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Investigation of the Cardio Protective Role of Justicia Adhotoda Leaf Extract Against Isoproterenol-Induced Myocardial Infarction in Rat Model

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Abstract | **Original Research Article**

Myocardial infarction (MI) continues to be a predominant cause of mortality globally and is characterized by restricted therapeutic alternatives and considerable adverse effects linked to traditional treatments. This study assessed the cardioprotective properties of Justicia adhatoda leaf extract against isoproterenol-induced myocardial infarction in rats at GC, University Faisalabad. A total of 32 albino Wistar rats were randomly allocated into four groups, with one group designated as the control and the remaining groups administered Justicia adhatoda leaf extract (400 mg/kg) or metoprolol (10 mg/kg) for six days following myocardial infarction induction. This study assessed hematological parameters, liver enzyme concentrations, oxidative stress indicators, inflammatory cytokines, and apoptotic gene expression. Statistical analysis was conducted using ANOVA, with the results expressed as the mean ± standard error of the mean (SEM). The findings indicated that herbal treatment markedly elevated RBC and WBC counts, diminished liver enzyme levels, and augmented total antioxidant capacity (TAC) while lowering total oxidant status (TOS). Moreover, gene expression analysis demonstrated a significant decrease in the therapy groups' levels of proinflammatory cytokines (IL-6 and IL-10) and apoptotic markers (BAX). Histopathological analysis verified a decrease in myocardial damage, signifying the preventive effect of Justicia adhatoda against myocardial infarction-induced harm. These findings indicate that Justicia adhatoda leaf extract may serve as an effective natural option for preventing and managing myocardial infarction, providing a promising adjunct to conventional therapies. Additional investigations are required to examine fundamental molecular pathways and assess their therapeutic efficacy in human clinical trials.

Keywords: Myocardial Infarction, *Justicia Adhatoda*, Cardioprotection, Antioxidants, Oxidative Stress, Inflammation, and Herbal Treatments.

1. INTRODUCTION

Cardiovascular disorders (CVDs) remain a serious global health problem, with high mortality and morbidity rates (Guerrero & Calmette, 2020). CVDs, including myocardial infarction (MI), have become a major burden on the public health system, the economy, and society (Zibaei, 2017). Heart attack or myocardial infarction occurs when there is a sudden blockage in the coronary arteries, preventing the heart muscle from receiving oxygen and nutrients and causing tissue damage and potentially fatal consequences if untreated (Choi, 2019; Rabizadeh *et al.*, 2019). Oxidative stress, inflammation, and alterations in cellular signaling cascades during and after myocardial infarction are often implicated in the perpetuation of injury and myocardial dysfunction (Mastrocola *et al.*, 2018; Zhou *et al.*, 2018).

Although considerable progress has been made in pharmaceutical treatments (e.g. beta-blockers, angiotensin-converting enzyme inhibitors, and thrombolytics), the limitations and unwanted effects of these treatments highlight the need for novel and more effective therapies (Bahreyni *et al*., 2019). The present study was conducted to evaluate the cardioprotective effect of local (Justicia adhatoda) leaf extract, which has antioxidant and anti-inflammatory effects, on isoproterenol-induced myocardial infarction in rat models (Delgado-Maroto *et al*., 2017; Kim *et al*., 2019).

Many studies have reported the potential use of phytochemicals with antioxidant and anti-inflammatory activities as novel treatments for cardiovascular diseases, as their cardiovascular protective effects help reduce myocardial injury (Lyu *et al*., 2017). Justicia adhatoda has been studied for its pharmacological activities such as free radical scavenging, anti-inflammatory, and oxidative damage prevention effects (Jayaweera *et al*., 2024). Because of the therapeutic properties of the plant, recent research has shown that the leaves of Justicia adhatoda contain bioactive compounds such as vasicine, vasicinone, and flavonoids, which are effective in the treatment of many respiratory and cardiovascular diseases (Duggal *et al*., 2016; Gal *et al.*, 2019). While these trials have shown the medicinal value of the plant, there is a lack of preliminary studies exploring its cardioprotective effects in a myocardial infarction model, particularly against known therapies such as metoprolol (Bongers-Karmaoui *et al*., 2020). While the biological activity of Justicia adhatoda leaves is well understood, there is a lack of a more comprehensive molecular understanding of J. adhatoda, especially with respect to oxidative stress, inflammatory pathways, and gene expression (Kim *et al*., 2019).

