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***Polyalthia Longifolia* Ameliorates Isoprenaline-Induced Myocardial Toxicity via Markers of Oxidative Stress and Inflammation in Wistar Rats**

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ABSTRACT

Cardiovascular disease conditions, such as myocardial infarction (MI), are prominent contributors to global mortality. Isoprenaline induces acute myocardial damage and infarction. *Polyalthia longifolia* (PL), has been reported to possess various potential health benefits. Thus, this study evaluated the protective role of the phenol-rich fraction of PL leaf on isoprenaline (ISO)-mediated myocardial infarction in rats. Forty male Wistar rats (265±15g) were randomly and equally grouped into five (n=8). Group A (control) received 1 mL/kg distilled water, B: ISO at 90 mg/kg, C: vitamin C (Vit C) at 100 mg/kg and ISO, and D and E: PL at 100 mg/kg and 200 mg/kg, respectively and ISO. Treatment was done orally and lasted for 13 consecutive days except for ISO which was given subcutaneously on the 13th day. Blood pressure was monitored following acclimatisation. The whole blood and the heart tissue were collected and analysed for antioxidants, inflammation, oxidative stress markers, and histopathology. Isoprenaline increased blood pressure parameters in group B. These parameters were reversed in Vit-C and PL-exposed groups. Isoprenaline significantly (p<0.05) induced oxidative stress and inflammation, and reduced antioxidant markers in group B. Vit C and PL ameliorated the isoprenaline-induced toxicity in groups C, D, and E. ISO induced inflammatory cells, infarction, and oedema in the heart tissue in group B. These changes were mildly reversed in Vit-C and PL-treated rats. In conclusion, *Polyalthia longifolia* phenol-rich fraction mitigated isoprenaline-induced myocardial toxicity in rats, demonstrating effects comparable to those of Vitamin C.

Key words: *Polyalthia longifolia*, Isoprenaline, Cardiovascular diseases, Oxidative stress, Antioxidants

INTRODUCTION

Cardiovascular diseases (CVDs) account for approximately 20% of total annual global mortality (Vaduganathan *et al.*, 2022). It has been projected that the annual incidence of cardiovascular diseases will reach 23.6 million by 2030 (Ramic-Catak *et al.*, 2023). CVDs encompass a range of pathological conditions that impact the cardiovascular system, including myocardial infarction. Myocardial infarction, the prevailing manifestation of cardiovascular disease, results in tissue damage that is characterised by acute necrosis and apoptosis, along with a reduction in systolic and diastolic functions (Krijnen *et al.*, 2002; Song *et al.*, 2008; Lee and Gustafsson, 2009).

The aetiology of myocardial infarction encompasses a range of factors and multiple elements that affect the integrity of the arterial wall (Hall *et al.*, 1989; Boersma *et al.*, 2003; Mnafigui *et al.*, 2016). Myocardial infarction participates in the induction of free radicals and the presence of supplementary toxic reactions that cause cardiac cell death. Scientific reports affirmed that endogenous catecholamines like synthetic beta-agonist isoprenaline in excessive concentrations can trigger acute myocardial damage and infarction (Schömig 1990; Kloner 2006; Hosseini *et al.*, 2022; Hareeri *et al.*, 2023). These myocardial damage and infarction activities result from the creation of a disparity between reactive species generation and anti-oxidative defence system (Rajadurai and Stanely,

2007; Zhou *et al.*, 2008; Mohan *et al.*, 2019; Hosseini *et al.*, 2022).

A number of synthetic pharmaceuticals are used to treat cardiovascular conditions including myocardial infarction. Their effectiveness is reduced due to accompanying adverse reactions. It was reported that plant-derived drugs are effective, safer and produce little to no side effects (Manjunatha *et al.*, 2020). These plants contribute to the prevention of myocardial infarction via different mechanisms (Hertog *et al.*, 1993; Panda *et al.*, 2017).

