, respectively, in comparison to control rats. When *Clerodendrum serratum* (15 mg/kg) was pre-treated orally, the AST level significantly decreased (16.32% compared to the control (MI) group and significantly decreased from the normal group. In comparison to the control (MI) group, the AST level was considerably lowered by 24.00 and 36.24%, respectively, after receiving 30 and 60 mg/kg of *Clerodendrum serratum* treatment. Although *Clerodendrum serratum* (15 mg/kg) was administered orally, the LDH level did not significantly decrease in the MI control group.

Even at 30 mg/kg, *Clerodendrum serratum* caused a significant rise in LDH levels, comparable to those of the MI control group. When compared to control (MI) rats, *Clerodendrum serratum* dramatically decreased LDH levels by 31.29% at a dosage of 60 mg/ kg. In terms of CK level, *Clerodendrum serratum* (15 mg/kg) raised CK level by 15.77% compared to the normal group and considerably lowered it by 27.63% compared to the control (MI) group. Compared to control rats, oral pre-treatment with 30 mg/kg of *Clerodendrum serratum* dramatically decreased the level of CK by 30.35%. When compared to control rats, *Clodrendrum serratum* (60 mg/kg) dramatically decreased the CK level by 16.73%, which was statistically different from the normal value.

Impact of *Clerodendrum serratum* on indicators of cardiac oxidative stress

MDA cardiac content was significantly elevated in isoprenaline-induced MI rats compared to normal rats, as revealed in. When compared to control rats, oral pre-treatment with *Clerodendrum serratum* (15, 30, and 60 mg/kg) substantially decreased the cardiac MDA content by 54.34, 56.58, and 54.14%, respectively. In comparison to normal rats, control (MI) animals showed a substantial drop in myocardial GSH content of 34.65%. In comparison to control rats, Clodrendrum serratum (15, 30, and 60 mg/kg) substantially recovered myocardial GSH content by 40.77, 76.21, and 52.20%, respectively.

Impact of Clerodendrum serratum on inflammatory mediators in the heart

The NF-κB and IL-1β cardiac contents in control MI rats were found to be considerably higher by 372.18% and 7.92%, respectively, as compared to normal rats. Following pre- treatment with *Clerodendrum serratum* (15, 30, 60 mg/kg), a dose-dependent reduction in cardiac NF-κB content was seen in MI rats, with reductions of 42.78, 60.785, and 72.41%, respectively, in comparison to control rats. Compared to control rats, *Clodrendrum serratum* (15, 30, and 60 mg/kg) substantially decreased the amount of IL-1β in the heart by 5.34, 6.20, and 6.73%, respectively.

Immunohistochemistry

Immunohistochemistry analysis findings for both treated and normal hearts. Caspases- 3 protein expression that is activated in a normal heart, no caspase-3 expression was seen. The endothelial lining of blood vessels, the cardiomyocyte sarcoplasm, and apoptotic nuclei all showed a substantial increase in caspase-3 expression in the control (MI) group. Furthermore, there was strong immunological staining in the inflammatory cells that surrounded the necrotic muscle fibres. The pre-treated group with 15 mg/kg of *Clerodendrum serratum* showed reduced expression of activated caspase-3. A small number of cardiomyocytes

Table 1: Effect of *Clerodendrum serratum* on various biochemical parameters in serum and heart homogenates of Isoprenaline-induced myocardial infarction rats

Treatments Parameters	Control	Isoprenline	*Clerodendrum serratum* + Isoprenline
AST (IU/l)	33.02±2.24	62.57* ±2.81	49.32†±2.92
ALT (IU/l)	23.48 ± 2.62	51.31* ± 2.29	41.59† ± 4.19
LDH (IU/l)	81.98 ± 3.63	162.03* ± 2.21	115.07† ± 4.02
CK (IU/l)	164.76 ± 4.5	281.47* ± 8.57	196.06† ± 6.96
cTnI (ng/ml)	0.15 ± 0.02	2.35* ± 0.015	1.10† ± 0.049
GSH (mmol/g tissue)	12.63 ± 0.84	3.91* ± 0.39	8.41† ± 0.79
SOD (U/g tissue)	17.57± 1.34	6.03* ± 0.66	11.25† ± 1.01
MDA (nmol/g tissue)	1.05 ± 0.16	2.66* ± 0.19	1.50† ± 0.15

and the endothelial lining of blood vessels displayed signs of an immunological response (Figure 2c). The pre-treated groups with *Clerodendrum serratum* (15, 30, and 60 mg/kg) showed a significant reduction in activated caspase-3. The Cytoplasm of sparse cardiomyocytes (Figure 2d & e, respectively).