The present study aimed to investigate the cardioprotective effects of Justicia adhatoda leaf extract against isoproterenol-induced myocardial infarction in rats. This study assessed the biochemical, histological, and molecular changes in cardiac tissue following treatment with the plant extract (Zeng *et al*., 2018). The present study provided novel perspectives on the potential effectiveness of Justicia adhatoda as a natural substitute for conventional therapy for myocardial infarction through the evaluation of oxidative stress, inflammatory cytokines, and myocardial injury markers and comparison with metoprolol (Waxman *et al*., 2018). This study investigated whether the plant extract can substantially reduce myocardial damage, improve cardiac function, and modulate fundamental cellular pathways that are of pathophysiological relevance in myocardial infarction (Geldenhuys *et al*., 2017). With the expansion of research on therapeutics from plants, this work may represent a unique method for the prevention and treatment of MI that will influence future treatment strategies in cardiac-urged care (Gupta *et al.*, 2018).

2. MATERIALS AND METHODS

2.1 Experimental Design

An experimental study was conducted on 32 albino Wistar rats, which were obtained from the animal house at GC University, Faisalabad. The rats were randomly divided into four groups, with 8 rats in each group:

- **Group 1 (G1):** Negative control group, received routine feed and water.
- **Group 2 (G2):** Positive control group, received a normal diet, high-fat diet (HFD), and two doses of isoproterenol (30 mg/kg body weight) on days 13 and 14.
- **Group 3 (G3):** Standard treatment group, received a normal diet, HFD, isoproterenol (30 mg/kg), and metoprolol (10 mg/kg) for 6 days.
- **Group 4 (G4):** Treatment group, received a normal diet, HFD, isoproterenol (30 mg/kg), and *Justicia adhatoda* leaf extract (400 mg/kg) for 6 days.

Table 1: Experimental Design

Groups	Treatments
G1: Control negative group	Routine feed + Water
G2: Control positive group	Normal Diet + HFD + Isoproterenol 30 mg/kg
G3: Standard group	Normal Diet + HFD + Isoproterenol 30 mg/kg + Metoprolol 10 mg/kg
G4: Treatment group	Normal Diet + HFD + Isoproterenol 30 mg/kg + *Justicia adhatoda* 400 mg/kg

HFD = High-fat diet

2.2 Sample Collection

At the end of the experimental trial, the rats were euthanized by decapitation. Blood samples were collected in labeled gel-clot activators and centrifuged at 15,000 rpm for 10 minutes to isolate the serum. The organs (heart and liver) were carefully dissected, washed with normal saline to remove blood and debris, and stored in 10% neutral buffered formalin at room temperature for histopathological analysis. All samples were preserved at suitable temperatures until further processing.

2.3 Serum Parameters and Liver Function Tests

Liver function was assessed using specific enzymatic kits for the following enzymes:

1. **Aspartate Aminotransferase (AST):** A liver enzyme that plays a key role in amino acid metabolism. Elevated AST levels indicate liver damage or myocardial infarction.

2. **Alanine Aminotransferase (ALT):** A liver-specific enzyme involved in amino acid metabolism. Increased ALT levels are associated with liver and myocardial dysfunction.
3. **Alkaline Phosphatase (ALP):** This enzyme's elevated levels are often indicative of liver disorders such as obstructive jaundice.

The enzyme activities were measured using commercially available diagnostic kits, and serum samples were processed as per the kit instructions.

2.4 Histopathological Analysis

The heart and liver tissues were processed for histological examination using standard tissue preparation techniques. The steps followed included:

1. **Fixation:** Tissues were fixed in 10% neutral buffered formalin.
2. **Dehydration:** Tissues underwent a graded ethanol series (70%, 80%, 95%, and 100% alcohol) for dehydration.
3. **Clearing:** Xylene was used for clearing to prepare tissues for embedding.
4. **Infiltration and Embedding:** Paraffin wax was used to infiltrate and embed the tissues for sectioning.
5. **Sectioning and Staining:** Thin sections (4-5 µm) were cut using a microtome and stained using the Hematoxylin and Eosin (H&E) protocol to evaluate histopathological changes under a microscope.