One of the highly valued plants is *Polyalthia longifolia* (Annonaceae), a tree with a conical crown and drooping branches. It is naturalised to India and called 'Ashoka' (Sastri, 1969). The plant is used as an antipyretic agent (Raghunathan and Mitra, 1985), and the bark and leaves have demonstrated effective antimicrobial, hepatoprotective, anti-inflammatory, and cytotoxic activities, especially against cancer cells (Chen *et al.*, 2000; Faizis *et al.*, 2008; Tanna *et al.*, 2009; Ravikumar *et al.*, 2010). PL is rich in antioxidant phytochemicals such as diterpenoids and alkaloids and is found in various parts of the plant (Jossang *et al.*, 1982; Ravikumar *et al.*, 2008). Therefore, we investigated the protective effect of the phenol-rich fraction of PL on isoprenaline-mediated myocardial infarction in a rodent model.

MATERIALS AND METHODS

Chemicals

All chemicals and reagents, including isoprenaline and 1, 2-dichloro-4-nitrobenzene (Sigma-Aldrich) were of standard analytical grade.

Experimental Animals

Forty (40) male Wistar rats (265±15g) were purchased from the University of Ibadan Central Animal House and accommodated in similar facility of the Faculty of Veterinary Medicine. The rats were kept in well-ventilated cages, and provided with commercial chow and water was served all through the research. All protocol adheres to the National Institute of Health publication 1985 guidelines for animal care and use with institutional ethical approval number, UJ/FPS/F17-00379.

Experimental Protocol

Forty (40) experimental rats were equally grouped into five (A to E). Group A (control) received 1 mL/kg body weight of distilled water for 13 consecutive days. B: received distilled water for 12 days and 90 mg/kg body weight of isoprenaline on day 13. Animals in Groups C, D, and E, were pre-exposed for 12 days with 100 mg/kg of Vitamin C, 100 mg/kg of PL, and 200 mg/kg of PL, respectively, followed by a combination with isoprenaline administration on day 13.

Blood Pressure Indices and Electrocardiogram

Blood pressure measurement was done using an electro-sphygmomanometer (CODA, Kent Scientific) as reported (Oyagbemi *et al.*, 2017). A mean of nine data points was taken per animal after acclimatization. For the electrocardiogram, a seven-lead ECG machine (EDAN VE-1010, Shanghai, China) was used to record the heart

rate, QT segment, and Bazett's correction of the QT interval was assessed in conscious animals.

Blood Sample Collection

Following the completion of treatment, blood samples were collected from the medial canthus using heparin-coated capillary tubes into plain tubes and left to clot. The animals were euthanized by cervical dislocation after the completion of blood collection. The blood samples were centrifuged (10,000 rpm) for 10 mins to obtain samples that were refrigerated at -4°C until analysis.

Serum Biochemical Assay

Estimation of superoxide dismutase activity and reduced glutathione level

Superoxide dismutase (SOD) activity and reduced glutathione (GSH) level were assessed in the serum as reported by Misra and Fridovich, (1972) (modified by Oyagbemi *et al.*, 2015) and Beutler *et al.* (1963), respectively. The estimation of superoxide dismutase activity was based on inhibiting the auto-oxidation of adrenaline in a reaction mixture containing the serum in 0.05 M carbonate buffer (pH 10.2) and 0.3 M epinephrine. The absorbance was determined at 340 nm every 30 seconds for five consecutive times to assess the activity of SOD. However, GSH level was measured by utilising Ellman's reagent, which was prepared in 0.1 M phosphate buffer that reacts with sulfhydryl groups to yield a stable yellow colour and was measured spectrophotometrically (412 nm).

Estimation of myocardial nitric oxide and advanced oxidation protein products level

Nitric oxide (NO) level in the cardiac tissues and advanced oxidation protein products (AOPP) level in the serum was assessed as described by Olaleye *et al.* (2007) and Kayali *et al.* (2006), respectively. NO content was measured by mixing Griess' reagent (0.1% N-(1-naphthyl)-ethylene diamine dihydrochloride (NED) and sulfanilic acid) to the cardiac tissues at 25 °C and absorbance measured (540 nm). The NO content was estimated from the plotted standard curve.

Preparation of the Heart Tissue for Biochemical Assay

Following the method of Oyagbemi *et al.* (2017), the heart tissue was prepared for the biochemical assay. The heart tissue was homogenized, and the homogenate centrifuged (10,000 rpm) for 10 mins at 4 °C. The supernatant was obtained and used to perform biochemical assays.