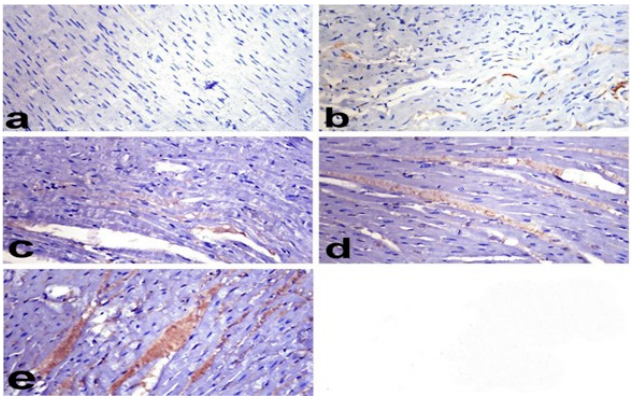

Figure 2: Immunohistochemistry image of myocardial tissue treated by standard and plant extract

Discussion

The study demonstrates the potential cardioprotective effects of *Clerodendrum serratum* in attenuating myocardial infarction induced by isoprenaline. The results show that pretreatment with *Clerodendrum serratum* significantly reduced the severity of myocardial damage, as evidenced by decreased levels of cardiac biomarkers and improved histopathological findings.

This work offers further proof of *Clerodendrum serratum's* cardioprotective benefits (15, 30, and 60 mg/kg) against isoprenaline-induced myocardial infarction in rats.

To the best of the authors' knowledge, this is the first study to look at the involvement of *Clerodendrum serratum's* histopathological changes, oxidative stress, inflammation, apoptosis, and cardiac enzymes in rats that have been given isoprenaline-induced MI (Tzortzakis & Nikolaos, 2018).

The cardioprotective effects of *Clerodendrum serratum* may be attributed to its antioxidant, anti-inflammatory, and free radical-scavenging properties. The plant's bioactive compounds may help mitigate oxidative stress and inflammation, which play a crucial role in the pathogenesis of myocardial infarction. The findings of this study are consistent with previous reports on the cardiovascular benefits of *Clerodendrum serratum.* However, further studies are needed to elucidate the exact mechanisms underlying the cardioprotective effects of *Clerodendrum serratum* and to identify the specific bioactive compounds responsible for its therapeutic effects.

The study on the cardioprotective effects of *Clerodendrum serratum* in reducing myocardial infarction caused by isoprenaline shows great promise for future treatments. The results suggest that *C. serratum* plays a significant role in protecting the heart, likely due to its antioxidant, anti-inflammatory, and anti-apoptotic qualities. By helping reduce oxidative stress, inflammation, and cell death in the heart, the plant extract could offer a potential natural alternative or supplement for preventing or managing the damage caused by heart attacks. However, more research and clinical trials are needed to fully understand how it works and to assess its safety and effectiveness for human use (Islam & Shanta, 2020).

Conclusion

Based on the findings presented, our study proves the evidence of *Clerodendrum serratum's* cardioprotective effects at doses of 15 mg/kg, 30 mg/kg, and 60 mg/kg against isoprenaline-induced myocardial infarction in rats. Our investigation, encompassing histopathological changes, oxidative stress markers, inflammation indicators, apoptosis pathways, and cardiac enzyme levels, underscores the significant potential of *Clerodendrum serratum* in mitigating myocardial damage. This research represents the inaugural exploration into these multifaceted aspects of *Clerodendrum serratum's* impact on myocardial infarction induced by isoprenaline in experimental models. These findings advocate for further exploration of *Clerodendrum serratum* as a promising candidate for developing therapies aimed at protecting against myocardial infarction and related cardiac pathologies. Further investigations are needed to elucidate the active compounds and molecular mechanisms involved in the observed effects.

Disclosure

Ethics approval and consent to participate

Not Applicable

Availability of data and materials

Data Available upon request

Competing interests

NIL

Funding

Nil

Authors' contributions

All authors are equally contributed to this work

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