Table 2: Ascending Concentrations of Ethyl Alcohol for Dehydration Protocol

Graded Concentrations	Time
70% Alcohol	2 hours
80% Alcohol	1 hour
95% Alcohol I	1 hour
95% Alcohol II	1 hour
100% Alcohol I	1.5 hours
100% Alcohol II	1.5 hours

2.5 Plant Extraction

Justicia adhatoda leaves were collected, identified, and authenticated by the Botany Department of GC University, Faisalabad. The leaves were air-dried, powdered, and subjected to ethanolic extraction. The extraction process involved:

1. **Grinding:** The dried leaves were ground into a fine powder.
2. **Extraction:** Ethanol was used as the solvent to extract active compounds, and the samples were agitated for 3 days.
3. **Evaporation:** The solvent was removed using a rotary evaporator, and the residue was collected for further analysis.

2.6 Quantification of Phytochemicals by HPLC

To determine the phytochemical profile of the *Justicia adhatoda* extract, high-performance liquid chromatography (HPLC) was performed. The extract was diluted, centrifuged, and filtered before injection into the HPLC system.

2.7 Statistical Analysis

All experimental data were statistically analyzed using ANOVA, and results were graphically represented using GraphPad Prism software.

3. RESULTS

3.1 Hematological Analysis:

The red blood cell (RBC) count was significantly lower in the positive control group (isoproterenol-induced MI) compared to the negative control group. The herbal treatment group showed a significant increase in RBC count compared to the positive control group, suggesting a recovery of hematological parameters after treatment with *Justicia adhatoda*. Similarly, white blood cell (WBC) count was significantly elevated in the positive control group, indicative of an inflammatory response following MI. Both the standard treatment (metoprolol) and herbal treatment groups showed a reduction in WBC count, with the herbal treatment showing a recovery closer to normal values.

Table 3: RBC and WBC Counts (Mean ± SEM)

Group	RBC (×10^6/µL)	WBC (×10^3/µL)
G0: Negative Control	59.70 ± 0.12	6.51 ± 0.06
G1: Positive Control	7.26 ± 0.06	10.56 ± 0.16
G2: Standard Treatment	7.51 ± 0.06	8.52 ± 0.14
G3: Herbal Treatment	8.56 ± 0.05	6.68 ± 0.70