Assessment of myocardial glutathione-S-transferase, glutathione peroxidase, and myeloperoxidase activities

Glutathione-S-transferase (GST) activity was monitored following the method of Habig *et al.* (1974). Glutathione peroxidase and myeloperoxidase activities were determined as described by Xia and Zweier (1997).

Assessment of myocardial carbonyl content and lipid peroxidation level

Protein carbonyl, non-protein thiol, and lipid peroxidation were determined in the heart tissue according to the method of Levine *et al.* (1990) and Varshney and Kale, (1990), respectively. Lipid peroxidation was evaluated by determining the colonic content of malondialdehyde

according to the method described by Varshney and Kale (1990). The procedure involved initial protein precipitation with trichloroacetic acid (TCA) and subsequent reaction with thiobarbituric acid (TBA). The mixture was boiled in a water bath at about 80 °C for 45 min, and the samples were centrifuged at 3000 g for 15 min. The calculation of MDA concentration was made with a formula using the molar extinction coefficient of $1.56 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$.

Determination of myocardia hydrogen peroxide level

Hydrogen peroxide level in the cardiac tissues was determined as described by Wolff (1994). The H_2O_2 contents determination involved a reaction mixture of ammonium ferrous sulphate, sorbitol, xylenol orange, and sulphuric acid. The mixture was incubated for 30 minutes at 25 °C and a subsequent reading of absorbance at 560 nm.

Histological Examination

Following euthanasia by cervical dislocation, the hearts tissues were excised and observed for any sign of gross morphological changes. The heart samples were fixed in 4% buffered formalin solution, prepared using paraffin embedding, and sectioned (5 μm -thick) for Haematoxylin and Eosin (H & E) staining. The sections were mounted on plain glass slides, examined under a bright field light microscope, and microscopy evaluations performed (Avwioro, 2002).

Statistical Analysis

Data were analysed using ANOVA with Tukey's post-hoc test. Graph Pad Prism version 6 was used to carry out the

analysis and were expressed as mean $\pm$ standard deviation (SD). A p-value of <0.05 was considered statistically significant.

RESULTS

Figures 1 and 2 show the effect of isoprenaline (ISO), Vit C (Vit C) and *Polyalthia longifolia* (PL) on oxidative stress and inflammatory biomarkers in rats. The ISO-exposed rats displayed a significantly ($p<0.05$) higher level of hydrogen peroxide, protein carbonyl, malondialdehyde, total thiol, non-total thiol, advanced oxidation protein product, and myeloperoxidase activity as compared to the control (Figures 1 and 2). The pre-treatment with Vit C did not result in any significant differences in total thiol and malondialdehyde (Figure 1), and hydrogen peroxide levels (Figure 2). Also, PL at the dosages used could not ameliorate the ISO-induced hydrogen peroxide and malondialdehyde contents in the co-exposed rats relative to the control (Figures 1 and 2). However, Vit C and PL caused a significant ($p<0.05$) reduction in protein carbonyl levels relative to both the control and ISO-exposed groups (Figure 1).

Rats pre-exposed to PL at 100 mg/kg showed a significant ($p<0.05$) reduction in total thiol levels compared to rats treated with ISO alone (Figure 1). However, the rats that were pre-exposed to both Vit C and PL at 100 and 200 mg/kg, respectively, showed a significant ($p<0.005$) reduction in non-total thiol levels compared to rats treated with ISO alone (Figure 1). Serum nitric oxide levels were significantly ($p<0.05$) reduced in all the treatment groups except for the group pre-exposed to PL at 200 mg/kg (Figure 2).