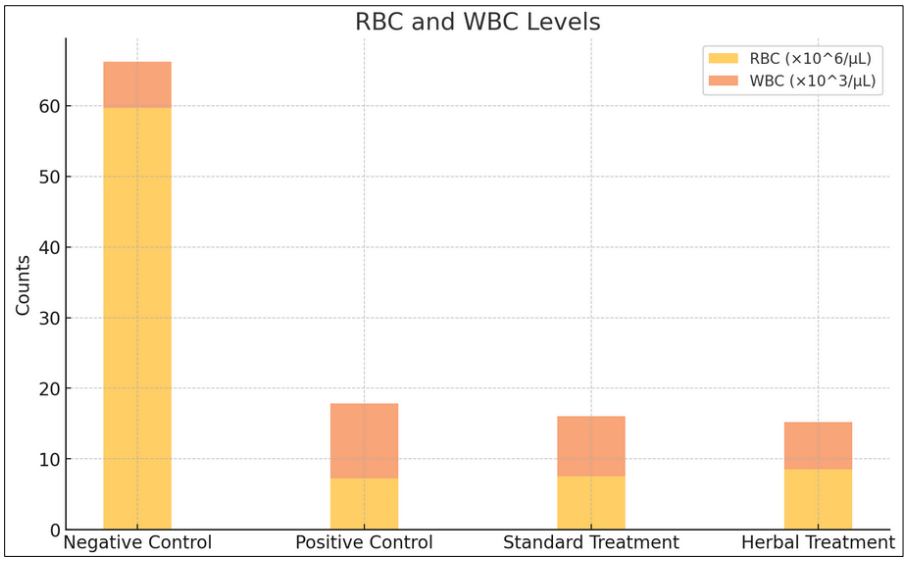

Figure 1: This chart compares the counts of red blood cells (RBCs) and white blood cells (WBCs) among the four experimental groups. The positive control group (isoproterenol-induced myocardial infarction) exhibits a significant reduction in RBC count and a substantial WBC count relative to the negative control. This indicates the hematological disruptions created by myocardial infarction. The conventional treatment group (metoprolol) and the herbal therapy group (Justicia adhatoda) demonstrate enhancements in both RBC and WBC counts, with the herbal treatment group displaying a recovery nearer to normal levels, indicating its potential to restore hematological equilibrium

3.2 Liver Function Tests:

Levels of liver enzymes including Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP) were significantly higher in the positive control group, indicating liver dysfunction due to isoproterenol-induced MI. The herbal treatment group showed a reduction in enzyme levels, suggesting hepatoprotective effects of *Justicia adhatoda*. The standard treatment (metoprolol) also demonstrated some improvement, but the herbal treatment exhibited a more significant effect.

Table 4: Liver Enzyme Levels (Mean ± SEM)

Group	AST (U/L)	ALT (U/L)	ALP (U/L)
G0: Negative Control	358.0 ± 0.58	38.10 ± 1.24	1836 ± 1.73
G1: Positive Control	363.0 ± 0.58	307.0 ± 1.16	4274 ± 0.58
G2: Standard Treatment	342.7 ± 0.88	283.0 ± 1.45	2167 ± 0.58
G3: Herbal Treatment	337.0 ± 0.58	332.3 ± 1.45	3146 ± 0.58

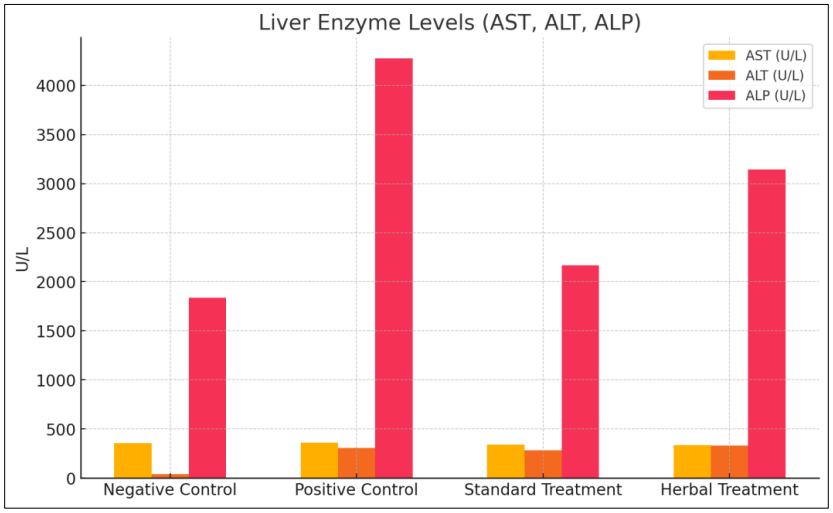

Figure 2: This chart represents the concentrations of liver enzymes—aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP)—across various experimental groups. The positive control group exhibits markedly elevated enzyme levels, signifying hepatic injury resulting from myocardial infarction. Conversely, both the standard therapy (metoprolol) and the herbal treatment groups exhibit a decline in enzyme levels, with the herbal treatment group showing a more pronounced reduction, indicating the hepatoprotective properties of Justicia adhatoda

3.3 Antioxidant and Oxidant Status:

Total Antioxidant Capacity (TAC) was significantly higher in the herbal treatment group compared to the positive control group. This indicates the potential antioxidant effect of *Justicia adhatoda* in reducing oxidative stress. In contrast, the Total Oxidant Status (TOS) was significantly lower in the herbal treatment group, further suggesting a protective role against oxidative damage.