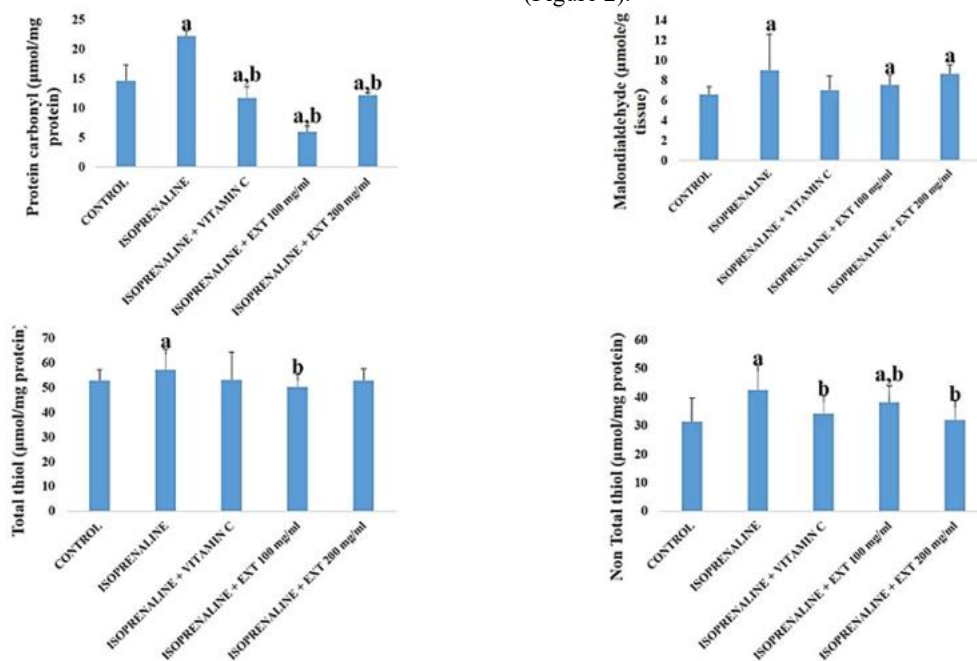


Figure 1: Isoprenaline induced oxidative stress biomarkers in the myocardium of treated rats. Values are presented as mean $\pm$ SD. ^a significantly different ($p<0.05$) from control. ^b significantly different ($p<0.05$) from isoprenaline. Control: Distilled water (1mL/kg), ISO (90 mg/kg), Vitamin C (100 mg/kg), *Polyalthia longifolia* (100 mg/kg and 200 mg/kg).

The administration of isoprenaline resulted in a significant reduction in GSH level and GPx activity in the ISO-treated group (Figure 3). Similarly, ISO caused a non-significant reduction in SOD activity (Figure 3). There was a non-significant difference in GSH level, and GPx and SOD

activities in the Vit C and PL pre-treated groups compared to the control. However, there was an elevation in these parameters in the pre-treated groups as compared to ISO-treated rats (Figure 3).

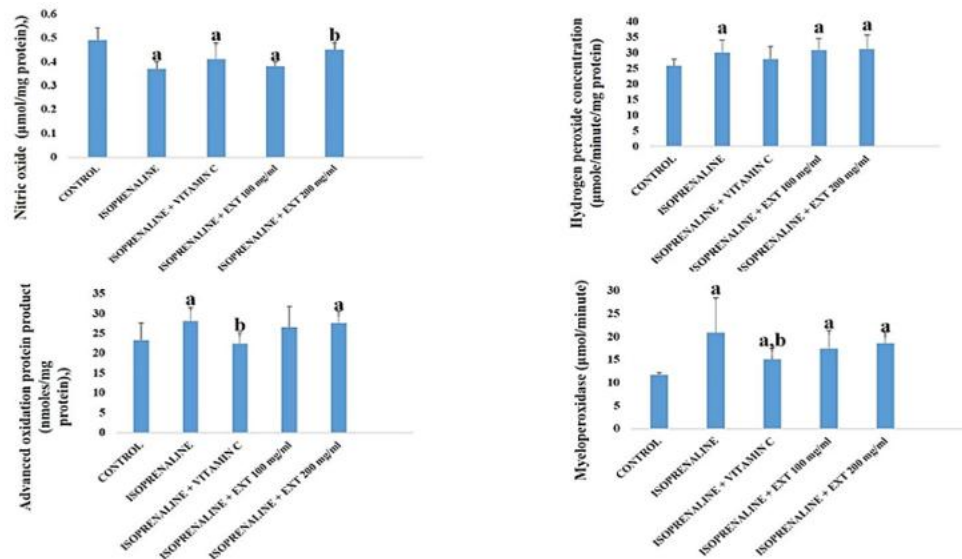


Figure 2: Isoprenaline induced oxidative stress biomarkers in the myocardium of treated rats. Values are presented as mean $\pm$ SD. ^a significantly different ($p < 0.05$) from control. ^b significantly different ($p < 0.05$) from isoprenaline. Control: Distilled water (1mL/kg), ISO (90 mg/kg), Vitamin C (100 mg/kg), *Polyalthia longifolia* (100 mg/kg and 200 mg/kg).

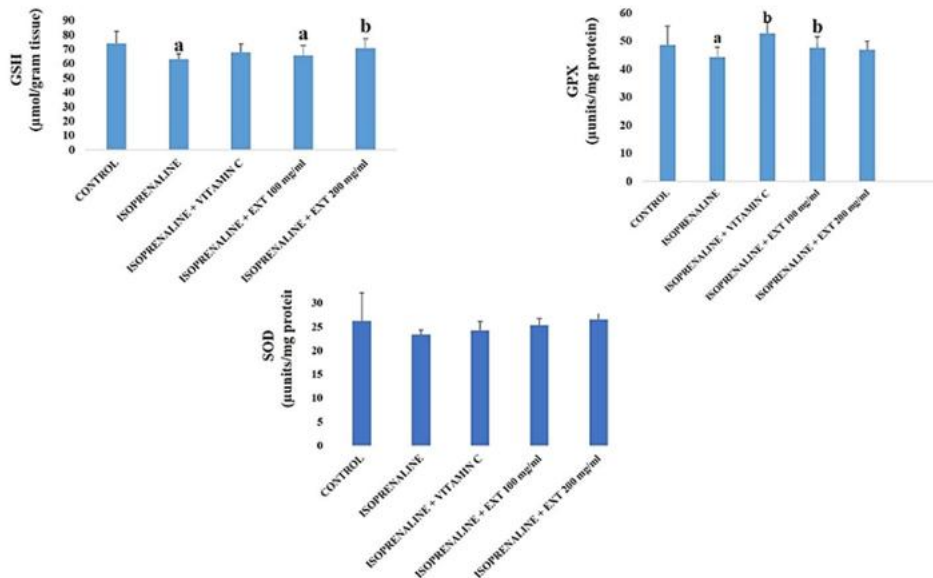


Figure 3: Isoprenaline reduced antioxidant biomarkers in the myocardial of treated rats. Values are presented as mean $\pm$ SD. ^a significantly different ($p < 0.05$) from control. ^b significantly different ($p < 0.05$) from isoprenaline. Control: Distilled water (1mL/kg), ISO (90 mg/kg), Vitamin C (100 mg/kg), *Polyalthia longifolia* (100 mg/kg and 200 mg/kg).

In all the groups, there was a non-significant ($p > 0.05$) rise in the heart rate and QT/QTc values (Figure 4). 100 mg/kg of PL-treated group displayed a significant rise in QT/QTc values compared to the control. In addition, a significant ($p < 0.05$) elevation in the systolic and diastolic blood pressure and mean arterial pressure levels were seen in the ISO-alone group compared to the control (Figure 5). Vit C and PL reduced these parameters in the co-treated groups

to a significant level ($p < 0.05$) relative to the ISO alone-exposed group (Figure 5).

Figure 6 shows the effect of treatments with ISO, Vit C and *Polyalthia longifolia* on the heart tissues histology. Isoprenaline caused severe extensive degeneration and necrosis of the muscle fibres, with cellular infiltration in the treated rats (Figure 6). Vit C and PL mildly reversed the lesions in the co-treated groups (Figure 6).