Table 5: Antioxidant and Oxidant Status (Mean ± SEM)

Group	TAC (mmol/L)	TOS (µmol/mL)
G0: Negative Control	16.19 ± 0.42	29.00 ± 0.58
G1: Positive Control	4.22 ± 0.40	117.0 ± 0.58
G2: Standard Treatment	1.22 ± 0.40	63.00 ± 0.58
G3: Herbal Treatment	31.06 ± 0.53	54.00 ± 0.58

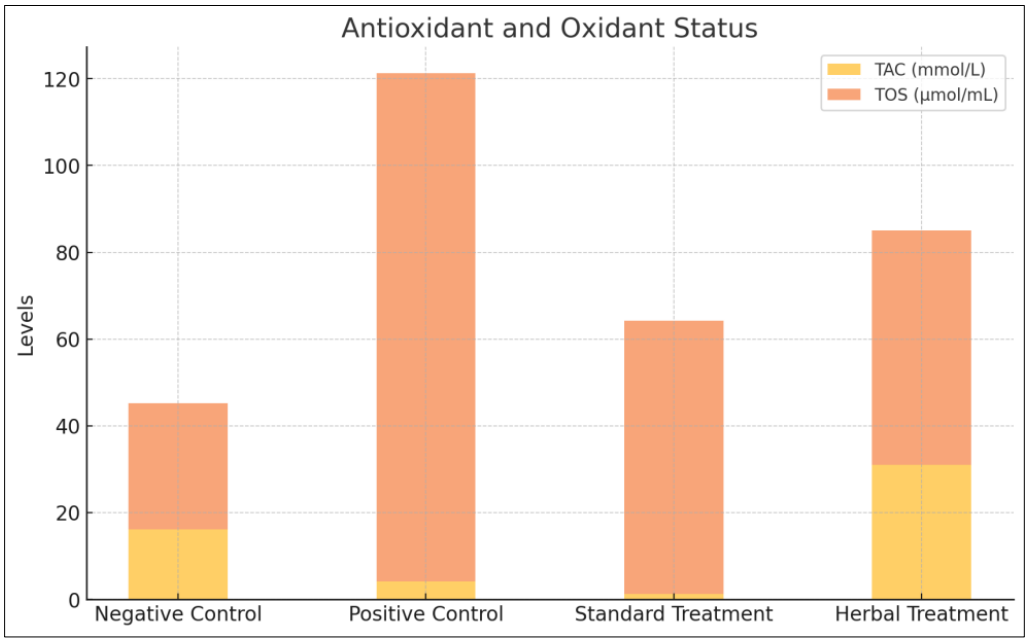

Figure 3: This figure shows the values of Total Antioxidant Capacity (TAC) and Total Oxidant Status (TOS) in the experimental groups. The positive control group has a significant decrease in TAC and an elevation in TOS, signifying increased oxidative stress resulting from myocardial infarction. The herbal treatment group demonstrates a notable increase in total antioxidant capacity (TAC) and a decrease in total oxidant status (TOS), suggesting the possible antioxidant properties of Justicia adhatoda. These findings indicate that herbal therapy aids in reestablishing the equilibrium between antioxidants and oxidants, hence alleviating oxidative damage

3.4 Gene Expression Analysis:

Gene expression of inflammatory cytokines such as IL-6, IL-10, and IL-33 was significantly downregulated in the herbal treatment group compared to the positive control group. Additionally, markers of cell stress and apoptosis such as BAX, BAD, and Bcl-2 were also downregulated, indicating a protective effect of *Justicia adhatoda* on myocardial cells. These findings suggest that the herbal treatment reduces the inflammatory response and apoptotic cell death pathways associated with MI.

Table 6: Gene Expression Levels (Mean ± SEM)

Gene	G0: Negative Control	G1: Positive Control	G2: Standard Treatment	G3: Herbal Treatment
IL-6	0.46 ± 0.01	3.99 ± 0.01	1.88 ± 0.01	1.03 ± 0.01
IL-10	0.57 ± 0.01	3.99 ± 0.01	1.02 ± 0.01	0.72 ± 0.01
IL-33	0.68 ± 0.01	3.98 ± 0.01	1.09 ± 0.01	1.82 ± 0.01
BAX	0.32 ± 0.01	2.90 ± 0.01	1.05 ± 0.01	1.03 ± 0.01

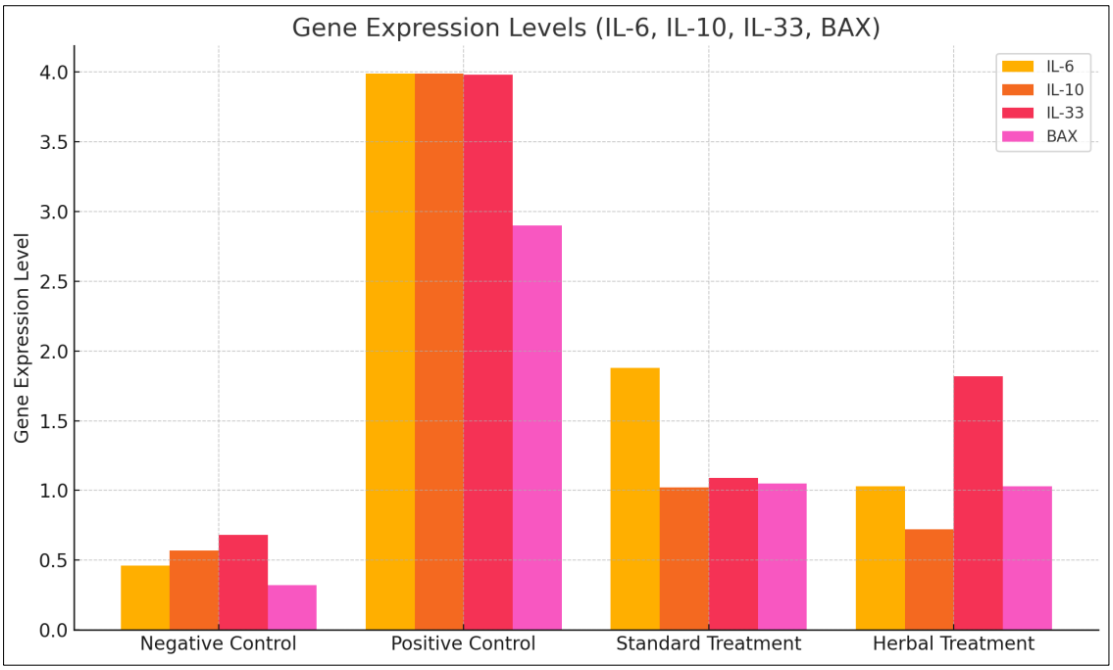

Figure 4: This figure illustrates the expression levels of inflammatory cytokines (IL-6, IL-10, IL-33) and apoptotic markers (BAX) among the various groups. The positive control group demonstrates elevated levels of pro-inflammatory cytokines and apoptotic genes, indicating the inflammatory and apoptotic mechanisms linked to myocardial infarction. The herbal treatment group demonstrates a notable downregulation of these genes, signifying a decrease in inflammation and apoptosis. This indicates that Justicia adhatoda possesses anti-inflammatory and anti-apoptotic actions, enhancing its cardioprotective attributes

4. DISCUSSION

The results of this study demonstrated that the leaf extract of Justicia adhatoda can significantly improve hematological parameters, reduce oxidative stress, and ameliorate myocardial damage induced by isoproterenol-induced MI in rats (Liu & Huang, 2016). We further established that Justicia adhatoda improves antioxidant capacity and reduces hepatic inflammation (by lowering hepatic enzyme levels and pro-inflammatory cytokine gene expression), supporting the cardioprotective potential of Justicia adhatoda (Shaito *et al*., 2020). The present findings align with our research aimed at assessing the therapeutic potential of Justicia adhatoda against myocardial infarction. This supports the current study's hypothesis that different plant extract fractions effectively ameliorate MI-induced damage. This work fills the gap in research by utilizing experimental evidence demonstrating the protective mechanisms of herbal extract. It provides a novel therapeutic approach for myocardial infarction based on plant-derived therapy (Liu & Huang, 2016).