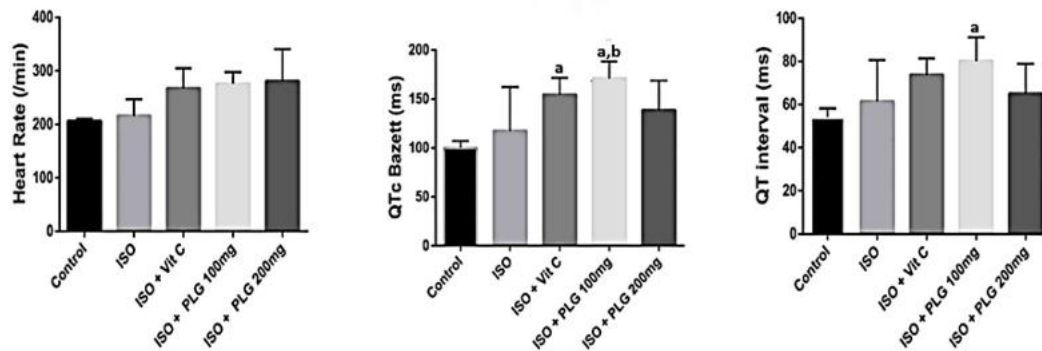


Figure 4 Effect of *Polyalthia longifolia* on the heart rate and QT/QTc in ISO-treated rats. Values are presented as mean $\pm$ SD. ^a significantly different ($p < 0.05$) from control. ^b significantly different ($p < 0.05$) from isoprenaline. Control: Distilled water (1mL/kg), ISO (Isoprenaline at 90 mg/kg), Vit C (Vitamin C at 100 mg/kg), PL (*Polyalthia longifolia* at 100 mg/kg and 200 mg/kg).

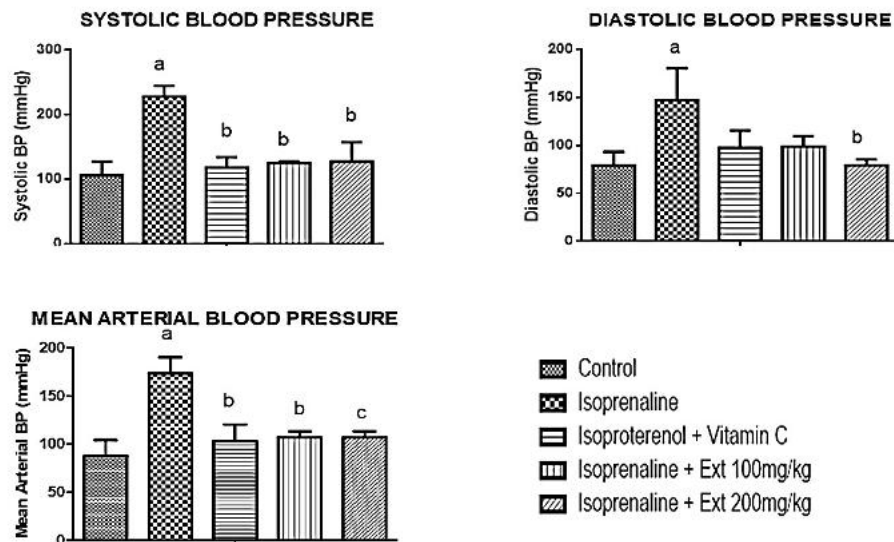


Figure 5: *Polyalthia longifolia* ameliorates ISO-induced dysfunctions in blood pressure indices. Values are presented as mean $\pm$ SD. ^a significantly different ($p < 0.05$) from control. ^b significantly different ($p < 0.05$) from isoprenaline. Control: Distilled water (1mL/kg), ISO (90 mg/kg), Vitamin C (100 mg/kg), Ext: *Polyalthia longifolia* (100 mg/kg and 200 mg/kg).