Comparing these results to earlier studies, many parallels were observed, especially in plant antioxidant research and cardioprotective properties. Numerous studies have confirmed diverse plant extracts' antioxidative and anti-inflammatory properties, such as Garlic and Ginger, in preventing myocardial damage. Justicia Adhatoda also demonstrated potent antioxidants (Neag *et al*., 2018). Nevertheless, the present investigation makes a unique contribution to the existing literature, as we have specifically observed the effects of Justicia adhatoda in an isoproterenol-induced myocardial infarction rat model and compared it with a commercially available drug, metoprolol (Diniz *et al*., 2017). This investigation of this herbal drug versus an established pharmaceutical (a beta-adrenergic antagonist) for efficacy in experimentally induced MI in rodents is an important aspect of studying the possible clinical application of Justicia adhatoda in human cardiovascular disease states such as MI (Geetha & Ramachandran, 2021; Wen *et al*., 2018).

Despite its strengths, this study has several limitations. The small sample size of this study (32 rats) has the potential to limit the generalisability of the findings (Ojha *et al*., 2016). However, increased statistical power would provide more robust conclusions with a larger sample size. Furthermore, the significance of this study is limited, as it was performed in a rat model, which may not necessarily mimic human physiology, where the efficacy of Justicia adhatoda has also to be replicated in case of expected efficacy in humans (Choudhury *et al*., 2018). Hence, these findings should be confirmed in future studies involving human clinical trials or larger animal models. In addition, although instant quantitative polymerase chain reaction analysis was used to determine the molecular mechanisms that contributed to the extract's therapeutic effects, quantifying protein levels for a broader range of molecular pathways would clarify the mechanisms by which the plant prevents cardiovascular events (Wen *et al*., 2018).

These findings suggest that Justicia adhatoda leaf extract could be studied as a promising leaf extract for treating myocardial infarction in an additional/alternative manner, particularly in local settings where the accessibility of pharmaceutical treatment is complex. To conclude, clinical trials on the efficacy and safety of Justicia adhatoda in human subjects with myocardial infarction are needed to investigate its benefits further. In addition, studies on the combined effect of Justicia adhatoda and other cardioprotective agents, including antioxidants or anti-inflammatory agents, may be beneficial for developing new combination therapies (Ota & Ulrih, 2017). In addition, the amount, technique of extraction, and chronic effect of Justicia adhatoda should be evaluated in future studies to unfold the capability of this herb to treat cardiovascular diseases (Cid-Ortega & Monroy-Rivera, 2018).

5. CONCLUSION

In conclusion, our findings highlight the ability of Justicia adhatoda leaf extract to manipulate various hematological parameters, attenuate oxidative stress, and ameliorate myocardial necrosis in isoproterenol-induced MI in a rat model. The present findings may have important implications regarding the cardioprotective potential of Justicia adhatoda and validate our hypothesis that plant extracts exert protective effects against myocardial injury. These results also demonstrated lower levels of liver enzymes and inflammatory markers, further implicating plant-based diets in mitigating systemic injury post-MI. These findings provide greater insight into plant-based approaches that can be combined with conventional cardiovascular disease treatment. These findings have significant implications on a broader scale, especially as they relate to understanding the potential herbal treatments for myocardial infarction and the effects of plant-derived pharmaceutical agents. These results indicate that Justicia adhatoda is an inexpensive natural therapy option in third-world regions with restricted access to traditional pharmaceuticals. Although this survey has come a long way, there are still some gaps in the literature, especially concerning the specific molecular and cellular action pathways purportedly affected by Justicia adhatoda and its synergistic effect with other compounds. Further elucidation of these mechanisms would involve consideration of the key signaling pathways of oxidative stress and inflammation in future work. This study has some limitations, including the small sample size and animal model, which limited the generalisability of the results. However, these limitations could be addressed by testing the therapeutic action of Justicia adhatoda in human populations with larger sample sizes. Our results suggest the cardioprotective potential of Justicia adhatoda and pave the way for future research and clinical avenues for natural therapies for cardiovascular diseases.

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