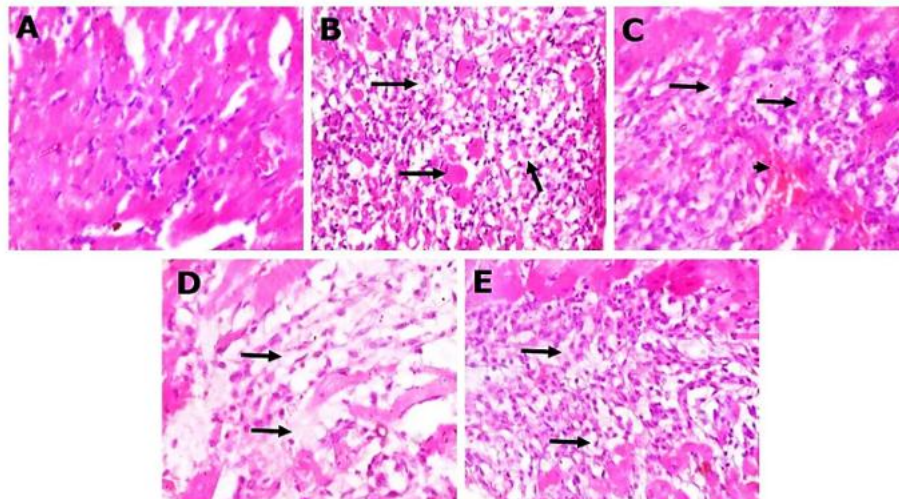


Figure 6: Photomicrographs of the myocardial tissue of treated rats. A: Control (distilled water at 1mL/kg), shows focus of mild cellular infiltration of the muscle fibres (arrow). B: Isoprenaline at 90 mg/kg, shows severe extensive degeneration and necrosis of the muscle fibres, with cellular infiltration of inflammatory cells. C: Vit C at 100 mg/kg, shows moderate focally extensive area of degeneration, interstitial congestion (arrowhead) and cellular infiltration of the muscle fibres, D: *Polyalthia longifolia* at 100 mg/kg, shows severe necrosis of the muscle fibres, with cellular infiltration (arrow). E: *Polyalthia longifolia* at 200 mg/kg, shows moderate to severe necrosis of the muscle fibres, with cellular infiltration of inflammatory cells (arrow). H&E. x400 Magnification.

DISCUSSION

Cardiovascular diseases encompass a range of pathological conditions that impact the cardiovascular system, including myocardial infarction. There are reports affirming that endogenous catecholamines like synthetic beta-agonist isoprenaline in excessive concentrations can trigger acute myocardial damage and infarction (Schömig 1990; Kloner 2006; Hosseini *et al.*, 2022). Isoprenaline induces oxidative stress by creating an imbalance between oxidant and antioxidant levels (Terentyev *et al.*, 2008; Meeran *et al.*, 2015; Shaikh *et al.*, 2019; Sharma *et al.*, 2020). This imbalance can lead to various myocardial lesions, increased lipid peroxidation, depletion of antioxidant levels in the heart, and increased generation of ROS (Raish, 2017; Shahzad *et al.*, 2019).

The exposure of rats to isoprenaline alone in the present study was characterized by reduced glutathione level, glutathione peroxidase and superoxide dismutase activities. These findings corroborate the reports that ISO suppresses the anti-oxidative defence system in experimental animal models (Rajadurai and Stanely, 2007; Zhou *et al.*, 2008; Mohan *et al.*, 2019; Hosseini *et al.*, 2022). This activity of ISO compromises the function of GSH in the removal of ROS (Troudi *et al.*, 2012) and superoxide dismutase that catalyses the conversion of superoxide radicals to H_2O_2 and glutathione peroxidase that detoxify H_2O_2 into H_2O and O_2 (Wang *et al.*, 2018). The reversal of this toxic effect of ISO by PL in this study corroborates the reports of PL anti-oxidative activity (Jossang *et al.*, 1982; Ravikumar *et al.*, 2008). The treatment with Vit C did not show significant improvement relative to the PL treatment group. Hence, the anti-oxidative activity of PL was comparable to that of Vit C in our study. This comparative activity buttresses the statement of Akila and Vennila (2016) that the use of plant phenolics with antioxidant properties is capable of restraining the generation of free radical or reactive oxygen species, myocardial lesions and progression of myocardial toxicity is of research interest.

Similarly, ISO at 90 mg/kg induced biomarkers of oxidative stress and inflammation, especially H_2O_2 , protein carbonyl, malondialdehyde, total thiol, non-total thiol, advanced oxidation protein product, and myeloperoxidase proteins. Isoprenaline, a non-selective β -adrenoceptor agonist, induces substantial myocardial injury (Boarescu *et al.*, 2019). It promotes the formation of cytotoxic free radicals, enhances lipid peroxidation and impairs antioxidant defences, leading to severe myocardial damage marked by increased cardiac enzyme levels (Song *et al.*, 2020). The formation and expression of these markers have been linked to myocardial dysfunction and infarction (Tang *et al.*, 2015). However, pretreatment with Vit C and PL did not show any significant recovery from the myocardial damage. Reports indicated that certain phytochemicals have mitigated isoprenaline-induced damage to cardiac tissue, as evidenced by decreased oxidative stress markers and increased antioxidant levels (Priscilla and Prince, 2009; Shahzad *et al.*, 2019; Manjunatha *et al.*, 2020).

Findings from our study show that ISO treatment led to slight increases in heart rate and QT/QTc intervals,

consistent with its known chronotropic effects and potential to alter cardiac repolarization (Zhang *et al.*, 2012). The heart rate, while not reaching statistical significance, showed a trend towards increase with *P. longifolia* treatment, particularly at the higher dose. This chronotropic effect of *P. longifolia* might be attributed to compounds in the plant that have sympathomimetic properties or that modulate autonomic nervous system activity.

Isoprenaline induces an increase in diastolic $[Ca^{2+}]$ and intracellular Ca^{2+} overload and disrupts intracellular Ca^{2+} homeostasis which drives myocardial injury and disruptions in cardiac repolarization (Qin *et al.*, 2013). Administration of PL, especially at the 100 mg/kg dose, significantly prolonged both QT and QTc intervals, with QTc also being notably higher than in the ISO-only group. This QT-prolonging effect is important, as it may increase the risk of arrhythmias. Comparable effects have been observed with other plant-derived compounds, such as certain flavonoids, which are likely due to the blockage of HERG channels (Zitron *et al.*, 2005). Interestingly, the higher dose of PLG (200mg/kg) showed less pronounced effects on QT/QTc intervals compared to the 100mg/kg dose. This non-linear dose-response relationship suggests a potential hermetic effect, where lower doses elicit a more substantial biological response than higher doses (Wan *et al.*, 2024). Phytochemicals can activate hermetic pathways that involve kinases and transcription factors, leading to the upregulation of genes responsible for encoding anti-oxidative enzymes, chaperones, neurotrophic factors, and other cell protection mechanisms (Son *et al.*, 2008). The effects of *P. longifolia* on cardiac parameters, particularly the prolongation of the QT interval, require further investigation. Although traditional uses of *P. longifolia* have indicated various therapeutic benefits (Katkar *et al.*, 2010), our findings emphasize the need for comprehensive safety assessments of herbal formulations, particularly concerning their cardiovascular impact.

Histological examination of the heart after isoprenaline administration to the rats revealed severe cardiac lesions. These lesions were mildly reversed with the pre-treatment with Vit C and PL in the co-treated groups. This finding corroborates the reported structural changes in the myocardium of ISO-treated rats (Shahzad *et al.*, 2019). Hence, PL and Vit C offer mild protection to the myocardium architecture.

Meanwhile, findings from our study have shown the need to characterize and isolate bioactive compounds from and further explore other pathways and mechanisms of action of PL. Also, other routes of treatment and dosages can be investigated to assess the possibility of better cardioprotective functions of PL.

Conclusion

This study explored the protective role of *Polyalthia longifolia* on isoprenaline-mediated myocardial toxicity. The findings from this study demonstrated that *Polyalthia longifolia* mitigated isoprenaline-mediated myocardial toxicity in Wistar rats, demonstrating effects comparable to those of Vitamin C. However, the observed increase in QT/QTc intervals in rats treated with *Polyalthia longifolia* warrants caution in its use.

Conflict of Interest

The authors have no conflict of interest to declare

Author Contribution

Conceptualization OTO, OAA, OT; Data curation SES, OT, OTO, ATO; Formal analysis SES, OT, ATO, OTO, OAA; Investigation OT, ATO, OAA, OTO; Methodology OTO, OAA, ATO; Project administration OTO, OAA, IOO ; Resources; Software OT, ATO, OTO, SES; Supervision OAA, OTO, ATO, IOO; Visualization; OTO, OOG; Roles/Writing - original draft OTO, SES, OT, OAA; and Writing - review & editing SES, AOA, EOO, AT, AO, ATO, IOO, AAS, OOG, BJA, OAA, YMA, OTO.

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